MULTIPLE RIB FRACTURES

EPIDEMIOLOGY, MANAGEMENT, AND OUTCOMES

JONNE T.H. PRINS

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EPIDEMIOLOGY, MANAGEMENT, AND OUTCOMES

1. Initial chest wall injury severity and treatment modality are not associated with long-term pulmonary function and quality of life. (this thesis)
2. Rib fractures negatively impact the patient's subjective well-being up to years after injury. (this thesis)
3. Early (48-72h after admission) surgical stabilization of rib fractures (SSRF) is recommended; late SSRF is not associated with improved in-hospital outcomes as compared to nonoperative management. (this thesis)
4. Patients with traumatic brain injury should not be withheld SSRF, but assessed on an individual basis as well as studied in well-designed multicenter research. (this thesis)
5. Patients after cardiopulmonary resuscitation often have extensive chest wall injury warranting early chest CT imaging and consultation for SSRF evaluation. (this thesis)
6. The scientific value of a retrospective multicenter study before conducting an expensive and potentially risky invasive prospective study, is underestimated.
7. Medical specialty may be deduced from parking skills. (McCain, BMJ 2010)
8. If we want to know what is going on, we should not ask. (George Beam)
9. Alles wat geen natuurwet is, is dogma. (Willem Frederik Hermans)
10. It is more important to know what sort of patient has a disease than what sort of disease a patient has. (William Osler)
11. C'est en forgeant qu'on devient Forgeron.

J.T.H. Prins

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Multipele ribfracturen:
Epidemiologie, behandeling en uitkomsten

Proefschrift

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Erasmus Universiteit Rotterdam
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CHAPTER 1

General introduction and thesis outline

GENERAL INTRODUCTION

The chest wall

The chest wall includes the sternum and rib cage. The rib cage consists of two hemithoraces which comprise twelve ribs each, offering attachments for the chest wall musculature and providing rigid support and protection of the lungs, cardiovascular structures, and upper abdominal viscera [1]. The intercostal groove alongside the inferior dorsal length of the rib encompasses the neurovascular bundle which holds the intercostal, artery, vein, and nerve. The intact rib cage accounts for up to 80% of the thoracic stability en enables respiration [2].

Anatomically, ribs can be classified based on their cartilaginous connection with the sternum: *true* ribs (ribs 1-7) are ribs with their costal cartilage attached directly to the sternum; *false* ribs (ribs 8-10) have a costal cartilage which attaches to the cartilage of the superior rib, while *floating ribs* (ribs 11-12) have no costal cartilage connection (Figure 1) [3]. Dorsally, the rib's head articulates with the corresponding thoracic vertebra and transverse process at the costovertebral and costotransverse joint. In addition, on the basis of morphology, ribs are determined *typical* (ribs 3-10) if they have an articular facet at the anterior and posterior end with a body connected to the head through a neck and tubercle. Ribs one and two are *atypical* because they are shaped to accommodate the thoracic inlet and provide attachments for upper extremity musculature whereas 11 and 12 are *atypical* as they lack an anterior facet, neck, and tubercle [4].

The ribs play a significant role in the generation of negative intra-thoracic pressure, allowing oxygen, fluids, and food to enter the body. Furthermore, the ribs are of great importance in the dynamics of the chest wall during respiration and protect intra-thoracic organs. The mechanics of respiration involve complex interactions between, among others, the lungs, diaphragm, chest wall, and musculature. Inspiration is facilitated by the outward elastic recoil of ribs and sternum allowing for lung expansion and generation of the negative intra-thoracic gradient by the diaphragm [5]. During expiration, the relaxation of the diaphragm and the tissue's elasticity result in a decreased thoracic volume and increased intra-thoracic gradient. Ribs three to 10 contribute most to respiration while ribs one, two, 11, and 12 are less critical [6]. The primary muscles of respiration are the external (inspiratory) and internal (expiratory) intercostal muscles with the diaphragm, innervated by the phrenic nerve, as the main contributor in respiratory motion [1].

Chest trauma and rib fractures

Chest trauma from an external mechanical origin accounts for over one third of trauma-related mortality and is the leading cause of death for persons up to 45 years [7]. Chest
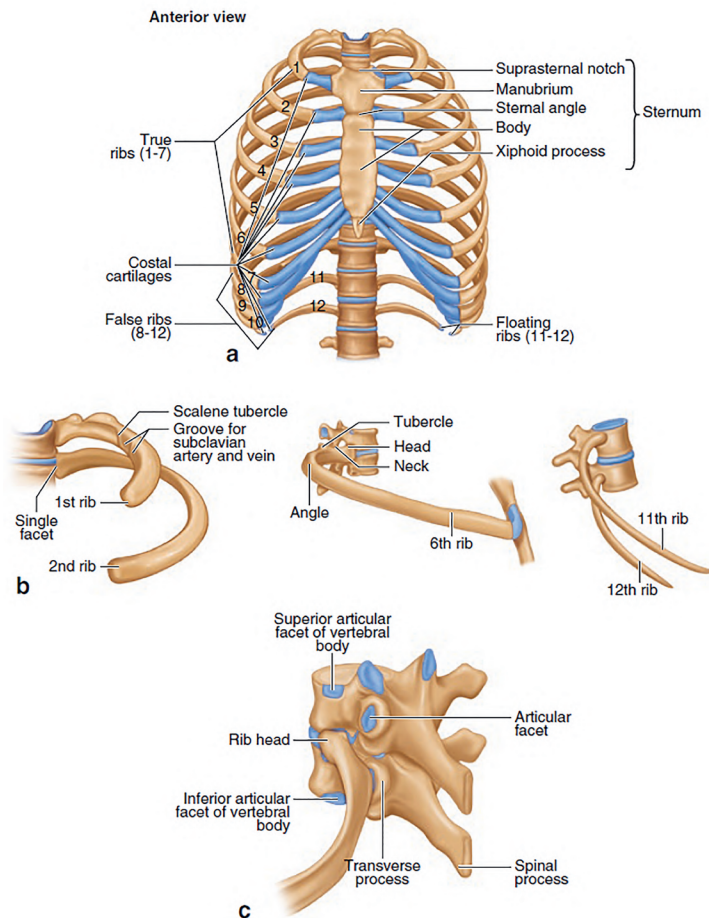
FIGURE 1
Osseous anatomy of the chest wall. From Saillant et al. [1]. Reprinted with permission from Springer Nature.

trauma can largely be subdivided into blunt and penetrating trauma. Blunt chest trauma is the most common chest trauma with motor vehicle collisions as the most prevalent cause [8]. Rib fractures are the most common bony injury following blunt thoracic trauma and are seen in up to four in every 10 patients [4, 9]. In patients undergoing cardiopulmonary resuscitation (CPR) for a sudden cardiac arrest, rib fracture rates are even higher (66-85%), but data on CPR-related chest wall injury characteristics is scarce [10-12].

Rib fractures can occur as single or multiple rib fractures or as a flail segment, commonly defined as three adjacent ribs fractured in two or more places [13]. Rib

fractures in younger adults are often a result of high-energy trauma such as motor vehicle collisions or a fall from height, whereas over half of the elderly patients (≥65 years) sustain rib fractures following a ground level fall [14, 15]. One hypothesized risk factor for rib fractures might be a diminished bone mineral density (BMD), but this has not been evaluated specifically to date. Rib fractures are a marker of severe injury as about 45% these patients are polytraumatized (ISS>15) and one in two requires Intensive Care Unit (ICU) admission while concomitant injuries are common [16-21]. The effect of these comorbidities on rib fracture management and outcomes is less clear.

There is little data regarding the exact incidence rate of rib fractures and associated economic costs during and after hospitalization. The incidence rate of patients with rib fractures is 29 per 100,000 person years, but this only accounts for admitted patients [22]. Costs associated with rib fractures are high and increase with among others a higher injury severity score and longer length of stay, but this only includes in-hospital care [23].
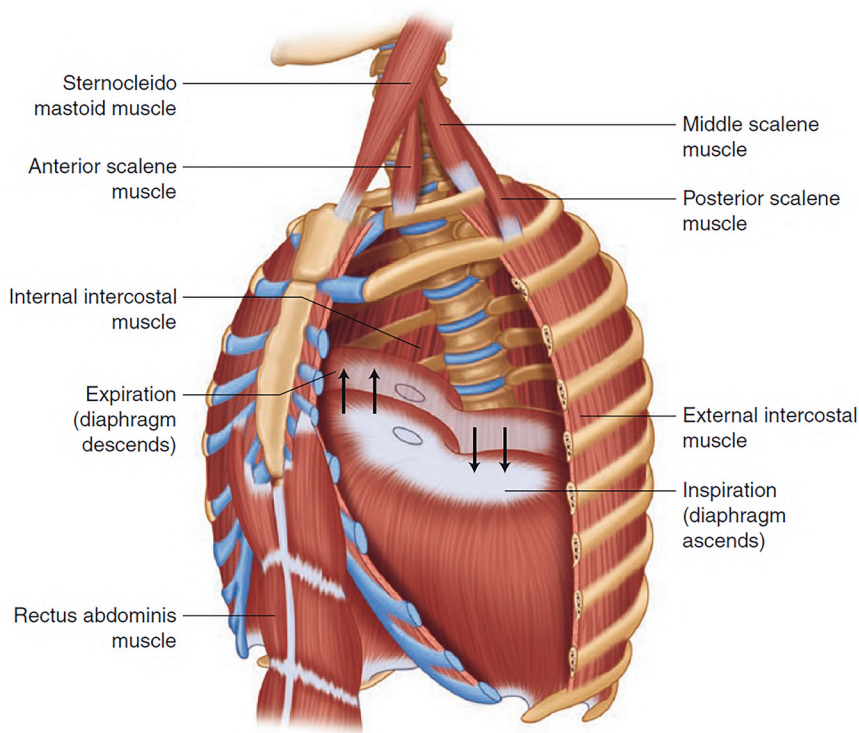
FIGURE 2
Musculature associated with in- and expiration. From Saillant *et al*. [1]. Reprinted with permission from Springer Nature.

Clinical and radiological assessment, and fracture classification

The diagnosis and management of rib fractures centers around radiological and clinical examination. At hospital presentation, patients might experience thoracic pain, swelling and bruising of the chest wall, dyspnea, or respiratory distress. On clinical examination, findings range from tenderness and crepitus on palpation of affected ribs, low oxygen saturation, or decreased breath sounds because of a pneumothorax, hemothorax, or pulmonary contusion, to chest wall deformity or paradoxical breathing.

The two most common imaging modalities used in rib fracture diagnostics are chest radiography (CXR) and computed tomography (CT). Although CXR has a high specificity for diagnosing fractured ribs and is useful in detecting pulmonary morbidity, a negative CXR does not reliably rule out rib fractures [24, 25]. Chest CT has a higher sensitivity and is the golden standard for rib fracture delineation as it finds on average two to three additional rib fractures that were missed on CXR [24, 26-28]. The clinical impact of these imaging modalities remains a matter of debate.

Due to the more widely incorporated use of the chest CT, rib fracture injury characteristics are diagnosed in a more detailed way. Recently, the Chest Wall Injury Society (www.cwisociety.org) has adopted a rib fracture classification system [13, 29]. This taxonomy classifies rib fractures based on rib fracture location, type, and degree of displacement. The location of a rib fracture can be classified, from sternum to vertebral column as costochondral, anterior, lateral, or posterior. There is currently no consensus on the exact anatomic boundaries of these locations, but it is recommended to use these sectors and provide the method of definition. Regarding type, fractures can be characterized as either simple, wedge, or complex (Figure 3). In terms of dislocation, there are three categories: undisplaced (>90% cortical contact), offset (cortical contact ≤90%), and displaced (no cortical contact; Figure 4). These rib fracture characterizations and their effect on for example treatment and outcomes has not yet been validated.
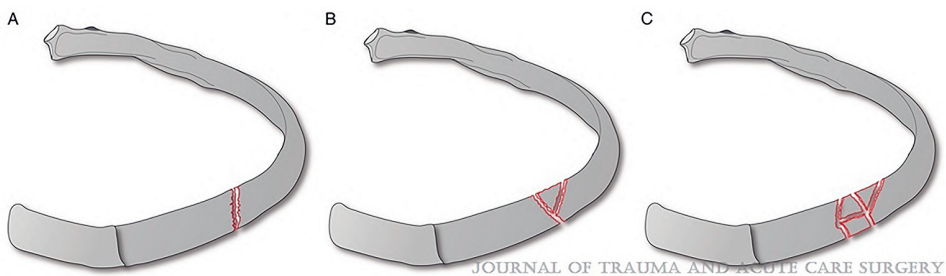
FIGURE 3
Rib fracture type following the CWIS taxonomy: simple (A), wedge (B), or complex (C).
From Edwards et al. [13]. Reprinted with permission from Wolters Kluwer Health, Inc.

FIGURE 4
Rib fracture dislocation following CWIS taxonomy: undisplaced (A), offset (B), or displaced (C).
From Edwards et al. [13]. Reprinted with permission from Wolters Kluwer Health, Inc.

Rib fracture morbidity and mortality

Rib fractures disrupt chest wall stability and can interfere with the respiratory mechanics described above. This interference impairs the required intrathoracic expansion and reduces lung volumes which increases the risk of adverse pulmonary outcomes such as pneumonia or mechanical ventilation requirement [5, 30]. The anticipation that the respiratory status deteriorates over the first days after sustaining rib fractures is a clinical precept which dates back to Hippocrates and Sushruta [31]. Rib fractures cause pain with every respiratory cycle which might lead to splinting, the inability to sufficiently clear secretions and subsequently the development of pneumonia [32].

Due to its interference with respiratory mechanics, both the presence of rib fractures as well as an increasing number of rib fractures are associated with increased rates of pulmonary complications and other adverse outcomes [17, 33, 34]. Pneumonia is the most common pulmonary complication following rib fractures with reported rates up to 47% which is affected by an increasing number of rib fractures or presence of a flail chest [17, 33, 35-38]. A reduced pulmonary function in patients with rib fractures is associated with longer hospital length of stay and a higher risk of developing pulmonary complications [39, 40]. Moreover, rib fractures pose a serious health burden beyond hospital discharge. In the long-term, rib fractures have been associated with chronic pain, disability, and decreased quality of life [41-45]. These studies however often address a single outcome, chest wall injury or treatment modality. Literature on the effect of more detailed chest wall injury characteristics on these outcomes is limited.

The presence of rib fractures are often a sign of concomitant injuries, both thoracic and extra-thoracic. Whereas fractures of ribs five through nine are associated with cardiac and pulmonary injuries such as pulmonary contusion, pneumothorax, hemo-thorax, fractures of ribs 10-12 are associated with solid organ injuries of the liver, spleen, and diaphragm [4, 32]. Injuries such as traumatic brain injury (TBI; 15%), sternum (10%), scapular (16%) and clavicle (19%) fractures as well as pneumothorax (78%),

hemothorax (80%), and pulmonary contusion (59%) are common in patients with multiple rib fractures [16, 17, 19, 20].

Adverse outcomes such as mechanical ventilation requirement and mortality are independently associated with sustaining rib fractures [34, 46, 47]. Mortality rates of 16-17% in patients with a flail chest have been reported, up to 20% in patients with >6 rib fractures [48, 49]. This effect is even more prominent in elderly patients (>65 years) in which mortality is 2- to 5-fold higher than in younger patients with an associated increase in mortality rate of 19% for each additionally fractured rib [14, 15, 50]. Besides the presence and number of rib fractures, the degree of rib fracture dislocation is also associated with pulmonary complications and more severe (intra)thoracic injuries [51-53].

Traditionally, rib fracture management has centered around nonoperative manage-ment. Ancient medical literature from the Egyptians in 1600 BCE, provides the first known mention of rib injuries, treated with supportive binding and daily honey application [31]. To date, nonoperative management includes multimodal pain management, oxygen support, (pulmonary) physical therapy, and mechanical ventilation if required [4, 54]. However, as the results above demonstrate, short- and long-term outcomes remain poor in the nonoperatively managed patient with rib fractures and this has sparked interest in a new treatment modality [37].

Surgical stabilization of rib fractures (SSRF)

Conventionally, SSRF has been performed in the patient with a flail chest.
In the 1950s, one of the first studies specifically addressed rib fixation in 15 patients with a flail chest, through wiring the fractures in two planes, but it was not until the 1980s when an increase in SSRF became apparent [31]. The effect of SSRF has been studied extensively, with fixation techniques ranging from cerclage wiring, plating with clips, absorbable implants or intramedullary struts, to the current most commonly used method of outer rib cortex plating with bicortical screw fixation [55, 56]. Lately, intrathoracic plating techniques have also been described [57, 58].

Also, in several randomized controlled trials and various meta-analyses, following SSRF, an improvement in outcomes such as pneumonia rate, duration of mechanical ventilation (DMV), hospital and Intensive Care Unit length of stay (HLOS and ICU LOS, respectively) has been demonstrated [59-64]. In addition, SSRF, while an expensive procedure, is associated with decreased hospitalization costs [65-67]. Other studies however, found no benefit of SSRF over nonoperative management or only for specific outcomes or patients such as in the in-hospital setting or for a flail chest [68, 69]. Over the last decades, the use of SSRF has been increasing rapidly and is now implemented in many international Trauma Centers for a widening indication of severe rib fractures [70-73].

It is hypothesized that nonoperative management through pain control is ineffective and negatively impacts pulmonary mechanisms and negative intra-thoracic pressure generation while rib fractures also result in poor secretion clearance, increasing the risk of respiratory failure [54]. Stabilizing the chest wall and irrigating the chest cavity would alleviate pain, restore breathing mechanisms, and increase lung volumes, which has been shown to increase with 70% on 3D chest CT as compared to post-traumatic parenchymal lung volumes in patients with both a flail chest and non-flail fracture pattern [74].

In general, fractures of ribs three to nine with at least three centimeters from the vertebral column for posterior fractures, are considered amenable for surgery. Ribs one and two are technically difficult to approach extra-thoracically because of neuro-vascular structures, while fractures of ribs 11 and 12 have less impact on respiration and consequent pulmonary morbidity [75]. In case of a flail segment, it is recommended to fixate both fractures of the single rib. To optimize outcomes after SSRF, additional intra-operative procedures have been described such as video-assisted thoracoscopic surgery (VATS)-inspection of the thorax, evacuation of retained hemothorax, pleural irrigation, fiberoptic bronchoscopy, chest tube placement, and pain catheter placement or intercostal nerve blockade [76]. It is believed that early SSRF (≤72 hours) is associated with improved outcomes as compared to late salvage SSRF, but the exact impact of time to SSRF is uncertain.

Complications following SSRF include revision surgery (2.9%), wound infection (2.2%), intra- or post-operative bleeding (1.4%) and fracture-related infection (1.3%) [77]. Hardware failure has been reported to develop in 3-4% of patients [78, 79]. When revision surgery is performed, this is most often for implant removal because of implant irritation [77]. The exact etiology of this complication is not known, but might be associated with the implant's biomechanical properties such as stiffness or in relation to scapular movement. There are currently numerous rib fixation systems available, but (dis)similarities in their characteristics have not yet been collectively examined.

Nowadays, SSRF is recommended by several consensus guidelines for patients with a flail chest [6, 80]. However, (contra-)indications for SSRF are shifting and broadening. From 2007-2014, one nationwide study highlighted that while utilization of SSRF increased most strongly for a flail chest (6% to 17% vs. 4% to 5% for a non-flail fracture pattern), 97% of SSRF was performed in patients with a non-flail fracture pattern [71]. Other assessed indications for SSRF have been three or more severely (bicortically) displaced rib fractures, ≥30% hemithorax volume loss, and failure of nonoperative medical management [75, 81]. Specific traditional relative contra-indications such as age and TBI require further analysis as SSRF becomes a more widespread procedure with associated improved outcomes [6]. While the use of the SSRF procedure and

literature on this treatment modality is increasing, the evolution of a SSRF program over time and effect on patient selection and outcomes has not been studied.

Studies on patients with a non-flail fracture pattern remain limited. Most studies combine patients with a flail chest and non-flail fracture pattern when evaluating outcomes after SSRF, but it is debated whether these might require individual assessment because of the differences in injury characteristics [82]. To our knowledge, only one high-quality prospective controlled trial has evaluated SSRF versus nonoperative management in the patient with a non-flail fracture pattern, in which SSRF was associated with less pleural space complications and improved pain control at 2 week follow-up [83]. A prospective randomized controlled trial with longer follow-up is still missing.

The effect of SSRF over nonoperative management on long-term outcomes is less clear. Pulmonary function and quality of life have been shown to recover to values considered normal at two years after SSRF [42, 84]. Comparative studies are rare however and have not indicated a benefit of SSRF over nonoperative management in the first two years, while an effect after this time has not been studied to our knowledge [42, 85].

GENERAL AIM

The aim of this thesis is to provide insight into the epidemiology, management, and outcomes of patients with one or more rib fractures. It aims to determine the incidence and socio-economic burden of this injury on a national scale, but also outcomes in individual patients in the acute setting and long-term. It includes trauma patients as a whole, but also assesses outcomes in specific patient subgroups. This thesis intends to present outcomes after SSRF and compare these with nonoperative management, through analyzing current literature as well as single and multicenter, retrospective and prospective, clinical, and biomechanical research.

THESIS OUTLINE

Chapter 1 introduces rib fractures and several associated topics.
Part I focuses on the epidemiology and socio-economic impact of rib fractures. **Chapter 2** examines the population-based trends in the incidence rate of rib fractures in the Netherlands over a four year period (2015-2018). This includes admitted and non-admitted patients with a single or multiple (≥2) rib fractures. Furthermore, it gives a detailed overview of the health care consumption and duration of work absence with associated costs after sustaining rib fractures.
Part II centers around the prevalence and impact of rib fractures in specific subgroups of patients and in the acute and long-term setting. Rib fractures are common in the elderly (≥65 years), both in men and women. **Chapter 3** determines the rib fracture rate after blunt thoracic trauma in patients aged 50 years and older with normal versus diminished BMD (*i.e.,* osteopenia or osteoporosis). It also assesses injury and rib fracture characteristics.

As stated, there is little data on CPR-related chest wall injury characteristics and the effect of these injuries on in-hospital outcomes remains unknown. **Chapter 4** evaluates the prevalence of chest wall injuries following CPR for out-of-hospital cardiac arrest in patients admitted to the ICU. Furthermore, it compares in-hospital outcomes in patients with versus without chest wall injuries and aims to identify a possible subgroup of patients who might benefit from SSRF.

Literature on rib fractures is increasing rapidly but the larger part of these studies focus on in-hospital outcomes. **Chapter 5** assesses combined long-term outcomes pulmonary function, thoracic pain, and quality of life in patients with one or more rib fractures through a single prospective follow-up visit. Also, it determines the effect of chest wall injury severity and treatment modality on these outcomes.

Part III sets out to evaluate aspects of and outcomes after SSRF in patients with multiple rib fractures. Comparative studies on patients with a non-flail fracture pattern are scarce and almost all combine both patients with and without a flail chest. **Chapter 6** analyses current literature on rib fracture treatment. This systematic review and meta-analysis evaluates the effect of operative versus nonoperative treatment in patients with a non-flail fracture pattern on clinical outcomes such as pneumonia, mortality, wound infection, and ICU and hospital length of stay. Due to the low number and quality of the available literature on this topic, high-quality research is needed.

Chapter 7 presents the study protocol of the first multicenter randomized controlled trial with a one-year follow-up period which investigates the effect of SSRF versus nonoperative treatment in patients with multiple rib fractures without a flail fracture pattern. This includes in-hospital outcomes as well as pulmonary function, thoracic pain, quality of life, and cost-effectiveness.

Little is known on how a SSRF program evolves over time. **Chapter 8** hypothesizes that with increasing years of SSRF performance, patient selection changes, time to SSRF and operative time decrease, and in-hospital outcomes improve. This is studied in a level I trauma center where the SSRF program began in 2010.

Two aspects of SSRF which remain matters of debate, are the optimal timing to perform SSRF and contra-indications to SSRF. **Chapter 9** presents and discusses current literature on the optimal timing to perform SSRF after trauma. **Chapter 10** focuses on one historically considered relative contra-indication to SSRF, traumatic brain injury (TBI). It compares the effect of SSRF and nonoperative treatment in patients with multiple rib fractures and moderate to severe TBI (Glasgow Coma Scale [GCS] score ≤12). This includes in-hospital outcomes such as the number of ventilator-free days, ICU and hospital length of stay, complication and mortality rate, as well as neurological recovery (motor GCS recovery to 6). Since studies on the effect of SSRF in the patient with a non-flail fracture pattern are scarce, a post-hoc subgroup analysis of the population with TBI (**Chapter 10**) was performed in **Chapter 11**, stratified by having sustained a non-flail fracture pattern or flail chest.

Contemporary data on the effect of SSRF in the patient with rib fractures following CPR is limited to small case series without control group. Following **Chapter 4** which aimed to identify patients who might benefit from SSRF after CPR, **Chapter 12** compared SSRF and nonoperative management in the post-CPR population with rib fractures. This international, retrospective, matched case-control study evaluated in-hospital outcomes such as the number of ventilator-free days, ICU LOS, HLOS, and complication and mortality rate.

With the increase in SSRF utilization, there has also been a concurrent increase in available systems for rib fixation. **Chapter 13** is an anatomic and biomechanical study

which collectively evaluates the stiffness, load to and mode of failure in intact and fractured ribs fixated with the available implants and compares these with intact, non-fixated ribs.

Chapter 14 provides a general discussion and future perspectives. **Chapter 15** summarizes the main findings of the included works.

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PART I

EPIDEMIOLOGY

CHAPTER 2

Trends in incidence rate, health care use,
and costs due to rib fractures in the Netherlands

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ABSTRACT

Background
This study aimed to examine population-based trends in the incidence rate, health care consumption, and work absence with associated costs in patients with rib fractures.

Methods
A retrospective nationwide epidemiologic study was performed with data from patients with one or more rib fractures presented or admitted to a hospital in the Netherlands between January 1, 2015 and December 31, 2018 and have been registered in the Dutch Injury Surveillance System (DISS) or the Hospital Discharge Registry (HDR). Incidence rates were calculated using data from Statistics Netherlands. The associated direct health care costs, costs for lost productivity, and years lived with disability (YLD) were calculated using data from a questionnaire.

Results
In the 4-year study period, a total of 32,124 patients were registered of which 19,885 (61.9%) required hospitalization with a mean duration of 7.7 days. The incidence rate for the total cohort was 47.1 per 100,000 person years and increased with age. The mean associated direct health care costs were €6785 per patient and showed a sharp increase after the age of 75 years. The mean duration of work absence was 44.2 days with associated mean indirect costs for lost productivity of €22,886 per patient. The mean YLD was 0.35 years and decreased with age.

Conclusion
Rib fractures are common and associated with lengthy HLOS and work absenteeism as well as high direct and indirect costs which appear to be similar between patients with one or multiple rib fractures and mostly affected by admitted patients and age.

INTRODUCTION

Thoracic wall injury after blunt chest trauma is common and rib fractures are diagnosed in 10% of patients after trauma and 30% of patients after blunt thoracic trauma [1-3]. In younger patients, most rib fractures are caused by a high-energy trauma (HET), whereas more than half of the patients aged 65 years or older sustain rib fractures following low-energy trauma (LET) [4, 5]. Rib fractures can occur as single or multiple simple rib fractures or as a flail segment in which three or more rib fractures are fractured in two or more places [6]. Patient and injury characteristics influence the outcome after rib fractures. Increased age, increased number of rib fractures, and presence of concomitant thoracic injuries are associated with poorer outcome including higher pneumonia risk, increased hospital and Intensive Care Unit length of stay (HLOS and ICLOS, respectively), and increased mortality [5, 7-12]. While negatively affecting in-hospital outcome, rib fractures are also associated with long-term disability, chronic pain, and reduction of quality of life [13-16]. At 2 years post-injury, almost one-third of patients has not yet returned to their pre-injury work level [17]. While the prevalence of rib fractures is known, the incidence rate of rib fractures has only been studied in hospitalized patients or the elderly [18-20]. Although the disabling effect of rib fractures on short- and long-term outcomes is indisputable, the economic effect on health care use, work absence, and associated detailed evaluations of direct and indirect costs has hardly been studied. Insight into the occurrence and economic impact of rib fractures can both assist in daily allocation of health care services and provide a projection for the future.

Therefore, the aim of this nationwide study was to examine population-based trends in the incidence rate of rib fractures for a 4-year period (2015-2018) and to give a detailed overview of the health care consumption and work absence with associated costs in these patients.

METHODS

Data sources

For this retrospective nationwide epidemiologic study, data from all patients with rib fractures, delineated on chest computed tomography (CT) scan or radiograph, presented to a Dutch hospital between January 1, 2015 and December 31, 2018 were collected. Data were obtained from two different databases: the Dutch Injury Surveillance System (DISS) and the Hospital Discharge Registry (HDR) [21, 22]. "Veiligheid NL" collects this information directly from the Emergency Department (ED) of 14 Dutch hospitals, representing 12% of all injury-related ED visits in the Netherlands. These hospitals are

a combination of level 1-3 Trauma Centers, both academic and regional, and geographically distributed across the country with a population that is representative of the Dutch population regarding age and gender. To generate national estimates of injury-related ED visits in the Netherlands, an extrapolation factor was calculated in which the injury-related ED visits registered in the participating hospitals is multiplied by the ratio of nationwide ED visits and DISS ED visits [23]. The DISS database also contains data about health care costs, costs for lost productivity, and quality of life. In the DISS database, the distinction is made between non-admitted patients and admitted patients. Admitted patients are patients who presented to an ED and were immediately admitted to the hospital. Non-admitted patients did not require hospital admission. As all hospitals in the Netherlands are obliged to register data of admitted patients, the data of the HDR have national coverage. The HDR registers all diagnoses, medical procedures, and length of stay in admitted patients. Since the DISS database does not contain patients who are admitted through referral from the outpatient clinic or another hospital and the HDR counts patients who have been admitted more than once (e.g., for removal of surgical implants) as a new patient for every single admission, a correction factor has been used.

The DISS database and HDR do not distinguish patients with rib fractures as primary diagnosis or secondary diagnosis. For each outcome measure, the differences in severity of chest wall injury (one or multiple rib fractures, or a flail chest (for HLOS, extracted from the HDR)) and in admitted and non-admitted patients were analyzed. The effect over time was evaluated. Also, the average of the 4 years was determined for each outcome measure. The study was exempted by the local Medical Research Ethics Committee (No. MEC-2020-0179).

Incidence rate

The primary outcome measure was the age- and gender standardized incidence rate of rib fractures provided by the DISS database. To calculate incidence rates, the study population was divided into age groups (0-24 years, 25-34 years, 35-44 years, etc.) using "direct standardization" as described before [24]. Because a low number of registered patients were younger than 25 years, patients aged 0-24 years were merged into one group. The age-specific incidence rates per 100,000 person years in patients with one or multiple rib fractures were calculated based upon the Dutch mid-year standard population. Mid-year population sizes for all age groups were obtained from Statistics Netherlands [25].

Hospital length of stay

Data on HLOS were obtained from the HDR database which include the number of patients and the mean hospital length of stay including standard deviation. Mean and

cumulative HLOS were calculated for 10-year age groups in patients with either one or multiple rib fractures. To calculate the cumulative HLOS, the number of patients was multiplied with the mean HLOS per patient per age group.

Costs for health care use

A random sample of patients registered in the DISS database received a follow-up questionnaire on used health care, quality of life (EuroQoL-5D, EQ-5D), and work absence during the first 24 months after trauma [26, 27].

Estimated direct costs due to health care use included the HLOS, ambulance care, general practitioner (GP) visits, in-hospital care, home care, rehabilitation and nursing home care, and physical therapy. Mean and cumulative health care costs were calculated for different age groups, analogous to incidence rate, in patients with either one or multiple rib fractures. Cumulative costs were calculated by multiplying the number of patients by the average medical costs per patient.

Costs for lost productivity

Costs for lost productivity were divided in duration of work absence and work absence costs. These outcome measures were calculated with the results of the same question-naire mentioned above which also contained questions on work absenteeism. Work absence costs were defined as costs associated with production loss and replacement due to illness, disability, and premature death. A model to calculate costs due to lost productivity has been developed by VeiligheidNL ("The Dutch Burden of Injury model") [28, 29]. The model consists of three sub-models: the care model, the absenteeism model, and the performance model. Costs were determined as described previously [30]. The number of patients unable to work after their accident and the duration of work absence were extracted by VeiligheidNL. In this study, the friction cost method was used, which estimates the indirect costs due to productivity loss [31]. For this outcome measure, calculations were made with data from patients aged 15 to 60+ years, in 5 year age groups of patients with one or multiple rib fractures. Cumulative duration of work absence and costs for lost productivity for different age groups were calculated by multiplying the number of patients with the mean duration of work absence per patient per age group.

Years lived with disability (YLD)

The EQ-5D data of the questionnaire were used for calculating the number of YLD per patient. Mean and cumulative YLD were calculated for different age groups (the same as mentioned for incidence rate) in patients with either one or multiple rib fractures. To calculate the cumulative YLD, the number of patients was multiplied with the mean YLD per patient per age group.

RESULTS

Incidence rate

During the 4-year study period, a total of 32,124 patients were registered after sustaining one or multiple traumatic rib fractures of which 19,885 (61.9%) patients required hospitalization. In total, 18,887 (58.8%) patients sustained multiple rib fractures. In the elderly (≥65 years or older), 72.5% of patients with multiple rib fractures required hospitalization. The total number of patients registered with rib fractures over this time period increased with 37.4% (Figures 1a-c). The incidence rate for the total cohort was 47.1 per 100,000 person years (19.4 in patients with one rib fracture and 27.7 in patients with multiple rib fractures). The incidence rate of all admitted patients with rib fractures was 29.2 per 100,000 person years. In patients aged ≥65 years, the incidence rate was 107.4 per 100,000 person years (40.3 in patients with one rib fracture and 67.1 in patients with multiple rib fractures). The incidence rate of admitted patients aged ≥65 years with
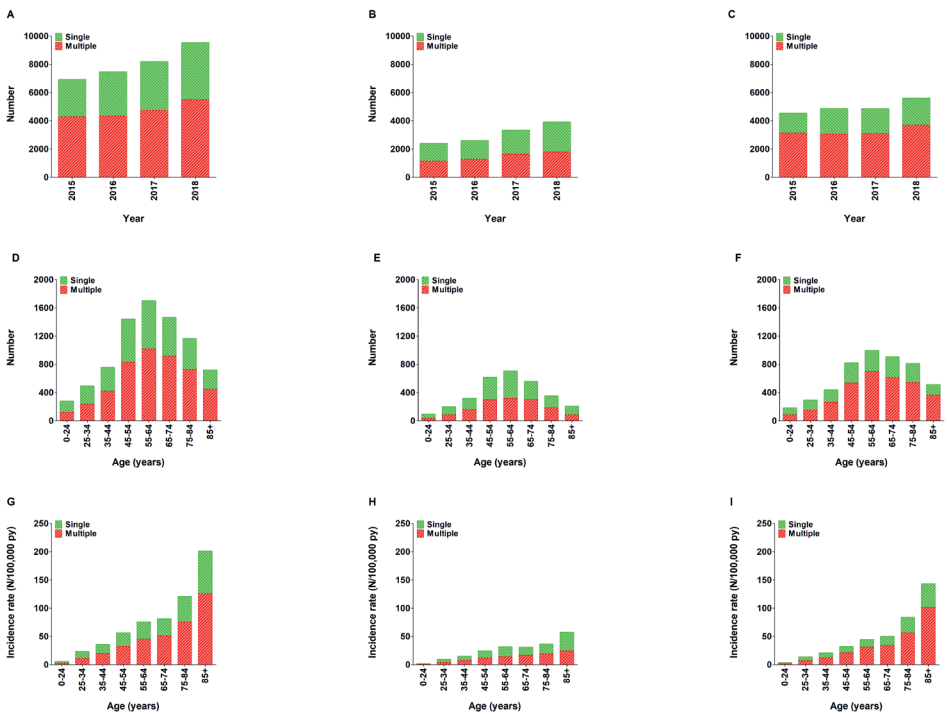
FIGURE 1
Number of patients with one or multiple (≥2) rib fractures per year (a-c), number of patients per age group (d-f), and incidence rate per age group (g-i).
Data are presented for the total population (a, d, and g), as well as for non-admitted (b, e, and h) and admitted (c, f, and i) patients.
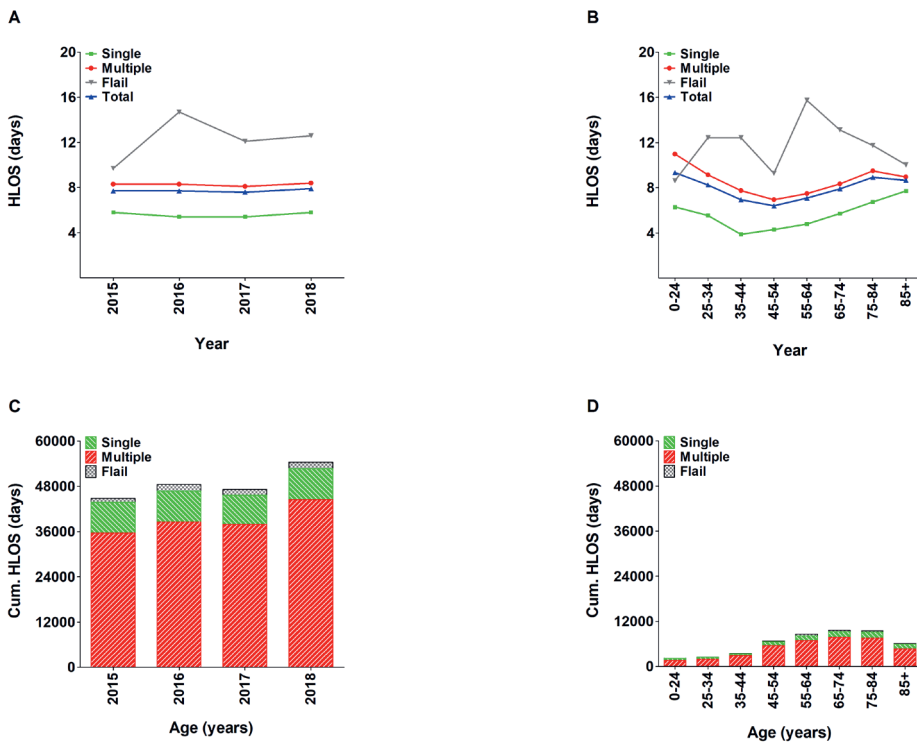
FIGURE 2
Mean HLOS in patients with one or multiple (≥2) rib fractures, or a flail chest per year (a), per age group (b), and cumulative HLOS per year (c), and per age group (d).

rib fractures was 71.5 per 100,000 person years. Both the total number of patients as well as the incidence rate increased strongly with age in the admitted patients and remained relatively similar in the non-admitted patients (Figures 1d-i).

HLOS

Annually, the cumulative HLOS of patients with rib fractures comprised 48,737 days. Patients with multiple rib fractures or a flail chest accounted for 83.4% of the yearly cumulative HLOS (39,117 days). Patients aged ≥65 years accounted for 51.8% of the average cumulative HLOS (25,256 days) in the study period. The mean HLOS per patient with rib fractures was 7.7 days: 5.6 days for patients with one rib fracture, 8.3 days for patients with multiple rib fractures, and 12.3 days for patients with a flail chest (Figure 2a). For patients with one or multiple rib fractures, the mean HLOS decreased up to the age of 45 (3.9 days) and 55 (6.9 days), respectively, after which it increased (Figure 2b). The age-specific distribution of the cumulative HLOS showed an increase after the age of 45 years (Figures 2c-d).

Costs for health care use

Nationwide, the cumulative direct health care costs for patients with rib fractures were €54.5 million per year. Admitted patients accounted for 90.5% of the cumulative direct health care costs (€49.3 million). The cumulative direct health care costs were €19.2 million for patients with one rib fracture and €35.3 million for patients with multiple rib fractures. Patients aged ≥65 years accounted for 59.5% (€32.4 million) of the cumulative direct health care costs.

The mean direct health care costs for a patient with rib fractures were €6,785 and were similar for patients with one or multiple rib fractures (Figures 3a-c). The mean costs for an admitted patient with one rib fracture were €9557 and €10,115 for a patient with multiple rib fractures (Table 1). Both admitted and non-admitted patients showed an increase of costs after the age of 75 years (ranging from €4220 to €5850 up to the age of 74 years and €13,390 for patients aged 75 years and older; Figures 3d-f). The age-dependent distribution of cumulative direct health care costs showed a sharp
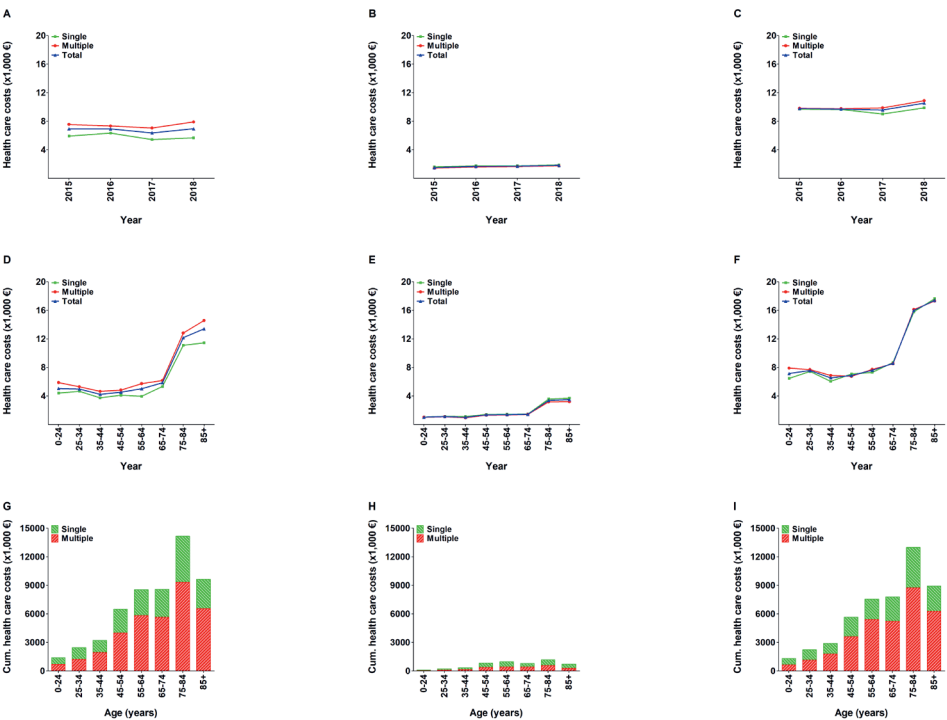
FIGURE 3

Mean direct health care costs of patients with one or multiple (≥2) rib fractures per year (a-c), per age group (d-f), and cumulative direct health costs per age group (g-i).

Data are presented for the total population (a, d, and g), as well as for non-admitted (b, e, and h) and admitted (c, f, and i) patients.

increase after the age of 45 years with the larger part of costs in admitted patients (Figures 3g-i). Admitted patients older than 45 years patients covered 90.0% of the cumulative costs (€42.9 million).

Duration of work absence and costs for lost productivity

In total, patients with rib fractures accounted for an annual cumulative duration of work absenteeism of 140,638 days. The mean duration of work absence per patient with rib fractures was 44.2 days (65.1 days for admitted patients and 8.1 days for non-admitted patients). The mean duration of work absence in patients with multiple rib fractures was 64.9 days for admitted patients and 7.8 days for non-admitted patients. The mean duration of work absence was stable over the years and appeared un-related to number of rib fractures but related to hospital admission (Figures 4a-c). In the age-specific distribution, the duration of work absence increased in the admitted patients aged 20-30 years, with patients aged 25-30 having the longest mean duration of work absence (74.7 days). After that age and in the age-specific distribution in non-admitted patients, the duration of work absence was relatively similar (Figures 4d-f).

TABLE 1
Direct medical costs and indirect costs for lost productivity by type of rib fracture (2015-2018).

	Total			One rib fracture			Multiple (≥2) rib fractures		
	N	Mean (€)	Cumulative (million €)	N	Mean (€)	Cumulative (million €)	N	Mean (€)	Cumulative (million €)
Health care costs (€)									
Admitted	4971	9922	49.3	1719	9557	16.4	3252	10,115	32.9
Non-admitted	3060	1689	51.7	1590	1755	2.8	1470	1619	2.4
Total	8031	6785	54.5	3309	5808	19.2	4722	7471	35.3
Costs for lost productivity (€)									
Admitted	2015	22,886	46.1	751	22,303	16.7	1265	23,233	29.4
Non-admitted	1168	2880	33.6	627	2956	1.9	541	2793	1.5
Total	3183	15,547	49.5	1378	13,496	18.6	1805	17,112	30.9
Combined direct and indirect costs (€)									
Admitted	6986	32,808	95.4	2470	31,860	33.1	4517	33,348	62.3
Non-admitted	4228	4569	85.3	2217	4711	4.7	2011	4412	3.9
Total	11,214	37,377	180.7	4687	36,571	37.8	6528	37,760	66.2

N, number of patients.
Direct and indirect costs are presented as the mean costs per patient and the cumulative costs of the entire study period, 2015-2018.

In total, 93.3% of the cumulative duration of work absenteeism was attributable to admitted patients (131,184 days) and 61.4% to patients with multiple rib fractures (86,307 days; Figures 4g-i).

Annually, the cumulative costs for lost productivity were €49.5 million and the highest in patients aged 55-60 years (€10.5 million). The mean costs for lost productivity were €15,547 per patient (Table 1, Figures 5a-c). The mean costs for lost productivity per patient increased with age for admitted patients and were highest in patients aged 55-60 years (€17,570). In both admitted and non-admitted patients, costs for lost productivity were similar for patients with one or multiple rib fractures (Figures 5d-i). Admitted patients accounted for 93.2% of the cumulative costs and the costs increased with age (€46.1 million; Figures 5g-i).
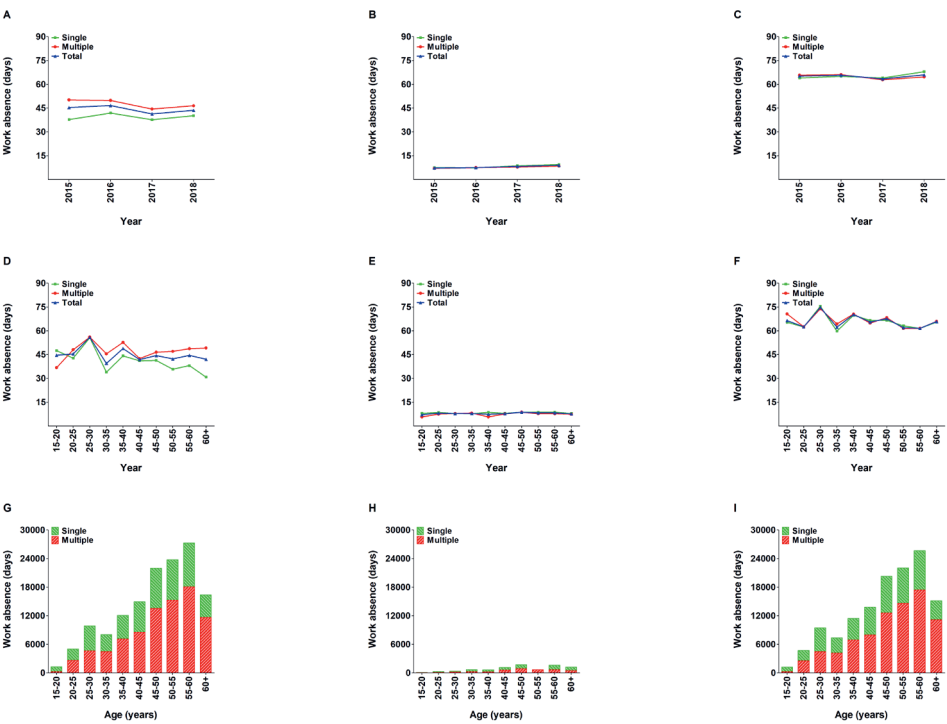
FIGURE 4
Mean duration of work absence in patients with one or multiple (≥2) rib fractures per year (a-c), per age group (d-f), and cumulative duration of work absence per age group (g-i).
Data are presented for the total population (a, d, and g), as well as for non-admitted (b, e, and h) and admitted (c, f, and i) patients.

Years lived with disability

The average cumulative YLD for patients with rib fractures were 2792 years per year with a mean YLD per patient of 0.35 years. The mean YLD per patient was 0.5 years in admitted patients and 0.1 years in non-admitted patients (Figures 6a-c). In the age-specific distribution, the YLD decreased with age (highest in patients aged 0 to 24, 0.85 years) and was most pronounced in admitted patients (Figure 6d-f). The average YLD for the working population age groups was 0.39 years and 0.25 years for patients aged ≥65 years. Patients in the working population age groups (25-64 years) had a cumulative YLD of 1713 years which was 61.4% of the total YLD (Figure 6g-i).
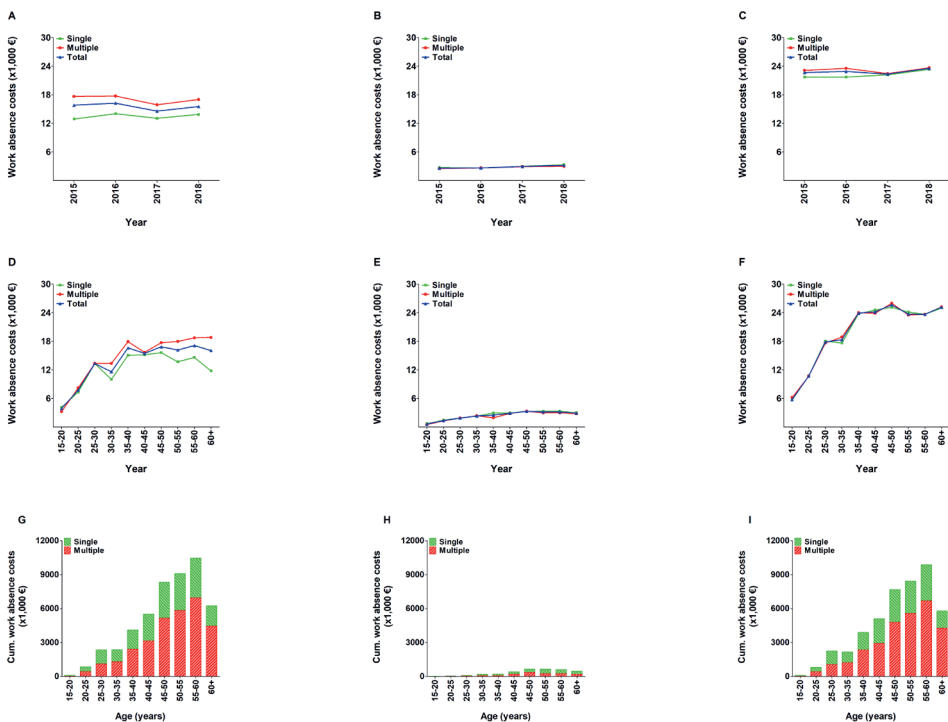
FIGURE 5
Mean indirect costs for lost productivity in patients with one or multiple (≥2) rib fractures per year (a-c), per age group (d-f), and cumulative costs for lost productivity per age group (g-i).
Data are presented for the total population (a, d, and g), as well as for non-admitted (b, e, and h) and admitted (c, f, and i) patients.
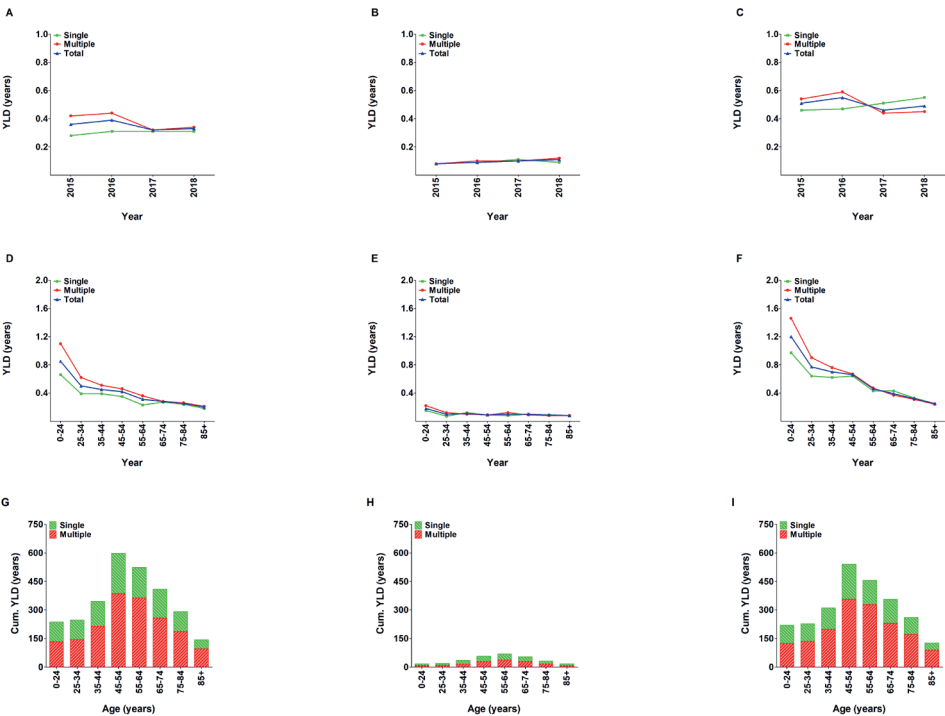
FIGURE 6
Mean years lived with disability (YLD) in patients with one or multiple (≥2) rib fractures per year (a-c), per age group (d-f), and cumulative YLD per age group (g-i).
Data are presented for the total population (a, d, and g), as well as for non-admitted (b, e, and h) and admitted (c, f, and i) patients.

DISCUSSION

This epidemiologic nationwide study is the first to describe health care use and costs in admitted and non-admitted patients with rib fractures. Patients registered with rib fractures were more prevalent over time and the incidence rate increased with age. Almost two-thirds of patients with rib fractures required hospital admission with a mean stay of about 8 days with associated significant direct and indirect costs, and over 2 months of work absenteeism. The direct and indirect costs, duration of work absence, and years lived with disability remained stable during the study period and appeared unrelated to having sustained one or multiple (≥2) rib fractures but increased considerably with age and in admitted patients compared with non-admitted patients.

The incidence rate of 29 per 100,000 person years for admitted patients is similar to the incidence rate demonstrated by a recent study focusing only on admitted patients [18]. The incidence rate for the total cohort of 47 per 100,000 person years showed

that rib fractures are common and not all patients require admission. To put things in perspective, the total incidence rate of patients with a humeral fracture is 40 per 100,000 person years [32]. The incidence rate increased sharply with age, from 34 to 107 per 100,000 person years in patients aged ≤65 years and ≥65 years, respectively. The incidence rate of 72 per 100,000 person years for admitted elderly patients is again in line with previous literature [18, 20]. Furthermore, the increase of 37% of the total number of patients with rib fractures between 2015 and 2018 demonstrates that rib fractures are a common and increasing problem, especially among the elderly [33]. Age is a known risk factor for mortality in patients with rib fractures [5, 9, 10, 12]. This highlights the need for improvement of preventive measures and a possibly more aggressive multimodal therapy in this type of patient.

While the cumulative HLOS of 48,737 days is not as high as for e.g. patients with foot and ankle injuries (58,708 days), the mean HLOS of almost 8 days is higher than for patients with a humeral or tibia shaft fracture in the Netherlands [24, 32, 34]. The mean HLOS increased with severity of the injury (single or multiple rib fractures, or a flail chest), but without data on concomitant injuries, need for additional interventions (e.g., chest tube, surgical stabilization of rib fractures (SSRF), or video-assisted thoraco-scopic surgery (VATS), or complications such as pneumonia, the true impact on the HLOS attributable to sustaining rib fractures, is not known. Nonetheless, it has been shown that almost half of the patients with rib fractures are polytraumatized (i.e., ISS>15) patients and require Intensive Care Unit admission, demonstrating that rib fractures are a marker of severe injury [35].

The annual cumulative direct health costs were €54.5 million of which 90% was accounted for by admitted patients. Similar age-dependent mean HLOS for patients with one or multiple rib fractures suggests that the high direct health care costs might mostly be accounted for by out of hospital care. The age-dependent distribution of direct health costs showed a sharp increase after the age of 45 years. Thus, efforts to improve the preventive measures and both in and out of hospital care should not only focus on the elderly but possibly on patients as young as 45 years [11]. Again, as there was no insight into treatment parameters such as need for medicinal, radiologic, or operative interventions, the exact impact of rib fracture injuries on health care costs could not be distilled.

With a mean duration of work absence of 44 days and cumulative indirect costs for lost productivity of €49.5 million, rib fractures pose a serious societal health burden. While many possible confounding variables are not known for this outcome, these results are reinforced by previous studies indicating long-term disability and long work absenteeism after rib fractures [15-17, 36]. The mean direct health care costs for a patient with rib fractures were €6785 which is higher than that of patients with ankle or foot injuries (€3461), but lower than for patients with a humeral fracture or a hip

fracture (€8864 and €10,458, respectively) [32, 34, 37]. Comparing these mean costs per patient with previous literature is difficult as most studies have focused solely on in-hospital costs of patients with a flail chest, injury severity score (ISS) of ≥16 and compared operatively and nonoperatively treated patients [22, 38-40]. With no information in this study on the received treatment modality, ISS, ICU admission, or costs in patients with flail chest, paralleling these results is not feasible. To our knowledge, the duration of work absenteeism and consequent costs for lost productivity in patients with rib fractures have not been studied before. However, rates of 33% to 42% of patients have been reported to be unable to work at their pre-injury capacity at three and even 12 months post-injury, respectively [41, 42]. These associated high costs with lengthy HLOS and work absenteeism, which increase with age, might consequently indicate the need for a different approach to the patient with rib fractures. Currently, most patients with rib fractures are treated nonoperatively, and SSRF is intended for the younger patient with a high ISS [42, 43]. Based on the age-dependent increase in HLOS and costs in admitted patients, the benefit of restoring the chest wall biomechanics through SSRF might actually be higher in the older population in which some physiological decompensation is present [44].

While this epidemiologic study is the first to evaluate health care use and costs in patients with rib fractures in the Netherlands, interpretation of the results should be done in the light of several limitations. First, miscoding and incomplete data are inherent to using nationwide or large registries such as the DISS and HDR. As rib fractures are often accompanied by other severe injuries, rib fractures might not have been registered, resulting in an underestimation of the incidence rate of rib fractures. Currently, different national registries are used for registration of trauma data and consequent research. The DISS database only records data from Dutch emergency departments, the HDR and the Dutch National Trauma Registry from admitted patients. The different registries provide complementary useful data, but currently cannot be linked. Thus, to provide adequate and complete data on for example the incidence rate, health care use, and costs, one national registry which includes complete short- and long-term data on both admitted and non-admitted patients is urgently needed.

Second, patients from the DISS were registered as having sustained one or multiple rib fractures where multiple was defined as 2 or more rib fractures. In current literature, multiple rib fractures are defined as having three or more rib fractures, regardless of side or adjacency [42, 45, 46]. Only for the HLOS, which was covered by the HDR, a third subgroup, patients with a flail chest, was available. This discrepancy in defining subgroups of patients with rib fractures hinders generalizability and providing practicable conclusions. In addition, rib fractures were diagnosed by either chest CT or radiograph, or both. The use of chest CT is more sensitive in the delineation of rib fractures as it finds two to three additional rib fractures compared with radiograph [47, 48]. Therefore, patients who were registered as having sustained one rib fracture, diagnosed through

chest radiograph, might have been registered as a patient with multiple rib fractures if a chest CT had been made. In this light, this might have introduced selection bias in diagnosing a patient with or without rib fractures, but also in the number of rib fractures. The diagnosis of these additional rib fractures on chest CT might result in increased admission rates and subsequently increased total health care costs, but the effect of the diagnostic modality on in-hospital outcome such as complication rate and mortality remains unclear [47, 49, 50]. This limitation does, however, reflect daily practice as a large number of hospitals and EDs still use chest radiograph as the primary diagnostic modality in patients with rib fractures.

Third, the distinction between patients with rib fractures as primary diagnosis or secondary diagnosis was not possible with the available data. Thus, patients were admitted with rib fractures and not because of rib fractures. This distinction in rib fracture as primary or secondary diagnosis could have helped in providing insight in the individual impact of rib fractures on the outcome measures. Another covariate which was not available, was treatment modality. Outcomes such as costs for health care, lost productivity, and YLD might be influenced by whether a patient underwent SSRF or nonoperative treatment. To date, studies have shown significant in-hospital differences in health care costs between treatment modalities in patients with rib fractures, but data on the effect of treatment modality on outcomes such as lost productivity or YLD remains limited [22, 39, 40]. Also, comorbidity, concomitant injury characteristics, trauma mechanism, the ISS, and abbreviated injury scale scores were not known for these patients. Therefore, the outcome measures could not be corrected for possible confounding variables. This might explain the relatively similar direct and indirect costs as well as years lived with disability in patients with either one or multiple rib fractures with admitted patients contributing most to these outcomes. While this stresses the need for improved nationwide registries, these results show that sustaining even a single rib fracture is a marker of severe injury as it might be accompanied by a long duration of health care use, work absence, and high costs.

In conclusion, this epidemiologic study shows that the number of patients registered with rib fractures has been increasing over time and the incidence rate increases with age. Although it was not possible with the current available data to prove causality between outcomes and rib fractures specifically, it does demonstrate that sustaining rib fractures indicates severe injury and may be associated with lengthy HLOS and work absenteeism as well as high direct and indirect costs. The duration of work absence and associated costs increase with age and are considerably higher in admitted patients than in non-admitted patients. The outcomes appear to be similar in patients with one or multiple rib fractures. However, due to the non-standard definitions of rib fractures, the lack of additional individual patient data, and impossibility to combine data of the different national registries, the generalizability and results of this study should be interpreted with caution.

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PART II

OUTCOMES

CHAPTER 3

Rib fractures after blunt thoracic trauma in patients with normal versus diminished bone mineral density: a retrospective cohort study

Jonne T.H. Prins, Esther M.M. Van Lieshout, Maarten R. L. Reijnders, Michael H.J. Verhofstad, Mathieu M.E. Wijffels

ABSTRACT

Background

This study aimed to evaluate rib fracture rate as well as rib fracture characteristics after thoracic trauma in patients with normal versus diminished bone mineral density (BMD).

Methods

A retrospective cohort study of persons aged 50 years or older presenting to the Emergency Department after sustaining blunt thoracic trauma between July 1, 2014 and December 31, 2017, was performed. Patient and trauma characteristics and DXA scan results were collected. Rib fracture rate and characteristics were evaluated on a radiograph and/or CT scan of the thorax.

Results

In total, 119 patients were included for analysis. Fifty-eight of them (49%) had a diminished BMD. In the remaining 61, the BMD was normal. The diminished BMD group experienced rib fractures more often than the normal BMD group (n = 43 (74%) versus n = 31 (51%); p = 0.014). Patients with diminished BMD suffered low-energy trauma more frequently than the normal BMD group (21 (36%) versus 11 patients (15%), respectively (p = 0.011)). Rib fracture characteristics such as the median number of rib fractures, concomitant intrathoracic injury rate, and rib fracture type distribution were not different between the groups.

Conclusion

The rate of rib fractures after blunt thoracic trauma was significantly higher in patients with diminished BMD than in patients with a normal BMD. Differences in number and location of rib fractures between groups could not be proven. When assessing patients aged 50 years or older presenting to the hospital after substantial blunt thoracic trauma, the presence of diminished BMD should be taken into account and the presence of rib fractures should be investigated with appropriate diagnostic procedures. Diminished bone mineral density (i.e., osteopenia or osteoporosis) is associated with increased fracture risk. This study evaluated if diminished BMD increases the rib fracture risk. Patients with diminished BMD have a higher risk of sustaining rib fractures after blunt thoracic trauma, which implicates a lower threshold for CT imaging of the chest.

INTRODUCTION

Rib fractures account for approximately 10% of all trauma admissions and are seen in up to 39% of patients sustaining blunt thoracic trauma [1-4]. Young patients often suffer rib fractures after high-energy trauma (HET) such as a motor vehicle collision (MVC) or a fall from height [5]. In elderly patients aged 65 years or older, over 50% have sustained rib fractures following low-energy trauma (LET) such as a fall from standing height [6, 7]. The number of rib fractures, pre-existent pulmonary pathology, and age are known risk factors for rib fracture associated mortality and morbidity [2-4, 7-13]. Rib fractures are the most common fractures in men and second most common in women over 65 years [14-16]. The mortality of rib fracture patients over 65 years is two- to fivefold higher than younger patient with similar injuries; therefore, this is a vulnerable patient group [7, 11].

Besides age, diminished bone mineral density (BMD) has been shown to increase fracture risk [17-20]. Osteoporosis, defined by the World Health Organization (WHO) as a BMD T-score of - 2.5 and lower, is a common and increasing disease resulting in a higher risk of spine, hip, and wrist fractures [21, 22]. In Europe, 27.5 million people suffer from osteoporosis and 3.5 million new fragility fractures are sustained annually [23].

Diminished BMD also increases the risk of rib fractures after blunt thoracic trauma [15, 24, 25]. In addition, a history of one or more rib fractures doubles the risk of any subsequent fracture, suggesting this to be a consequence of a diminished BMD [14, 15, 26, 27]. Concomitant injury after rib fractures is common [4, 6, 12, 28]. Thus, an increased probability of serious injury might be considered in patients aged 50 or older, even when rib fractures are sustained after low-energy trauma. The primary aim of this study was to determine the rate of rib fractures in patients with normal versus diminished BMD (i.e., osteopenia or osteoporosis) after blunt thoracic trauma. Secondary aims were to determine the number of fractures, the occurrence of concomitant intrathoracic injuries, and the rib fracture types in these patients.

METHODS

Design and participants

A retrospective observational cohort study was conducted at a Level 1 trauma center after approval by the local Medical Research Ethics Committee. All persons aged 50 years or older who attended the Emergency Department after having sustained blunt thoracic trauma in the period between July 1, 2014, and December 31, 2017, were considered eligible. Blunt thoracic trauma was defined as motor vehicle collisions, falls, vehicle versus pedestrian, acts of violence, and blast injury, excluding all penetrating

trauma such as stabbings and gunshots, as registered by the care provider at Emergency Department admission [29]. Patients were identified from the Trauma Department's osteoporosis registry. This registry includes all patients who attended the Emergency Department and were aged 50 years or older with a recently sustained fracture. These patients were invited for osteoporosis screening. The criteria for obtaining a DXA scan are an age of 50 years and older and having sustained a fracture or patients with a significantly increased fracture risk (e.g., the disorders mentioned in exclusion criterion 2, see below).

Patients with any of the following criteria were excluded: (1) time lapse of >12 months between thoracic trauma and DXA scan (as the BMD might have changed over this period of time); (2) (congenital) skeletal disorders associated with increased fracture risk (e.g., osteomalacia, Paget's disease, osteogenesis imperfecta, or malignancy [30]); (3) no results of osteoporosis screening registered in the patient's medical files or osteoporosis registry; (4) patients who were listed as having sustained thoracic trauma but no details on thoracic trauma were registered in the medical files; or (5) no radiographic image(s) of rib fractures available in the patient's electronic medical record (either thoracic CT scan or thoracic X-ray).

Data collection and outcome measures

Data were extracted from the patient's electronic medical record. The presence of at least one rib fracture as seen on X-ray or CT scan of the thorax served as the primary outcome measure. If available, the findings of the CT were used for analysis. Secondary outcome measures were:

Characteristics of rib fractures (as reported in the radiology report): number of fractured ribs (i.e., ribs 1 to 12); location of the fractured rib(s) (i.e., cranial (ribs 1-3), middle (ribs 4-10), or caudal (ribs 11-12) segment of the chest wall); location of the fracture (i.e., anterior, costochondral junction to axillary line at one-third of the rib length; axillary, from axillary line to the point perpendicular to a vertical line down from the inferior angle of the scapula; posterior, from axillary endpoint to the joint between transverse process and costal end, or overlapping between the three locations); the affected side (i.e., left, right, or both); presence of a flail chest (defined as three or more consecutive ribs fractured at two or more places [31, 32]), presence of concomitant intrathoracic injuries (i.e., pulmonary contusion, pneumothorax, hemothorax, intra-thoracic bleeding, or arterial dissection)

• Classification of every rib fracture seen on the CT scan (type A, non-displaced fracture; type B, >2mm displaced fracture; type C, complex fracture) (Figure 1) [33]. Classifications were done by a trained researcher (MRLR) and checked by a trauma surgeon (MMEW)
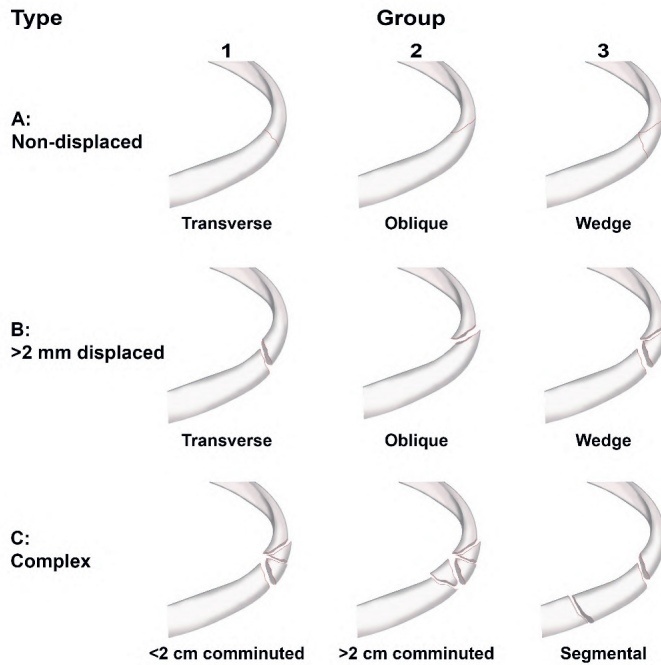
FIGURE 1
Classification of rib fractures.

In addition to the outcome measures, the following data were collected from the patient's electronic medical record: intrinsic variables (i.e., age, gender, and DXA scan result (lowest T-score of either the proximal femur or lower lumbar spine, and BMD categorization as normal, T-score > - 1.0; osteopenia, T-score of - 1.0 to - 2.5; or osteoporosis, T-score < - 2.5)) and suspected trauma mechanism defined as HET (traffic accident, pedestrian or person on bicycle hit by vehicle with a speed >10 km/h or any other accident involving vehicles with a speed >45 km/h; fall from height, fall from >2 times standing height; and other, trauma described as HET in the patient file that was not fall or traffic related) or LET (traffic accident, any traffic accident with speed lower than described for high-energy trauma; fall, fall from maximally standing height; and other, trauma described as LET in the patient file that was not a fall or traffic related, i.e., low-energy trauma or high-energy trauma).

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 24.0 (SPSS, Chicago, IL., USA). Normality of continuous variables was tested with the Shapiro-Wilk test. This showed that all continuous variables deviated from a standard

normal distribution. Statistical significance in patients with normal versus diminished BMD was tested; continuous, non-parametric data of two groups were tested using the Mann-Whitney U test. In cases of testing more than two groups, a Kruskal-Wallis one-way analysis of variance test was preformed, with post hoc pairwise comparison with the Mann-Whitney U test performed. Chi-square analysis or Fisher's exact test were used to test categorical data as applicable. A p value lower than 0.05 was considered statistically significant.

RESULTS

During the study period, a total of 488 patients were registered in the Trauma department's osteoporosis registry (Figure 2). Three hundred and fifteen patients were excluded because no DXA scan was performed and 54 patients met other exclusion criteria. A total of 119 patients remained for analysis.

First, analysis was performed comparing patients in the osteopenia group, osteo-porosis group, and normal BMD group (Table 1). Since separate groups were small and a diminished BMD might cause decreased bone strength and therefore a higher risk of sustaining fractures, results are presented as a pooled group of patients with diminished BMD (i.e., osteoporosis or osteopenia). Of the 119 patients, 61 (51%) had
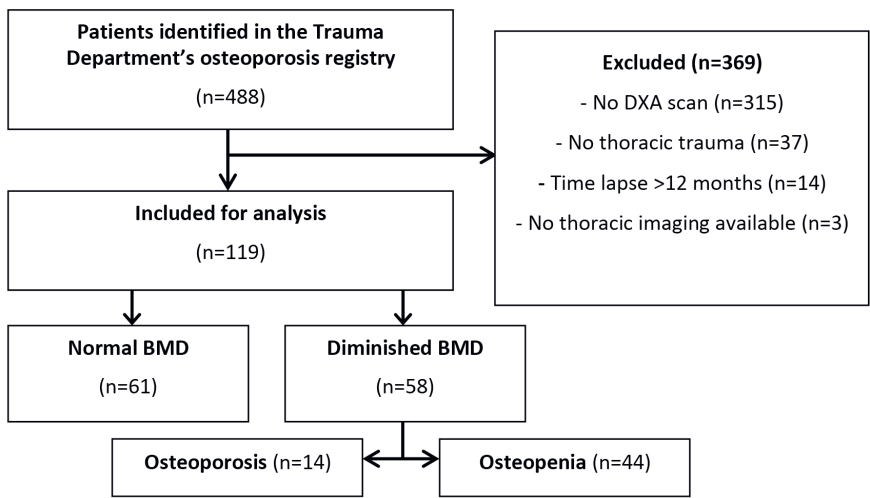
FIGURE 2
Flowchart showing inclusion of patients for analysis.

a normal BMD and 58 (49%) had a diminished BMD. Age and gender distribution did not differ between the normal and diminished BMD groups. The median age of all patients was 61 (P_{25}-P_{75}, 54-68) years and 44 (37%) were female (Table 2). In total, 74 (62%) patients sustained one or more rib fractures after thoracic trauma. The median number of fractures in the entire cohort was 3 (P_{25}-P_{75}, 0-7). The suspected mechanism of injury was low-energy trauma in 30 (25%) patients.

TABLE 1
Demographics and injury characteristics in patients with normal BMD, osteopenia, and osteoporosis.

	Overall (n = 119)	Normal BMD (n = 61)	Osteopenia (n = 44)	Osteoporosis (n = 14)	p
Rib fracture	74 (62%)	31 (51%)	31 (71%)	12 (86%)	**0.019**
Number of ribs fractured	4 (0-7)	1 (0-7)	3 (0-6)	6 (1-8)	0.196

Data are shown as N (%) or median (P_{25}-P_{75}), statistical significance was tested using chi-squared test or Kruskal-Wallis ANOVA, respectively.
Bold p-values are considered statistically significant.

TABLE 2
Demographics and injury characteristics in patients with normal BMD versus diminished BMD.

	Overall (n = 119)	Normal BMD (n = 61)	Diminished BMD (n = 58)	p
Female gender	44 (37%)	20 (33%)	24 (41%)	0.349
Age (years)	61 (54-68)	60 (54-65)	62 (55-73)	0.260
High energy trauma*	87 (74%)	50 (85%)	37 (64%)	**0.011**
Rib fracture	74 (62%)	31 (51%)	43 (74%)	**0.014**
Number of ribs fractured	3 (0-7)	1 (0-7)	3 (0-7)	0.137
Flail chest	23 (27%)	10 (26%)	13 (28%)	1.000
Proximal rib fracture	50 (68%)	22 (71%)	28 (65%)	0.625
Intrathoracic injury	42 (35%)	19 (31%)	23 (40%)	0.345
Pneumothorax	36 (30%)	16 (26%)	20 (35%)	0.425
Lung contusion	12 (10%)	7 (12%)	5 (9%)	0.763
Hemothorax	10 (8%)	3 (5%)	7 (12%)	0.197
Intrathoracic bleeding	1 (1%)	0 (0%)	1 (3%)	1.000
Arterial dissection	1 (1%)	0 (0%)	1 (3%)	1.000
Fracture type				
Type A	150 (36%)	72 (37%)	78 (35%)	0.724
Type B	121 (29%)	59 (30%)	62 (28%)	
Type C	149 (36%)	66 (34%)	83 (37%)	

Data are shown as N (%) or as median (P_{25}-P_{75}); bold p values are considered statistically significant.
*Data were missing for two patients, both in the diminished BMD group.

The diminished BMD group suffered low-energy trauma significantly more often than the normal BMD group (36% versus 15%, respectively (p = 0.011)). The diminished BMD group also suffered rib fractures more frequently, in 43 (74%) of the patients versus 31 (51%) in the normal BMD group (p = 0.014; Table 2). The median number of rib fractures in patients with at least one fracture did not differ between the groups. Ribs at the cranial segment of the chest wall (ribs 1 to 3) were not fractured more often in the diminished BMD group (Table 2). The number of patients with at least one rib fracture of the middle thoracic segment (ribs 4 to 10) was not different between groups (n = 39 (91%) patients of the diminished BMD group and n = 29 (94%) in the normal BMD group; p = 1.000). Intrathoracic injury was seen in 23 patients (40%) in the diminished BMD group and in 19 patients (31%) in the normal BMD group (p = 0.345). Patients with diminished BMD did not have more type A, B or C fractures (Table 2).

Figure 3 shows the rib fracture type distribution and fracture frequency per rib for both groups. At the end of every bar, the percentage of the displaced and complex fracture types, type B and C correspondingly, combined is given. Patients with diminished BMD did not have type B and C fractures (n = 145 (65%) of all fractures) more commonly than patients with normal BMD (n = 125 (64%); p = 0.760).

For each rib, the percentage of fractured ribs is shown relative to the total number of rib fractures in the group with normal BMD or diminished BMD, respectively. At the end of every bar, the percentage of type B and C fractures combined is given for every rib.
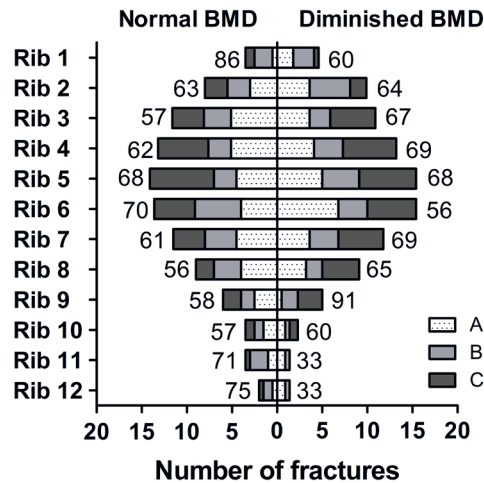
FIGURE 3
Distribution of rib fracture subtypes between the two groups.

DISCUSSION

This retrospective study showed that the rate of rib fractures was significantly higher in patients with diminished BMD after blunt thoracic trauma than in patients with a normal BMD.

The higher rib fracture frequency in the diminished BMD group appears to be in line with previous findings. Previous studies reported an almost two fold higher risk of sustaining rib fractures for every standard deviation decrease in BMD and identified diminished BMD as an independent risk factor for rib fractures after substantial thoracic trauma in elderly patients [24, 25]. Other studies reported that the risk of a future fracture of the ribs, hip, limb, wrist, or spine was at least doubled in elderly men and postmenopausal women with a rib fracture history [14, 15, 26, 27].

The overall HET rate of 74% in this cohort was high. Lowe et al. and Keller et al. reported a HET rate of around 10% of trauma admissions in elderly patients aged 65 or older [34, 35]. While these studies were also performed in a Level 1 trauma center to which the more severely injured patients are often referred, our inclusion criteria of sustaining thoracic trauma specifically and the relatively younger group of patients (aged 50 years and older) could be an explanation. As the classification of the suspected trauma mechanism is done on-site by a paramedic, the liberal use of defining trauma as high-energy trauma could be another explanation.

In addition, the overall rate of patients with rib fractures in the current cohort (62%) is high compared with that of Lafferty et al. who reported rib fractures in up to 39% of patients after blunt thoracic trauma [1]. As the level of the trauma center is not described in Lafferty's study, it remains unknown if a difference in trauma center levels may explain this difference. Also, since we excluded patients who were registered as having sustained thoracic trauma but had no recorded details of any thoracic trauma in their medical files, the remaining study population might have a higher probability of having sustained one or more rib fractures. In this study, over 60% of the included patients had CT imaging of the thorax after trauma whereas this percentage is unknown in the aforementioned study. In patients who have suffered from HET, there was a low threshold for performing a thoracic CT scan. However, the clinical situation in combination with conventional imaging is leading in this decision. Thoracic CT imaging is superior to chest radiography. Approximately 75% of all rib fractures which are seen on chest CT are missed on radiography [36, 37]. The low sensitivity is aggravated in the trauma setting because chest radiography is performed with the patient in the supine position. Moreover, other potentially severe intrathoracic injuries are much better visualized on a CT-scan than on plain radiographs. Accurate diagnosis of the number of rib fractures is relevant because it correlates to mortality [7-9]. As a result, a plain radiograph is inaccurate in identifying high-risk patients.

In a large retrospective review of the National Trauma Data Bank, Flagel et al. suggested that the rate of associated intrathoracic injuries, such as pneumothorax, significantly increased for every additional rib fracture [4]. In this cohort, the diminished BMD group sustained two additional rib fractures after thoracic trauma, but this difference and the frequency of concomitant intrathoracic injuries were not significant between these groups. While the suspected trauma mechanism was significantly more often low-energy trauma in patients with diminished BMD, rib fracture characteristics such as the occurrence of flail chest, concomitant intrathoracic injuries, and rib fracture type did not differ between groups.

While a CT scan is often performed after a HET, a lowered threshold might also be applied to patients aged 50 years and older. As the presence of diminished BMD is associated with both a high rate of rib fractures as well as concomitant intrathoracic injury, thoracic CT imaging should be considered liberally in these patients. The therapeutic consequence of CT diagnosed versus radiographically diagnosed rib fractures remains debatable and should be studied prospectively [38].

Kim et al. showed that in patients over 65 years with isolated rib fractures, only 12% were evaluated for BMD after trauma of which almost half (48%) had osteoporosis [39]. In our cohort, 35% of registered patients were evaluated for BMD of which almost half (49%) had diminished BMD. This highlights the current low awareness of the role of a low BMD and sustaining rib fractures. While rib fractures are considered an osteoporotic fracture by some, it is unknown if rib bones benefit from anti-osteoporotic treatment to prevent subsequent fractures [15, 26]. Besides, routinely performing a DXA scan after thoracic trauma in patients over 50 years can provide insight into the true prevalence of diminished BMD in this subpopulation.

In an attempt to stratify the injury characteristics, a rib fracture classification has been developed in accordance with the AO/OTA fracture classification (Figure 1). In this cohort, over 60% of rib fractures were either displaced (type B), or multifragmentary or segmental (both type C). With the best treatment for rib fractures remaining a subject of debate, a validated classification for rib fractures may aid in diagnosing the severity of rib fractures and would ideally predict outcome. Moreover, it could clearly define those patients who may benefit from operative treatment as flail chest and severely displaced rib fractures are currently indications for operative stabilization [31, 40]. It must be noted that in around 40% of patients, no thoracic CT scan was available. This might have affected the accuracy and distribution of the rib fracture types in the current study.

Fractures of the first and second ribs are associated with a higher risk of severe concomitant injuries to e.g. the subclavian structures and thoracic vertebrae [41]. In contrast to middle segment ribs, the individual ribs 1 and 2, and 11 and 12 are neither amenable for surgery nor essential in chest wall stability and respiration [31, 40].

Surgery therefore adds more to morbidity than benefit [31]. In our cohort, no difference was found in the number of patients who fractured ribs 1 to 3 or ribs 4 to 10. Thus, patients with diminished BMD are not more likely to sustain either a complex cranial fracture that is associated with a higher risk of severe complications or a fracture of the middle thoracic segment that could benefit from operative fixation.

The current study has several limitations. The patient group might not be representative of patients aged 50 or older with rib fractures, because it was a single-center study in a Level 1 trauma center, and DXA scans were only available for 35% of patients. The 119 patients selected from the 488 patients registered in the osteoporosis registry might not be able to avoid selection bias and inadequate power. The reason for the low rate of DXA scans remains unclear as this is not elaborated on in the patient's medical file. Possible explanations might include patient's unwillingness for screening or an institutional flaw in complying with the hospital's osteoporosis screening guideline. The sample size was possibly too low to detect small but potentially meaningful differences from a clinical perspective in both fracture and injury characteristics between the normal and diminished BMD groups. In addition, the present study population was too small to analyze outcomes in patients with osteopenia or osteoporosis separately, or to perform multivariable regression. Implementing a standard DXA scan in patients aged 50 or older after rib fractures is recommended to improve understanding of the true prevalence of diminished BMD in these patients. With the retrospective design of this study, outcome measures might have been affected due to missing data and underreporting. For example, the fracture history of the included patients was not available. As this is considered a confounding factor for sustaining fractures in the future, this might have affected the results. A prospective design with a larger sample size is necessary.

Despite these shortcomings, this cohort study is the largest to date that focuses on the role of BMD on rib fracture frequency and characteristics in the middle-aged and elderly patient.

CONCLUSION

Patients aged 50 years or older often sustain rib fractures after blunt thoracic trauma. The rate of rib fractures after blunt thoracic trauma was significantly higher in patients with diminished BMD than in patients with a normal BMD. Differences in number and location of rib fractures between groups could not be proven. When assessing patients aged 50 years or older presenting to the hospital after substantial blunt thoracic trauma, the presence of diminished BMD should be taken into account and the presence of rib fractures should be investigated with appropriate diagnostic procedures.

Future prospective studies should determine the impact of diminished BMD on complication and mortality rate after rib fractures, and focus on the therapeutic consequence of performing thoracic CT imaging at a lower threshold in elderly patients after thoracic trauma.

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CHAPTER 4

Chest wall injuries due to cardiopulmonary resuscitation and the effect on in-hospital outcomes in survivors of out-of-hospital cardiac arrest

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ABSTRACT

Background

This study aimed to assess the prevalence of chest wall injuries due to cardiopulmonary resuscitation for out-of-hospital cardiac arrest (OHCA) and to compare in-hospital outcomes in patients with versus without chest wall injuries.

Methods

A retrospective cohort study of all intensive care unit (ICU)–admitted patients who underwent cardiopulmonary resuscitation for OHCA between January 1, 2007, and December 2019 was performed. The primary outcome was the occurrence of chest wall injuries, as diagnosed on chest computed tomography. Chest wall injury characteristics such as rib fracture location, type, and dislocation were collected. Secondary outcomes were in-hospital outcomes and subgroup analysis of patients with good neurological recovery to identify those who could possibly benefit from the surgical stabilization of rib fractures.

Results

Three hundred forty-four patients were included, of which 291 (85%) sustained chest wall injury. Patients with chest wall injury had a median of 8 fractured ribs (P_{25}–P_{75}, 4–10 ribs), which were most often undisplaced (on chest computed tomography) (n = 1,574 [72.1%]), simple (n = 1,948 [89.2%]), and anterior (n = 1,785 [77.6%]) rib fractures of ribs 2 to 7. Eight patients (2.3%) had a flail segment, and 136 patients (39.5%) had an anterior flail segment. Patients with chest wall injury had fewer ventilator-free days (0 days [P_{25}–P_{75}, 0–16 days] vs. 13 days [P_{25}–P_{75}, 2–22 days]; p = 0.006) and a higher mortality rate (n = 102 [54.0%] vs. n = 8 [22.2%]; p < 0.001) than those without chest wall injury. For the subgroup of patients with good neurological recovery, the presence of six or more rib fractures or a single displaced rib fracture was associated with longer hospital and ICU length of stay, respectively.

Conclusion

Cardiopulmonary resuscitation–related chest wall injuries in survivors of OHCA and especially rib fractures are common. Patients with chest wall injury had fewer ventilator-free days and a higher mortality rate. Patients with good neurological recovery might represent a subgroup of patients who could benefit from surgical stabilization of rib fractures.

INTRODUCTION

Sudden cardiac arrest is associated with poor survival rates, ranging from 2 to 11% after out-of-hospital cardiac arrest (OHCA) and up to 25% after in-hospital cardiac arrest [1, 2]. Cardiopulmonary resuscitation (CPR) is vital for the survival of these patients and chest compressions are key in providing oxygenation to the brain and heart [3, 4]. While chest compressions are considered the most important component of CPR, this mechanism also causes traumatic injuries [5, 6]. For example, rib fractures are the most often sustained bony injury after blunt chest trauma with a prevalence of 40%, but following CPR, rib fractures have been found in over 80% of patients [4, 7-9]. Multiple rib fractures after CPR are mostly anterior fractures of three or more adjacent ribs of the second to seventh rib, often studied in postmortem subjects or as diagnosed on chest radiography [8-12]. Besides the number and location of rib fractures, there is relatively little information on CPR-related rib fracture severity characteristics such as fracture type and degree of dislocation.

Pneumonia is the most common infectious complication after OHCA and rates of approximately 25% have been described which is most likely due to the extensive iatrogenic pulmonary contusion and aspiration of stomach contents [13-17]. Sustaining traumatic rib fractures has been associated with a high risk of pneumonia and consequent high morbidity and mortality rates. Following thoracic trauma, the risk of pneumonia increases with age or a higher number of fractured ribs [18-20]. As a result, the already vulnerable patient because of the OHCA might be at increased risk of developing pneumonia after sustaining CPR-related rib fractures and consequently has an increased risk of poor in-hospital outcome and mortality. To our knowledge, the effect of chest wall injury severity characteristics on in-hospital outcomes has not previously been described in survivors of OHCA. The use of surgical stabilization of rib fractures (SSRF) for severe chest wall injury has increased exponentially over the last decade and established ground in a broadening trauma population in terms of shorter hospital and intensive care unit (ICU) length of stay, mitigation of pulmonary morbidity such as pneumonia, in comparison with nonoperative management [21-24]. The practice of SSRF in patients with chest wall injuries due to CPR has only been described in small case series after failure of nonoperative management [25, 26].

The primary aim of this study was to assess the prevalence of chest wall injuries due to CPR after OHCA with no obvious traumatic or extracardiac cause in patients admitted to the ICU. The secondary aim was to compare in-hospital outcomes in patients with versus without chest wall injuries due to CPR after OHCA and to identify a possible subgroup of patients who might benefit from SSRF.

CHAPTER 4

METHODS

Design and participants
A multicenter retrospective cohort study was performed at two hospitals, a level 1 and level 2 trauma center. The study was exempted by the local Medical Research Ethics Committee. All patients who had CPR after OHCA with no obvious traumatic or extracardiac cause between January 1, 2007 and December 31, 2019, and were admitted to the ICU with return of spontaneous circulation (ROSC) within 24 hours after CPR were included in the study. Eligible patients were identified by a local OHCA resuscitation or ICU database. Patients with any of the following criteria were excluded: (1) chest wall injury sustained within 3 months prior to CPR; (2) use of ventricular support device (i.e., extracorporal membrane oxygenation , Left Ventricular Assist Device , Impella device, or intra-aortic balloon pump) because of the risk of iatrogenic intrathoracic or abdominal injury due to placement. Given the exploratory nature of this study, a formal sample size calculation was not made.

Data collection and outcome measures
Data were extracted from the patient's medical files. The primary outcome measure was the occurrence of chest wall injuries, as diagnosed on chest computed tomography (CT) (i.e., rib fracture(s) including number of total fractured ribs, rib fracture location, dislocation, and type, presence of a flail segment, sternum fracture, and anterior flail segment). In case of an additional CPR setting, the last chest CT was used. All definitions on rib and chest wall injury characteristics were derived from the Chest Wall Injury Society (CWIS) international taxonomy paper [27]. The location of fracture per rib was defined as costochondral, anterior, lateral, posterior, or paravertebral. The degree of dislocation was defined as undisplaced (>90% cortical contact), offset (<90% cortical contact), or displaced (no cortical contact). Type of fracture per rib was defined as simple, wedge, or complex. The presence of a flail segment (three or more consecutive ribs fractured in two or more places) and anterior flail segment or flail sternum (three bilateral consecutive anterior rib or costochondral fractures) were radiological diagnoses. Collected intrathoracic injury characteristics were occurrence of pneumothorax, hemothorax, unilateral or bilateral pulmonary contusion, pneumomediastinum, intrathoracic arterial blush, abdominal injury and intrapulmonary aspiration at admission (defined as the presence of abnormal fluids or infiltrative consolidations at the time of the initial chest CT, as reported by the radiologist). The secondary outcomes were mechanical ventilation requirement, ventilator-free days (number of days the patient breathed without pulmonary assistance) during hospitalization, ICU LOS and hospital length of stay (HLOS) during primary admission, the occurrence of thoracic complications requiring medicinal or surgical interventions (i.e., pneumonia, pleural empyema, retained

hemothorax, or tracheostomy requirement), and in-hospital mortality. Patients were intubated and received targeted temperature management in case of a Glasgow Coma Scale (GCS) <8 according to international guidelines or if a patient had a motor GCS of <5 [28]. Also, to identify if a select patient group might benefit from SSRF over nonoperative management, subgroup analysis was performed to assess in-hospital outcomes in patients with good neurological recovery after targeted temperature management for OHCA, defined as a motor GCS of 5 or 6, and presence versus absence of increasing chest wall injury.

In addition, the following variables were collected: patient characteristics (i.e., age, sex, smoking status at age of OHCA, presence of cardiovascular comorbidities, previous cardiac interventions), OHCA-related characteristics (i.e., cause of arrest, time between OHCA and CPR, time between OHCA and ROSC, and GCS at presentation), CPR-related variables (i.e., manual or mechanical CPR, CPR performed by bystander, (helicopter) emergency medical service [(H)EMS], or a combination), and treatment-related variables (e.g., SSRF, video-assisted thoracoscopic surgery [VATS], or thoracotomy performed).

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 25 (SPSS, Chicago, IL). Normality of continuous variables was tested with the Shapiro-Wilk test, and homogeneity of variances was tested using the Levene's test. A p value lower than 0.05 was considered statistically significant and all tests were two-sided. Descriptive analysis was performed to report the data for the entire study population and for patients with or without chest wall injury. For continuous data, the median and percentiles (nonparametric data) were reported. Categorical data are reported as numbers and frequencies. Statistical significance of differences between patients with and without chest wall injuries was assessed using Mann-Whitney U test (two groups) for continuous data and χ-squared or Fisher's Exact test for categorical data, as applicable. Subgroup analysis of patients with good neurological recovery was performed to evaluate the effect of increasing severity of chest wall injury (increasing number of rib fractures, presence and increasing number of displaced rib fractures, and presence of any type of flail segment) on the in-hospital outcomes, as compared with patients in which these characteristics were absent.

RESULTS

In total, 344 of 386 eligible patients (89%) were included for analysis (Supplemental Figure 1). The median age was 66 years (P_{25}-P_{75}, 54-74 years), 259 (75.3%) were male, and the median GCS at admission was 3 (P_{25}-P_{75}, 3-5, range, 3-15) with an acute myocardial infarction as the most prevalent cause of the OHCA (n = 177 [51.5%]) (Table 1). The median time of OHCA to ROSC was 10 minutes (P_{25}-P_{75}, 6-17 minutes) with CPR initiation at a median of 0 minutes (P_{25}-P_{75}, 0-5 minutes) after OHCA.

Of the included patients, 291 (85%) had sustained chest wall injury due to CPR and rib fractures were the most common chest wall injury (n=285; 83%; Table 2). Patients with chest wall injury had a median of 8 fractured ribs (P_{25}-P_{75}, 4-10 ribs) which were most often undisplaced (n = 1,574; 72%), simple (n=1,948; 89%), anterior (n=1,785; 78%) fractures of ribs 2 to 7 (Figure 1). Of ribs 2 to 7, the rate of displaced rib fractures ranged from 4.0 to 13.4%. A total of 98 patients (28.5%) had a concomitant sternum fracture and 136 (39.5%) had an anterior flail segment.

Patients with chest wall injury were older (median [P_{25}-P_{75}], 67 [57-75] years vs. 50 [40-63] years; p < 0.001; Table 3) and less often had congenital heart disease (n = 4 [1.9%] vs. n = 3 [10.3%]; p = 0.038) than patients without chest wall injury. Other baseline characteristics were similar across the two groups. The two groups had similar time from OHCA to start of CPR and median GCS at admission, but the duration from OHCA to ROSC was significantly longer in patients with chest wall injury (median [P_{25}-P_{75}], 10 [6-18] minutes vs. 4 [1-6] minutes; p = 0.001). In addition, the distribution of CPR performed by (H)EMS or bystander was similar, but for patients with chest wall injury, the duration of CPR performed by (H)EMS was significantly longer than in those without chest wall injury (median [P_{25}-P_{75}], 8 [4-13] minutes vs. 4 [2-9] minutes; p = 0.003). With regard to intrathoracic injuries, patients with chest wall injury more frequently sustained a hemothorax (n = 84 [28.9%] vs. n = 7 [13.2%]; p = 0.018) and pulmonary contusion (n = 155 [53.3%] vs. n = 19 [35.8%]; p = 0.025) than those without chest wall injury. Other intrathoracic injury rates were similar across the two groups. The radiologically diagnosed abdominal injuries were two kidney hemorrhages, one spleen hemorrhage, one ureter hemorrhage, one adrenal gland hemorrhage, one colon injury, and one concomitant kidney and liver infarction in the chest wall injury group versus one spleen hemorrhage in the group without chest wall injury (p = 0.818).

In the chest wall injury group, seven patients (2.4%) underwent SSRF, because of insufficient respiratory function, after a median of 5 days (P_{25}-P_{75}, 2-5 days) following hospital admission. In these patients, a median of five ribs (P_{25}-P_{75}, 5-7 ribs) were surgically stabilized, totaling a ratio of ribs repaired to fractured (rib fixation ratio) of 0.70 (P_{25}-P_{75}, 0.38-0.83). In one patient, SSRF was complicated by a post-operative bleeding which required a thoracotomy and another patient required a VATS because

of a retained hemothorax. No surgical site infection or hardware failure was reported during hospitalization. All patients underwent SSRF in 2019 and all were discharged alive.
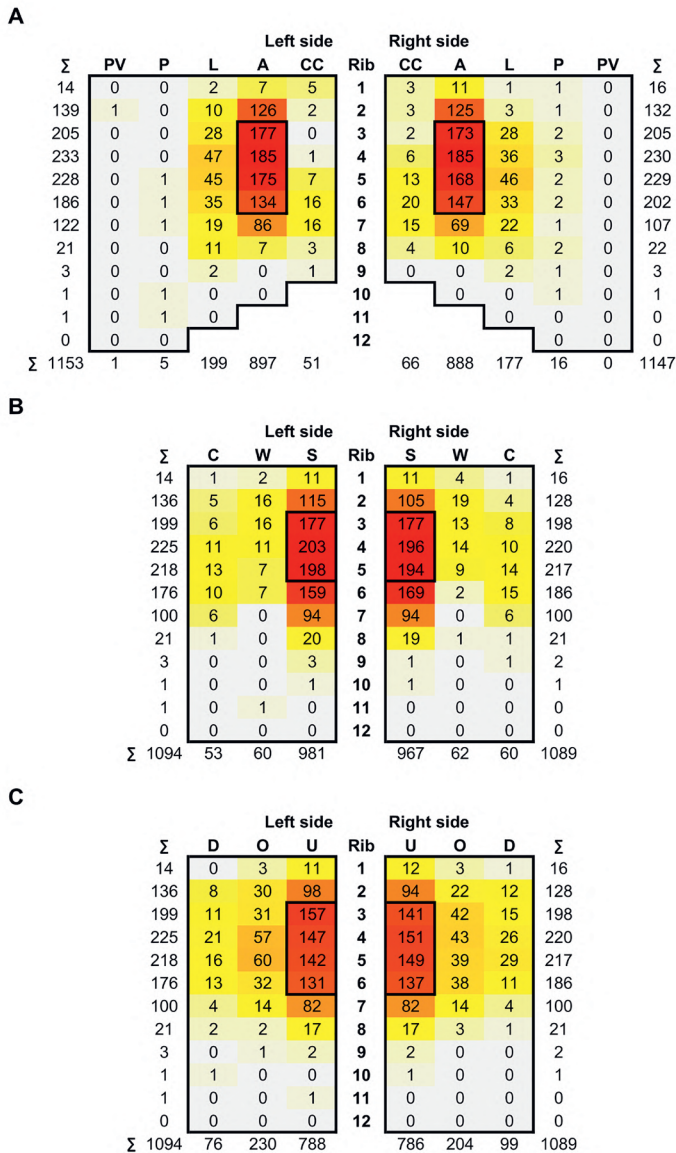
FIGURE 1
Heat map displaying the location (A), type (B), and degree of dislocation (C) per rib.

TABLE 1
Demographics, OHCA and CPR Characteristics in admitted patients who underwent CPR after OHCA.

	N*	Overall (n = 344)
Patient demographics		
Age, y	344	66 (54-74)
Sex (male)	344	259 (75.3%)
Smoking at age of CPR	241	90 (37.3%)
Hypertension	244	150 (61.5%)
Diabetes Mellitus	244	68 (27.9%)
COPD	244	35 (14.3%)
Pulmonary embolism	244	6 (2.5%)
Cerebrovascular accident	244	16 (6.6%)
Previous MI	244	72 (29.5%)
Cardiomyopathy	244	33 (13.5%)
Congenital heart disease	244	7 (2.9%)
Chronic heart failure	244	54 (22.1%)
Arrhythmia	244	63 (25.8%)
Cardiac valve disease	244	18 (7.4%)
Cardiac intervention	344	80 (23.3%)
Congenital heart disease operation	80	3 (3.8%)
Cardiac valve disease operation	80	10 (12.5%)
Previous PCI	80	54 (67.5%)
Previous CABG	80	24 (30.0%)
ICD or pacemaker in situ	80	17 (21.3%)
OHCA and CPR characteristics		
OHCA cause		
Acute MI	344	177 (51.5%)
Old MI/scar tissue	344	60 (17.4%)
Cardiomyopathy	344	42 (12.2%)
Primary rhythm disorder	344	48 (14.0%)
Intoxication	344	4 (1.2%)
Unknown	344	13 (3.8%)
GCS at presentation	331	3 (3-5)
OHCA to CPR duration, min	267	0.0 (0.0-5.0)
OHCA to ROSC duration, min	242	10.0 (6.0-17.3)
Bystander	253	0.0 (0.0-5.0)
(H)EMS	316	6.0 (4.0-12.0)
CPR mode		
Manual	344	344 (100.0%)
Manual + mechanical	344	19 (5.5%)

	N*	Overall (n = 344)
Type of compressor		
Bystander	344	27 (8.0%)
(H)EMS	344	137 (40.5%)
Combination	344	174 (51.5%)
Additional CPR setting	344	54 (15.7%)
<24 h	54	46 (85.2%)
>24 h	54	8 (14.8%)
Chest CT performed		
After first CPR setting	344	315 (91.6%)
After additional CPR setting	344	29 (8.4%)

Data are shown as median (P_{25}-P_{75}) or as n (%). *: provides the exact number of patients for whom data were available.
CABG, coronary artery bypass graft; COPD, Chronic Obstructive Pulmonary Disease; CWI, chest wall injury; ICD, implantable cardioverter defibrillator; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Thick borders around specific ribs represent hotspots which comprise ≥50% of the total number of rib fracture location, type, or dislocation degree. A, anterior; C, complete; D, displaced; CC, costochondral, L, lateral; O, offset; P, posterior PV, costovertebral; S, simple; U, undisplaced; W, wedge.

Of the entire cohort, 119 patients (34.6%) were transferred to another hospital during primary admission. In-hospital outcomes were evaluated for patients with complete data regarding their primary hospital stay (n = 225; Table 4). Median ventilator-free days were significantly lower in those with chest wall injury (0 days, P_{25}-P_{75}, 0-16 days) than in patients without chest wall injury (13 days, P_{25}-P_{75}, 2-22 days; p = 0.006). A total of 102 patients (54.0%) died in the group with chest wall injury while 8 patients (22.2%) patients died in the group without chest wall (p < 0.001). The ICU LOS, rate of mechanical ventilation requirement and thoracic complications were similar for both groups.

In subgroup analysis, the effect of a specific chest wall injury characteristic (indicator) on in-hospital outcomes was evaluated as compared with patients without this characteristic (reference), in patients with good neurologic recovery (motor GCS of 5 or 6). A motor GCS of 5 or 6 after targeted temperature management versus a motor GCS of 1 to 4 was associated with a higher number of ventilator-free days (15 days [P_{25}-P_{75},11-22 days] vs. 0 days [P_{25}-P_{75}, 0-11 days]; p< 0.001) and lower mortality rate (n = 3 [2.2%] vs. n = 89 [57.4%]; p < 0.001) (Table 5 and Supplemental Table 1). In this subgroup of patients with good neurological recovery, sustaining one to five rib fractures was not associated with any difference in in-hospital outcomes, but sustaining six or more rib fractures as compared with one to five rib fractures, was associated with a

longer hospital length of stay (22 days [P_{25}-P_{75}, 17-31 days] vs. 18 days [P_{25}-P_{75}, 12-22 days]; p = 0.040). The rate of pneumonia in patients with rib fractures was 30.9% (n = 17) versus 9.1% (n = 2) in patients without rib fractures (p = 0.077).

The presence of one or more displaced rib fractures as compared with having only undisplaced rib fractures was associated with longer ICU LOS (10 days [P_{25}-P_{75}, 3-12 days] vs. 5 days [P_{25}-P_{75}, 4-6 days]; p = 0.023). No effect was seen of the presence of the different number of rib fractures, number of displaced rib fractures, or a flail chest on mortality rate. Patients with a flail segment (anterior or flail sternum or other flail segment) had more ventilator-free days and longer HLOS as compared with those without any flail segment, but outcomes were not significantly different.

TABLE 2
Chest wall injury characteristics in admitted patients after CPR for OHCA.

	Overall (n = 344)
Chest wall injury characteristics	
Rib fracture	285 (82.9%)
No. of ribs fractured	8 (4-10)
Bilateral rib fractures	240 (84.2%)
No. of rib fractures	2,300
Rib fracture location	
Costochondral	117 (5.1%)
Anterior	1,785 (77.6%)
Lateral	376 (16.3%)
Posterior	21 (0.9%)
Costovertebral	1 (0.04%)
Rib fracture dislocation	
Undisplaced	1,578 (72.2%)
Offset	434 (19.9%)
Displaced	175 (8.0%)
Rib fracture type	
Simple	1,952 (89.3%)
Wedge	122 (5.6%)
Complex	113 (5.2%)
Flail segment	8 (2.3%)
Sternal fracture	98 (28.5%)
Anterior flail segment/flail sternum	136 (39.5%)

Data are shown as median (P_{25}-P_{75}) or as n (%). There were no missing data.
Undisplaced fracture, >90% cortical contact; offset, <90% cortical contact; displaced, no cortical contact. Flail segment, three or more consecutive ribs fractured in two or more places; anterior flail segment or flail sternum, three bilateral consecutive anterior rib or costochondral fractures. Complex fractures were evaluated for degree of dislocation once.

TABLE 3
Demographics, OHCA, CPR, and intrathoracic injury characteristics in admitted patients who underwent CPR after OHCA, stratified for presence or absence of chest wall injury.

	N*	With CWI (n = 291)	N*	Without CWI (n = 53)	p
Patient demographics					
Age, y	291	67 (57-75)	53	50 (40-63)	**<0.001**
Sex (male)	291	221 (75.9%)	53	38 (71.7%)	0.494
Smoking at age of CPR	198	76 (38.4%)	43	14 (32.6%)	0.602
Hypertension	215	134 (62.3%)	29	16 (55.2%)	0.543
Diabetes Mellitus	215	62 (28.8%)	29	6 (20.7%)	0.508
COPD	215	31 (14.4%)	29	4 (13.8%)	1.000
Pulmonary embolism	215	4 (1.9%)	29	2 (6.9%)	0.151
Cerebrovascular accident	215	14 (6.5%)	29	2 (6.9%)	1.000
Previous MI	215	65 (30.2%)	29	7 (24.1%)	0.665
Cardiomyopathy	215	27 (12.6%)	29	6 (20.7%)	0.247
Congenital heart disease	215	4 (1.9%)	29	3 (10.3%)	**0.038**
Chronic heart failure	215	50 (23.3%)	29	4 (13.8%)	0.342
Arrhythmia	215	55 (25.6%)	29	8 (27.6%)	0.823
Cardiac valve disease	215	17 (7.9%)	29	1 (3.4%)	0.704
Cardiac intervention	291	70 (24.1%)	53	10 (18.9%)	0.482
Congenital heart disease operation	70	1 (1.4%)	10	2 (20.0%)	**0.040**
Cardiac valve disease operation	70	9 (12.9%)	10	1 (10.0%)	1.000
Previous PCI	70	47 (67.1%)	10	7 (70.0%)	1.000
Previous CABG	70	22 (31.4%)	10	2 (20.0%)	0.715
ICD or pacemaker *in situ*	70	16 (22.9%)	10	1 (10.0%)	0.680
OHCA and CPR characteristics					
OHCA cause					
Acute MI	291	155 (53.3%)	53	22 (41.5%)	**0.018**
Old MI/scar tissue	291	55 (18.9%)	53	5 (9.4%)	
Cardiomyopathy	291	35 (12.0%)	53	7 (13.2%)	
Primary rhythm disorder	291	33 (11.3%)	53	15 (28.3%)	
Intoxication	291	3 (1.0%)	53	1 (1.9%)	
Unknown	291	10 (3.4%)	53	3 (5.7%)	
GCS at presentation	278	3 (3-5)	53	3 (3-6)	0.215
OHCA to CPR duration (minutes)	222	0 (0-5)	45	0 (0-5)	0.777
OHCA to ROSC duration (minutes)	207	10 (6-18)	35	4 (1-6)	**0.001**
Bystander	217	0 (0-5)	36	0 (0-5)	0.847
(H)EMS	266	8 (4-13)	50	4 (2-9)	**0.003**

TABLE 3 continued from page 75

	N*	With CWI (n = 291)	N*	Without CWI (n = 53)	p
CPR mode					
Manual	291	291 (100.0%)	53	53 (100.0%)	1.000
Manual + mechanical	291	17 (5.8%)	53	2 (3.8%)	0.749
Type of compressor					
Bystander	285	21 (7.4%)	53	6 (11.3%)	0.539
(H)EMS	285	118 (41.4%)	53	19 (35.8%)	
Combination	285	146 (51.2%)	53	28 (52.8%)	
Additional CPR setting	291	49 (16.8%)	53	5 (9.4%)	0.219
<24 hours	49	41 (83.7%)	5	5 (100.0%)	1.000
>24 hours	49	8 (16.3%)	5	0 (0.0%)	
Chest CT performed					
After first CPR setting	291	264 (90.7%)	53	51 (96.2%)	0.281
After additional CPR setting	291	27 (9.3%)	53	2 (3.8%)	
Intrathoracic injury characteristics					
Pneumothorax	291	19 (6.5%)	53	1 (1.9%)	0.334
Hemothorax	291	84 (28.9%)	53	7 (13.2%)	**0.018**
Pulmonary contusion	291	155 (53.3%)	53	19 (35.8%)	**0.025**
Unilateral	291	28 (18.1%)	53	6 (31.6%)	0.216
Bilateral	291	127 (81.9%)	53	13 (68.4%)	
Pneumomediastinum	291	7 (2.4%)	53	1 (1.9%)	1.000
Intrathoracic arterial blush	291	4 (1.4%)	53	0 (0.0%)	1.000
Abdominal injury	291	7 (2.4%)	53	1 (1.9%)	1.000
Aspiration at admission	291	36 (12.4%)	53	3 (5.7%)	0.236
Chest tube drainage	291	20 (6.9%)	53	1 (1.9%)	0.221

Data are shown as median (P_{25}-P_{75}) or as n (%); bold p-values are considered statistically significant.
*: provides the exact number of patients for whom data were available.
CABG, coronary artery bypass graft; COPD, Chronic Obstructive Pulmonary Disease; CWI, chest wall injury; GCS, Glasgow Coma Scale; ICD, implantable cardioverter defibrillator; MI, myocardial infarction; PCI, percutaneous coronary intervention.

DISCUSSION

This retrospective review is the first to assess CPR-related chest wall injuries in detail based on the validated taxonomy for rib fracture classification and evaluate the effect of these injuries on in-hospital outcomes in survivors of cardiopulmonary resuscitation. In this population of patients who are admitted following CPR for OHCA, chest wall injuries are common. The most prevalent injury were rib fractures, present in over 8

out of every 10 patients, with a median of 8 rib fractures per patient. These rib fractures were most often bilateral, anterior, and undisplaced simple rib fractures of ribs 2 to 7. Patients with chest wall injury had significant longer time from OHCA to ROSC and CPR performed by (H)EMS as well as higher intrathoracic injury rates of hemothorax and pulmonary contusion as compared with patients without chest wall injury. In-hospital outcomes differed between groups regarding mortality rates, which were higher (54% vs. 22%), and ventilator-free days, which were lower (0 vs. 13) in the chest wall injury group. For the subgroup of patients with good neurological recovery, a single displaced rib fracture was associated with longer ICU LOS. The same holds true for the HLOS in patients with six or more rib fractures, irrespective of the amount of dislocation.

The majority of chest wall injuries are still evaluated only at autopsy and most large-scale studies on chest wall injuries after CPR comprise postmortem subjects [7, 29-31]. Chest wall injuries and more specifically rib fractures due to CPR are common in survivors too with previously diagnosed rib fracture rates similar to our findings (80-85%) [4, 32, 33]. One of these studies also assessed the rate of displaced rib fractures and found a rate of 10% which is similar to the 9% in our cohort [4]. The mentioned study did however only include 39 patients. The current study is the first to describe rib fracture severity according to the validated taxonomy of the Chest Wall Injury Society in ICU-admitted patients who had CPR for OHCA with an available chest CT [27, 34]. Iatrogenic rib fractures as sustained after CPR are associated with longer HLOS and a higher mortality rate than blunt traumatic rib fractures [35]. Delineating chest wall injuries such as rib fractures is important because the presence and number of rib fractures as well as the degree of dislocation or presence of a flail segment after chest trauma have been associated with increased rates of mortality and pulmonary morbidity [20, 36-38]. In this cohort, patients with chest wall injury had worse in-hospital outcomes than their counterparts without chest wall injury regarding less ventilator-free days and a higher mortality rate. This suggests that there is a relationship between the presence of CPR-related chest wall injury and worse in-hospital outcomes, thus highlighting the importance of correctly identifying this injury. However, further prospective research is required to evaluate possible causality between chest wall injury and outcomes such as mechanical ventilation requirement.

Good motor GCS after targeted temperature management was associated with higher ventilator-free days, longer HLOS, and lower mortality. This might suggest that the neurological status after targeted temperature management is more predictive of worse in-hospital outcomes than the degree of chest wall injury severity. Age and duration from OHCA to ROSC were different among patients with and without chest wall injury in this study and have previously been shown to increase the risk of chest wall injury [39-41]. A higher age and longer OHCA setting might therefore, besides increasing chest wall injury risk, also precipitate a higher risk of neurological damage

CHAPTER 4

TABLE 4

In-hospital outcomes and thoracic complications in patients with ROSC after CPR for OHCA, stratified for presence or absence of CWI.

	Overall (n = 344)	With CWI (n = 291)	Without CWI (n = 53)	p
Transferred to other hospital	119 (34.6%)	102 (35.1%)	17 (32.1%)	0.755
HLOS, d	12 (4-23)	10 (4-23)	16 (8-25)	**0.024**
HLOS (survivors), d	23 (16-30)	23 (17-32)	21 (13-27)	0.125
ICU LOS, d	5 (3-8)	5 (3-8)	3 (1-5)	0.871
Mechanical ventilation	217 (96.4%)	184 (97.4%)	33 (91.7%)	0.119
Ventilator-free days	5 (0-18)	0 (0-16)	13 (2-22)	**0.006**
Thoracic complication	75 (33.3%)	66 (34.9%)	9 (25.0%)	0.335
Tracheostomy	11 (4.9%)	11 (5.8%)	0 (0.0%)	0.219
Pneumonia	45 (20.0%)	39 (20.6%)	6 (16.7%)	0.657
Pleural empyema	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.000
Retained hemothorax	1 (0.4%)	1 (0.5%)	0 (0.0%)	1.000
Mortality	110 (48.9%)	102 (54.0%)	8 (22.2%)	**<0.001**
Mortality, d	3 (1-6)	3 (1-6)	4 (2-8)	0.388
Mortality cause				
Postanoxic neurological damage	72 (65.5%)	66 (64.7%)	6 (75.0%)	0.696
Cardiogenic shock	14 (12.7%)	14 (13.7%)	0 (0.0%)	
Respiratory insufficiency	4 (3.6%)	4 (3.9%)	0 (0.0%)	
Multi-organ failure	14 (12.7%)	12 (11.8%)	2 (25.0%)	
DNR/DNI status	2 (1.8%)	2 (2.0%)	0 (0.0%)	
Unknown	4 (3.6%)	4 (3.9%)	0 (0.0%)	

Data are shown as median (P_{25}-P_{75}) or as n (%); bold p-values are considered statistically significant. There were no missing data.
CWI, chest wall injury; DNR/DNI, do not resuscitate/do not intubate.

and result in worse in-hospital outcomes.

Within the group of patients with chest wall injury with good motor GCS (5 or 6) after targeted temperature management, the effect of the presence or absence of specific chest wall injuries on in-hospital outcomes was less clear. Sustaining six rib fractures, as opposed to one to five, or one or more displaced rib fractures as compared with only undisplaced rib fractures was associated with longer HLOS and ICU LOS, respectively. Also, although being nonsignificant, some differences in in-hospital outcomes between patients with and without specific chest wall injuries might be clinically relevant. For example, patients with rib fractures and good motor GCS recovery had a three times higher (31% vs. 9%) rate of pneumonia than those without rib fractures (p = 0.077).

TABLE 5
Effect of neurological status and chest wall injury on in-hospital outcomes after CPR for OHCA

Indicator	Reference	Ventilator-free days		ICU LOS		HLOS		Pneumonia		Mortality	
		Indicator	Reference	Indicator	Reference	Indicator	Reference	Indicator	Reference	Indicator	Reference
GCS-M 5 or 6	GCS-M 1-4	15 (11-22)	0 (0-11)**	5 (3-7)	6 (4-9)	18 (13-25)	7 (4-19)**	19 (24.7%)	25 (20.5%)	3 (2.2%)	89 (57.4%)**
≥ 1 RF	0 RF	15 (11-21)	16 (11-24)	5 (4-8)	5 (3-6)	19 (14-25)	16 (12-26)	17 (30.9%)	2 (9.1%)	3 (2.9%)	0 (0.0%)
≥ 3 RF	1-2 RF	15 (11-21)	15 (7-22)	6 (4-9)	4 (3-6)	20 (15-25)	17 (9-26)	15 (34.9%)	2 (16.7%)	3 (3.4%)	0 (0.0%)
≥ 4 RF	1-3 RF	15 (12-23)	14 (9-18)	6 (4-10)	5 (3-6)	22 (16-27)	16 (10-21)	13 (36.1%)	4 (21.1%)	3 (3.8%)	0 (0.0%)
≥ 5 RF	1-4 RF	15 (12-23)	14 (9-19)	6 (4-10)	5 (3-7)	22 (16-30)	18 (12-23)	11 (35.5%)	6 (25.0%)	3 (4.3%)	0 (0.0%)
≥ 6 RF	1-5 RF	15 (13-24)	14 (9-19)	6 (4-10)	5 (3-7)	22 (17-31)	18 (12-22)*	11 (36.7%)	6 (24.0%)	3 (4.8%)	0 (0.0%)
≥ 1 displaced RF	No displaced RF	14 (8-17)	15 (11-23)	10 (3-12)	5 (4-6)*	21 (16-24)	18 (13-25)	6 (40.0%)	13 (21.0%)	2 (7.1%)	1 (0.9%)
≥ 2 displaced RF	1 displaced RF	15 (13-17)	12 (7-19)	8 (3-23)	10 (3-12)	22 (17-35)	19 (14-25)	1 (20.0%)	5 (50.0%)	0 (0.0%)	2 (12.5%)
≥ 3 displaced RF	1-2 displaced RF	17 (15-17)	13 (7-16)	10 (8-10)	10 (3-13)	21 (17-21)	21 (16-28)	0 (0.0%)	6 (46.2%)	0 (0.0%)	2 (8.7%)
Flail segment	No flail segment	19 (13-26)	14 (11-21)	5 (4-8)	5 (3-7)	22 (17-28)	18 (12-24)	6 (27.3%)	13 (23.6%)	1 (2.2%)	2 (2.1%)

Data are shown as median (P_{25}-P_{75}) or as N (%); bold values are considered statistically significant. *p<0.05. **p<0.001.
GCS-M, Glasgow Coma Scale-Motor score; RF, rib fracture.

CHAPTER 4

The practice of SSRF in patients with chest wall injuries due to CPR has been evaluated with good outcomes, improving chest wall stability and aiding ventilator support weaning [25, 26]. These studies, however, are case reports or series with no control group with patients undergoing SSRF at a late stage (>10 days) of hospitalization. Early SSRF (≤72 hours of admission) is associated with improved in-hospital outcomes as compared with nonoperative treatment, but late salvage rib fixation has actually been shown to be inferior to nonoperative treatment [42, 43]. In this cohort, seven patients underwent SSRF at a median of 5 days after their sudden cardiac arrest and all survived until discharge without perioperative complications with one patient requiring a VATS for retained hemothorax. Since SSRF has been shown to be safe in patients with traumatic brain injury and associated with a lower risk of pneumonia, SSRF (preferably in the early window) might also be safe and improve respiratory function in patients with severe chest wall injury due to CPR and possible OHCA-related post-anoxic brain injury [44]. Patients with good neurological recovery following targeted temperature management and severe chest wall injuries might represent a subgroup that could benefit from early SSRF. In these patients, the presence and increasing number of rib fractures or one displaced rib might be factors to be taken into account when considering SSRF to improve outcomes. The overall long HLOS, ICU LOS, and high rate of pneumonia in patients with chest wall injury due to CPR indicate that room for possibly clinically relevant improvements of these outcomes exists. Future comparative studies should focus on the effect of SSRF and nonoperative treatment in patients with chest wall injuries, which are currently deemed SSRF indications. While it is possible that these accepted SSRF indications do not apply to CPR-related chest wall injuries, chest wall injuries require identification and, if followed by good neurological recovery, might warrant further delineation regarding number of fractures and degree of dislocation, and consideration of SSRF to improve clinical outcomes.

When interpreting these results, several limitations should be considered. First, this was a retrospective study which might have introduced information bias through missing data. With a median admission GCS of 3, almost all patients (96%) requiring mechanical ventilation, and a mortality rate of 49% in the total cohort, missing data rates were possibly higher than in other original studies. Second, the analyses of in-hospital outcomes in the subgroups with good neurological recovery should be interpreted with caution because of the small sample sizes which were possibly too low to detect small but clinically relevant differences in outcomes between groups. This could be attributable to the inclusion criterion of an available chest CT, which is the golden standard for diagnosis and delineation of rib fractures [45]. About half of the total number of patients had to be excluded because of no available chest CT. This might be explained because there was no standardized protocol for performing a chest CT in these patients during the study period, the acute care most often centered around

cardiac and neurologic recovery requiring other diagnostic modalities, and this number of chest CTs might have been higher if patients had an unknown or non-cardiac cause (e.g., pulmonary embolism or intracranial hemorrhage) of the sudden cardiac arrest. While this could have introduced selection bias, it was not possible with this retrospective data to evaluate why patients did or did not receive a chest CT and, consequently, whether patients without a chest CT had lower rates of chest wall injuries. However, as one of the largest studies on CPR-related injuries in survivors of OHCA with data of two hospitals, the available data mimic current daily practice. We recommend performing a chest CT at a low threshold in the acute setting to adequately assess chest wall injuries. Third, only univariate subgroup analysis was performed because of the small sample sizes of the subgroups. As a result, differences in patient and OHCA characteristics between the two groups such as age and duration of CPR could not be corrected for while these might have impacted in-hospital outcomes. In addition, the effect of neurological motor recovery appeared to be more strongly associated with adverse outcomes than specific chest wall injuries. These small sample sizes of patients with good neurological recovery show that poor in-hospital outcomes might be multifactorial and require a multidisciplinary approach.

In summary, CPR-related chest wall injuries in survivors of OHCA have a high prevalence. Multiple, bilateral, anterior, and undisplaced simple rib fractures of ribs 2 to 7 are most common. The presence of chest wall injuries is associated with worse in-hospital outcomes such as less ventilator-free days and higher mortality. Patients with good neurological recovery and chest wall injury still have lengthy ICU LOS and high rates of pneumonia. While this study does not prove causality between chest wall injury and in-hospital outcomes, it does demonstrate an association, warranting further large-scale prospective investigation and identification of a subgroup of patients who might benefit from SSRF to restore chest wall function and respiratory capacity following CPR for OHCA.

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CHAPTER 4
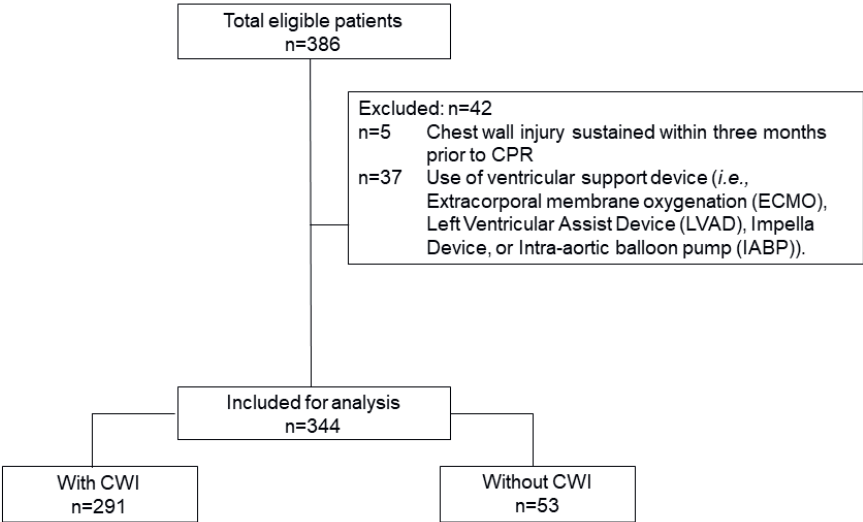
SUPPLEMENTAL DATA

SUPPLEMENTAL FIGURE 1
Study flow chart.
CWI, chest wall injury.

SUPPLEMENTAL TABLE 1
Sample sizes of the subgroups for the effect of neurological status and chest wall injury on in-hospital outcomes after cardiopulmonary resuscitation (CPR) for out-of-hospital cardiac arrest (OHCA).

Indicator	Reference	Ventilator-free days				
		Indicator		Reference		p
		N		N		
GCS-M 5 or 6	GCS-M 1-4	69	15 (11-22)	122	0 (0-11)	**<0.001**
≥ 1 RF	0 RF	50	15 (11-21)	19	16 (11-24)	0.803
≥ 3 RF	1-2 RF	39	15 (11-21)	11	15 (7-22)	0.888
≥ 4 RF	1-3 RF	32	15 (12-23)	18	14 (9-18)	0.311
≥ 5 RF	1-4 RF	27	15 (12-23)	23	14 (9-19)	0.305
≥ 6 RF	1-5 RF	26	15 (13-24)	24	14 (9-19)	0.196
≥ 1 displaced RF	No displaced RF	12	14 (8-17)	57	15 (11-23)	0.213
≥ 2 displaced RF	1 displaced RF	4	15 (13-17)	8	12 (7-19)	0.368
≥ 3 displaced RF	1-2 displaced RF	2	17 (15-17)	10	13 (7-16)	0.273
Flail segment	No flail segment	20	19 (13-26)	49	14 (11-21)	0.115

Indicator	Reference	Pneumonia				
		Indicator		Reference		p
		N		N		
GCS-M 5 or 6	GCS-M 1-4	77	19 (24.7%)	122	25 (20.5%)	0.489
≥ 1 RF	0 RF	55	17 (30.9%)	22	2 (9.1%)	0.077
≥ 3 RF	1-2 RF	43	15 (34.9%)	12	2 (16.7%)	0.304
≥ 4 RF	1-3 RF	36	13 (36.1%)	19	4 (21.1%)	0.360
≥ 5 RF	1-4 RF	31	11 (35.5%)	24	6 (25.0%)	0.558
≥ 6 RF	1-5 RF	30	11 (36.7%)	25	6 (24.0%)	0.386
≥ 1 displaced RF	No displaced RF	15	6 (40.0%)	62	13 (21.0%)	0.180
≥ 2 displaced RF	1 displaced RF	5	1 (20.0%)	10	5 (50.0%)	0.580
≥ 3 displaced RF	1-2 displaced RF	2	0 (0.0%)	13	6 (46.2%)	0.486
Flail segment	No flail segment	22	6 (27.3%)	55	13 (23.6%)	0.774

Data are shown as median (P_{25}-P_{75}) or as N (%); bold p-values are considered statistically significant.
GCS, Glasgow Coma Scale; HLOS, hospital length of stay; ICU LOS, Intensive Care Unit-length of stay; RF, rib fracture.

	ICU LOS					HLOS				
	Indicator		Reference		p	Indicator		Reference		p
	N		N			N		N		
	69	5 (3-7)	122	6 (4-9)	0.144	69	18 (13-25)	122	7 (4-19)	**<0.001**
	50	5 (4-8)	22	5 (3-6)	0.248	50	19 (14-25)	22	16 (12-26)	0.477
	43	6 (4-9)	11	4 (3-6)	0.127	43	20 (15-25)	12	17 (9-26)	0.249
	36	6 (4-10)	18	5 (3-6)	0.272	36	22 (16-27)	19	16 (10-21)	0.058
	31	6 (4-10)	23	5 (3-7)	0.393	31	22 (16-30)	24	18 (12-23)	0.067
	30	6 (4-10)	24	5 (3-7)	0.446	30	22 (17-31)	25	18 (12-22)	**0.040**
	15	10 (3-12)	61	5 (4-6)	**0.023**	15	21 (16-24)	62	18 (13-25)	0.406
	5	8 (3-23)	10	10 (3-12)	0.859	5	22 (17-35)	10	19 (14-25)	0.310
	2	10 (8-10)	13	10 (3-13)	0.933	2	21 (17-21)	13	21 (16-28)	0.800
	22	5 (4-8)	54	5 (3-7)	0.725	22	22 (17-28)	55	18 (12-24)	0.075

	Mortality				
	Indicator		Reference		p
	N		N		
	139	3 (2.2%)	155	89 (57.4%)	**<0.001**
	105	3 (2.9%)	34	0 (0.0%)	1.000
	89	3 (3.4%)	16	0 (0.0%)	1.000
	78	3 (3.8%)	27	0 (0.0%)	0.567
	69	3 (4.3%)	36	0 (0.0%)	0.549
	63	3 (4.8%)	42	0 (0.0%)	0.273
	28	2 (7.1%)	111	1 (0.9%)	0.103
	12	0 (0.0%)	16	2 (12.5%)	0.492
	5	0 (0.0%)	23	2 (8.7%)	1.000
	45	1 (2.2%)	94	2 (2.1%)	1.000

CHAPTER 4

CHAPTER 5

Long-term pulmonary function, thoracic pain, and quality of life in patients with one or more rib fractures

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ABSTRACT

Background
Long-term outcomes after rib fractures and the effect of treatment modality or chest wall injury severity on these outcomes remains uncertain. This retrospective cohort study evaluated the long-term pulmonary function, thoracic pain, and quality of life in patients admitted with rib fractures.

Methods
Patients admitted with rib fractures between January 1, 2012 and December 1, 2019 were included. Data on long-term outcomes were collected during one follow-up visit. Patients were stratified by chest wall injury severity (one or two rib fractures, ≥3 rib fractures, or a flail chest) and treatment modality (surgical stabilization of rib fractures [SSRF] or nonoperative management). Multivariable analysis was performed to compare outcomes after SSRF with nonoperative treatment in patients with three or more rib fractures.

Results
In total, 300 patients were included. The median follow-up was 39 months (P_{25}-P_{75}, 18-65 months). At follow-up, the corrected Forced Vital Capacity returned to 84.7% (P_{25}-P_{75}, 74.3-93.7) and the Forced Expiratory Volume in 1 s to 86.3% (P_{25}-P_{75}, 75.3-97.0) of the predicted reference values. Quality of life was determined using the Short Form-12 version 2 and EuroQoL-5D-5L. The Short Form-12 version 2 physical and mental component summary were 45 (P_{25}-P_{75}, 38-54) and 53 (P_{25}-P_{75}, 43-60), respectively. The EuroQoL-5D-5L utility score was 0.82 (P_{25}-P_{75}, 0.66-0.92) and visual analog scale score 75 (P_{25}-P_{75}, 70-85). This indicated a quality of life within normal population ranges. Moderate to severe thoracic pain was reported by 64 (21.3%) patients. Long-term outcomes returned to values within population ranges and were similar across chest wall injury severity and for patients treated with SSRF or nonoperatively.

Conclusion
While long-term pulmonary function and quality of life recover to values considered normal, subjective thoracic complaints such as pain and dyspnea remain frequently present following rib fractures. No effect of chest wall injury severity or treatment modality on long-term outcomes was demonstrated.

INTRODUCTION

Rib fractures are present in 10% of all trauma admissions and the most common bony injury following blunt chest trauma [1-5]. Most literature on patients with rib fractures focuses on the acute and subacute setting while studies on long-term outcomes often only evaluate a single outcome or the effect of one treatment modality. Persistent pain after sustaining traumatic rib fractures is common and the number of rib fractures has been correlated with posttraumatic pain and opioid dosage consumption [6, 7]. Studies have shown persistent chest pain and disability in 25-50% of patients with rib fractures six months after the trauma [8, 9]. Quality of life may also be significantly impacted after sustaining rib fractures, as at three months, patients still report significant challenges during activities of daily living (ADL) and slow recovery [10]. Rib fractures have also been shown to affect pulmonary function. Reduced pulmonary function after thoracic trauma is associated with poor outcome in the acute setting such as longer hospital length of stay and a higher risk of pulmonary complications [11, 12]. Pulmonary function at one year after rib fractures has been shown to recover to values similar to a healthy reference population [13]. Literature on pulmonary function after this first year following trauma or the effect of chest wall injury severity on these outcomes is still scarce.

The practice of surgical stabilization of rib fractures (SSRF) has become an important modality in rib fracture management [14, 15]. A beneficial effect of SSRF over non-operative management on pain in patients with multiple (≥3) rib fractures has been seen up to two months after trauma, but a long-term benefit of SSRF on thoracic pain has not yet been demonstrated [13, 16, 17]. Also, whether SSRF is associated with quicker return to work and better functional status as compared to nonoperative treatment remains a matter of debate [13, 17-20]. Thus, while both literature on rib fractures and the use of SSRF are increasing rapidly, the effect of treatment modality or chest wall injury severity on combined long-term outcomes remains uncertain.

This observational cohort study aimed to determine the long-term outcomes pulmonary function, thoracic pain, and quality of life in patients admitted with one or more rib fractures, and assess the effect of chest wall injury severity and treatment modality on these outcomes. We hypothesized that, in the long-term, pulmonary function and quality of life recover to values considered normal, but thoracic pain remains common, irrespective of initial chest wall injury severity and treatment modality.

METHODS

Design and participants

An observational cohort study with retrospective collection of clinical data and a single follow-up measurement was conducted at a Level I trauma center. Approval by the local medical research ethics committee was obtained. All patients aged 16 years or older at time of the initial trauma who sustained at least one fractured rib (as confirmed on chest computed tomography [CT]) after blunt force chest trauma and were treated at Erasmus MC since January 1, 2012 with a minimal follow-up of six months were eligible for inclusion. All patients provided written informed consent.

Patients were identified based upon registration in the Dutch national trauma registry. Patients with any of the following criteria were excluded: (1) rib fracture(s) sustained due to cardiopulmonary resuscitation; (2) history of thoracic or pulmonary complaints, either before or since sustaining rib fracture(s) (e.g., thoracic malignancy, other traumatic thoracic injuries or surgery, Chronic Obstructive Pulmonary Disease (COPD), chronic nonspecific respiratory conditions such as asthma and pulmonary emphysema), or medication use for pulmonary conditions, as this would impact the primary outcome of pulmonary function; (3) transferred to another hospital during clinical admission; (4) insufficient comprehension of Dutch language to understand the study information or moved abroad; (5) no known or incorrect contact information (6) verbal or written rejection of participation. Given the exploratory nature of this study, a formal sample size calculation was not made.

Data collection and outcome measures

Data were extracted from the patient's medical files. A single follow-up visit at the outpatient department or home of the patient was performed, by trained researchers, for measurement of the pulmonary function and filling out questionnaires on thoracic pain and quality of life. Pulmonary function served as the primary outcome measure and was measured using a spirometer (Microloop ML3535 MK8 spirometer, PT Medical, Leek, The Netherlands), compliant to American Thoracic Society's and European Respiratory Society's standard [21, 22]. The pulmonary function comprised forced vital capacity (FVC) (primary outcome measure), forced expiratory volume at 1 second (FEV1), vital capacity (VC), forced inspiratory vital capacity (FIVC), and tidal volume (TV). This was expressed in liters (L) for all pulmonary parameters and for the FVC and FEV1 in the percentage of the predicted individual's FVC (FVC% predicted) and FEV1 (FEV1% predicted). The predicted value was based on a healthy reference population with similar sex, age, ethnicity, length, weight, and smoking status. A value of 80% or higher was considered normal.

During the patient visit, patients were asked to complete three questionnaires,

which served as secondary outcome measures. Thoracic pain (Numeric Rating Scale [NRS], 0-10, where 0 indicates no pain and 10 indicates extreme pain) was evaluated for five daily activities: maximal inspiration, in rest, at night, during self-care, and ADL. Also, analgesic medication use for thoracic pain at follow-up was assessed. Health-related quality of life was determined using the Short Form-12 version 2 (SF-12v2) and EuroQoL-5D-5L (EQ-5D) questionnaires. The 12-item SF-12v2 is a shortened form of the 36-item Short Form-36. It comprises eight health domains that are combined into a physical component summary (PCS) and a mental component summary (MCS), both presented as an utility score (US) for which data is normalized to a mean of 50 and standard deviation of 10, using the American population of 1998 [23]. The 5 level EQ-5D consists of a descriptive system on perceived problems in five dimensions (i.e., mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), that is used to calculate an US ranging from 0 to 1. In addition, the EQ-5D has a visual analog scale (VAS) which records self-related health on a scale of zero to 100. Both for the US and VAS, increasing scores indicate better quality of life [24]. For the American population, a US of 0.83 and VAS score of 75 are considered normal [25].

The following data were collected from the patients' medical files: patient characteristics (i.e., age, gender, and smoking status at age of trauma) and injury-related variables (i.e., number of rib fractures, affected side (unilateral or bilateral), Injury Severity Score [ISS], severe concomitant injury of the head (defined as an Abbreviated Injury Scale [AIS] of 3 or higher), presence of thoracic injuries (e.g., flail chest [defined as three or more consecutive ribs fractured in two or more places [26]], pulmonary contusion, or fracture of the thoracic spine, sternum, clavicle, or scapula).

The following treatment- and in-hospital variables were collected: treatment (SSRF or nonoperative), surgical delay between trauma and SSRF (days), mechanical ventilation requirement, Intensive Care Unit (ICU) admission and ICU length of stay (ICU LOS) and hospital length of stay (HLOS). Thoracic complications requiring antibiotics (e.g., pneumonia (as diagnosed following the criteria of the Centers of Disease Control and Prevention [27]) or a surgical re-intervention (i.e., thoracotomy, video-assisted thoracoscopic surgery [VATS], hardware removal, tracheostomy, or additional chest tube drainage) were collected. Complications related to SSRF such as hardware failure requiring hardware removal, and symptomatic nonunion (diagnosed on chest CT, at least 6 months after trauma) were also collected.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 25.0 (SPSS, Chicago, IL). Normality of continuous variables was tested with the Shapiro-Wilk test, and homogeneity of variances was tested using the Levene's test. A p value lower than 0.05 was considered statistically significant and all tests were two-sided.

Descriptive analysis was performed in order to report data for the entire study population and for increasing chest wall injury severity. In order to generate representative groups with increasing chest wall injury severity, based on currently available literature and terminology, patients were divided in the following three groups: one or two rib fractures, multiple (≥3) rib fractures, or a flail chest. Subgroup analysis was performed for patients with ≥3 rib fractures, treated with SSRF or nonoperatively.

Continuous data are reported as median and percentiles, categorical data as numbers and frequencies. Statistical significance between groups has been determined using, as applicable, Mann-Whitney U test (two groups) or analysis for variance test (>2 groups) for continuous data and χ2 or Fisher's Exact test for categorical data.

For the long-term outcomes spirometry, quality of life, and thoracic pain, multivariable analysis was applied to compare the effect of SSRF versus nonoperative treatment in patients with multiple rib fractures or a flail chest. Logistic and linear regression models were developed for binary and continuous outcomes, respectively. A potential confounding effect was assessed for patient demographics, injury, and treatment characteristics with a known possible confounding effect or a p value less than 0.01 in the univariate analysis. This included the covariates age, sex, smoking status at age of trauma, number of ribs fractured, presence of a flail chest, pulmonary contusion, AIS head score of 3 or higher (≥3), ICU admission, mechanical ventilation requirement, presence of a thoracic complication during primary hospital stay, and the time to follow-up (months; within vs. over 1 year; within vs. over 2 years after trauma). Covariates with a statistically significant correlation with the outcomes and/or a statistically significant Odds Ratio (OR) or β value were included in the final regression model. These were the parameters sex, smoking status at age of trauma, AIS head score ≥3, thoracic complication during primary hospital stay, and time to follow-up (months). The crude regression model included the outcome measure as the dependent variable and SSRF as covariate. In the adjusted analysis, the covariates mentioned above were added. For binary regression analysis, the OR for SSRF over nonoperative treatment was reported with the 95% confidence interval (CI) and p value. For linear regression analysis, the β value with the 95% CI and p value was reported.

RESULTS

In total, 300 of 1,039 (28.9%) patients admitted with one or more rib fractures were included for analysis with a median time to follow-up of 39 months (P_{25}-P_{75}, 18-65 months; Figure 1). The most common exclusion criterion was rejection to participate (n = 287). A total of 52 (17.3%) patients had one or two rib fractures, 201 (67.0%) patients had ≥3 rib fractures, and 47 (15.7%) patients had a flail chest.
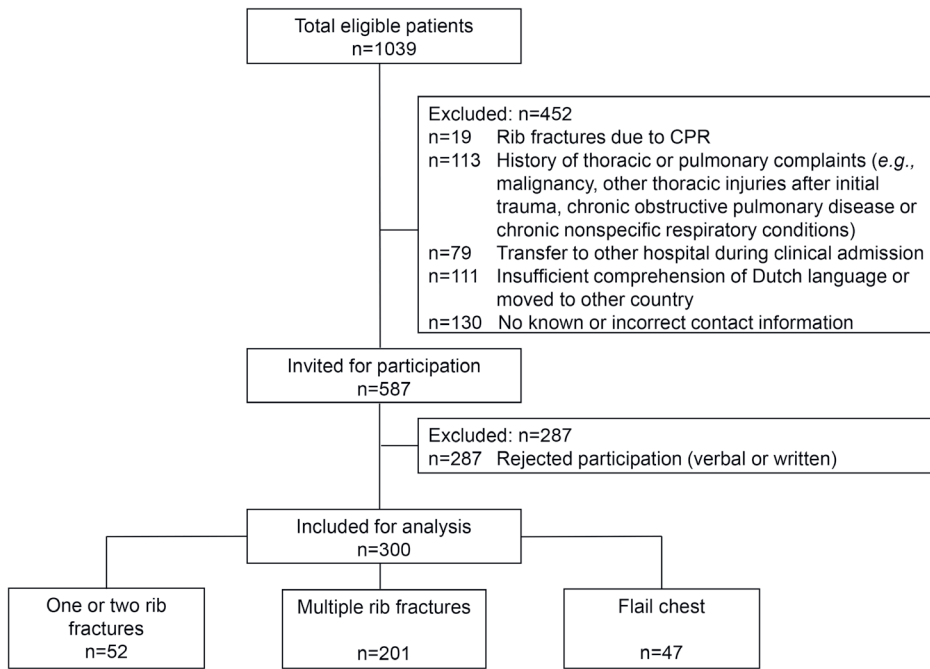
FIGURE 1
Study flowchart.

The total cohort had a median age of 53 years (P_{25}-P_{75}, 40-63 years) and sustained a median of 5 (P_{25}-P_{75}, 3-7) rib fractures which was significantly different across the groups (2 [P_{25}-P_{75}, 1-2] in patients with one or two rib fractures vs. 5 [P_{25}-P_{75}, 4-7] in those with ≥3 rib fractures vs. 8 [P_{25}-P_{75}, 6-10] in patients with a flail chest; p < 0.001; Table 1). In addition, the ISS, rate of bilateral rib fractures, fractures of ribs 1 to 2 and 3 to 10, and intrathoracic injuries (i.e., pneumothorax or hemothorax, or pulmonary contusion), increased with the severity of the chest wall injury . In total, 86 (28.7%) patients had severe concomitant head injury (AIS score, ≥3) with similar rates across the groups (p = 0.778). Except for the chest and neck, the rate of severe concomitant injuries (AIS score, ≥3) for the other body regions were similar across the groups (Supplemental Table 1).

A total of 113 (37.7%) patients required ICU admission with a median ICU LOS of 6 days (P_{25}-P_{75}, 3-11 days) and 73 (24.3%) patients required mechanical ventilation. The median HLOS for the total cohort was 10 days (P_{25}-P_{75}, 6-20 days). The median ICU LOS was similar across the groups, but the ICU admission, mechanical ventilation rate, and thoracic complication rate increased with the severity of the chest wall injury (Table 1). The median HLOS was 10 (P_{25}-P_{75}, 6-20) days and highest in patients with a flail chest

(19 days; P_{25}-P_{75}, 12-25). The rate of non-SSRF-related thoracic complications did not differ between the groups, but the number of required non-SSRF related surgical re-interventions increased with the chest wall injury severity (Table 1).

Table 2 depicts the long-term outcomes for the total cohort. The median FVC, L was significantly different between the chest wall injury severity groups: for patients with one or two rib fractures 4.2 L (P_{25}-P_{75}, 3.7-5.1 L), for ≥3 rib fractures 3.7 L (P_{25}-P_{75}, 3.0-4.6), and for a flail chest 3.7 L (P_{25}-P_{75}, 3.2-4.5; p = 0.014). This difference was also statistically significant between the groups one or two rib fractures versus ≥3 rib fractures (p=0.006) and one or two rib fractures versus a flail chest (p = 0.011; Table 2). The predicted individual's FVC and FEV1, %, corrected for baseline characteristics, as well as most other spirometry variables were similar across the groups (Table 2). For the entire study population and stratified for chest wall injury severity, no statistical difference was seen for any spirometry parameter when corrected for time to follow-up (months) or follow-up within versus over 1 year after trauma.

Chest tightness was reported in 48 patients (16.0%) of the total cohort (Table 2). Of patients experiencing dyspnea, 70 (45.4%) experienced dyspnea in rest or during mild effort.

Thoracic pain (NRS > 0) was reported by 116 (38.7%) patients of the total cohort of whom 64 (55.2%) experienced moderate to severe pain (NRS > 3) during at least one of the five evaluated daily activities. No difference was demonstrated across the groups in the number of patients who reported moderate to severe thoracic pain (Figure 2). A total of 19 (6.3%) patients used daily pain medication for thoracic pain at follow-up. Twelve patients required a non-steroidal anti-inflammatory drug or acetaminophen and seven patients required at least one opioid. Of these patients, two (10.5%) had underwent SSRF and used acetaminophen at follow-up.

The SF-12 quality of life questionnaire showed a median PCS score of 45 (P_{25}-P_{75}, 38-54) and MCS score of 53 (P_{25}-P_{75}, 43-60) in the total cohort with similar scores across the groups (Table 2). The median EQ-5D US was 0.82 (P_{25}-P_{75}, 0.66-0.92) and median EQ-5D VAS score was 75 (P_{25}-P_{75}, 70-85) for the entire group. The EQ-5D US and VAS were similar across the chest wall injury severity groups (Table 2).

Subgroup analysis was performed for patients with ≥3 rib fractures, stratified for treatment modality. The nonoperative group was statistically significantly younger than the SSRF group (54 years; P_{25}-P_{75}, 42-63 and 59 years; P_{25}-P_{75}, 49-70, respectively) but had similar rates of severe concomitant injuries (Supplemental Table 2; Supplemental Table 3). The SSRF group more often had intrathoracic injuries such as a flail chest and pulmonary contusion than the nonoperative group (20 [59%] vs. 27 [12.6%]; p < 0.001 and 25 [76%] vs. 116 [54.2%]; p = 0.023, respectively; Supplemental Table 2). Surgical stabilization of rib fractures was performed at a median of 2 days after injury (P_{25}-P_{75}, 1-3 days). In the acute setting, the SSRF group more often required mechanical ventilation

TABLE 1
Demographics, injury characteristics, in-hospital outcome, and complications in patients admitted with one or two rib fractures, ≥3 rib fractures, or flail chest.

	Overall	One or Two Rib Fractures	≥3 Rib Fractures	Flail Chest	p
	(n = 300)	(n = 52)	(n = 201)	(n = 47)	
Patient characteristics					
Age (y)	53 (40-63)	46 (29-57)	54 (23-64)	55 (44-64)	**0.007***
Sex (male)	225 (75.0%)	38 (73.1%)	151 (75.1%)	36 (76.6%)	0.919
Smoking at age of trauma	66 (22.0%)	17 (32.7%)	40 (19.9%)	9 (19.1%)	0.122
Injury characteristics					
No. of ribs fractured	5 (3-7)	2 (1-2)	5 (4-7)	8 (6-10)	**<0.001****
Bilateral rib fractures	74 (24.7%)	2 (3.8%)	59 (29.4%)	13 (27.7%)	**<0.001**
Fracture of ribs 1-2	137 (45.7%)	12 (23.1%)	91 (45.3%)	34 (72.3%)	**<0.001**
Fracture of ribs 3-10	281 (93.7%)	38 (73.1%)	196 (97.5%)	47 (100%)	**<0.001**
Fracture of ribs 11-12	60 (20.0%)	9 (17.3%)	36 (17.9%)	15 (31.9%)	0.084
Additional thoracic injury					
Pneumothorax	149 (53.0%)	25 (48.1%)	94 (46.8%)	40 (85.1%)	**<0.001**
Hemothorax	108 (36.0%)	6 (11.5%)	68 (33.8%)	34 (72.3%)	**<0.001**
Pulmonary contusion	162 (54.0%)	21 (40.4%)	106 (52.7%)	35 (74.5%)	**0.003**
Sternal fracture	35 (11.7%)	3 (5.8%)	24 (11.9%)	8 (17.0%)	0.215
Clavicular fracture	73 (24.3%)	7 (13.5%)	50 (24.9%)	16 (34.0%)	0.056
Scapular fracture	57 (19.0%)	9 (17.3%)	35 (17.4%)	13 (27.7%)	0.257
Thoracic vertebral fracture	75 (25.0%)	9 (17.3%)	52 (25.9%)	14 (29.8%)	0.317
ISS	19 (14-29)	14 (9-20)	19 (14-27)	27 (19-35)	**<0.001†**
AIS head score ≥3	86 (28.7%)	13 (25.0%)	60 (29.9%)	13 (27.7%)	0.778
AIS chest score ≥3	254 (85.7%)	15 (28.8%)	192 (95.5%)	47 (100%)	**<0.001**
Duration of follow-up (mo)	39 (18-65)	46 (13-72)	40 (19-62)	36 (19-64)	0.847
In hospital outcome					
Mechanical ventilation	73 (24.3%)	8 (15.4%)	47 (23.4%)	18 (38.3%)	**0.026**
ICU admission	113 (37.7%)	14 (26.9%)	69 (34.3%)	30 (63.8%)	**<0.001**
ICU LOS (d)	6 (3-11)	4 (2-17)	7 (3-12)	8 (3-11)	0.470
HLOS (d)	10 (6-20)	7 (5-13)	10 (6-18)	19 (12-25)	**<0.001‡**
Complications					
Thoracic complications	49 (16.3%)	7 (13.5%)	28 (13.9%)	14 (29.8%)	**0.025**
Non-SSRF related	45 (15.0%)	6 (11.5%)	27 (13.4%)	12 (25.5%)	0.084
Pneumonia	29 (9.7%)	5 (9.6%)	16 (8.0%)	8 (17.0%)	0.167
Pleural empyema	7 (2.3%)	0 (0.0%)	5 (2.5%)	2 (4.3%)	0.363
Retained hemothorax	4 (1.3%)	0 (0.0%)	2 (1.0%)	2 (4.3%)	0.140

TABLE 1 continued from page 97

	Overall	One or Two Rib Fractures	≥3 Rib Fractures	Flail Chest	p
	(n = 300)	(n = 52)	(n = 201)	(n = 47)	
Pleural effusion	6 (2.0%)	1 (1.9%)	4 (2.0%)	1 (2.1%)	0.997
Nonunion	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (2.1%)	0.067
Persistent pain	1 (0.3%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0.781
SSRF related§					
Hardware complaints	4 (11.4%)	1 (100%)	1 (7.1%)	2 (10.0%)	**0.018**
Hardware failure	2 (5.7%)	0 (0.0%)	0 (0.0%)	2 (10.0%)	0.451
Postoperative bleeding	1 (2.9%)	0 (0.0%)	0 (0.0%)	1 (5.0%)	0.680
Surgical reinterventions	28 (9.3%)	2 (3.8%)	16 (8.0%)	10 (21.3%)	**0.006**
Non-SSRF related	24 (8.0%)	1 (1.9%)	15 (7.5%)	8 (17.0%)	**0.019**
Chest tube drainage	15 (5.0%)	1 (1.9%)	10 (5.0%)	4 (8.5%)	0.324
Tracheostomy	5 (1.7%)	0 (0.0%)	4 (2.0%)	1 (2.1%)	0.586
VATS	3 (1.0%)	0 (0.0%)	1 (0.5%)	2 (4.3%)	**0.048**
Thoracotomy	3 (1.0%)	0 (0.0%)	1 (0.5%)	2 (4.3%)	**0.048**
SSRF related§					
Hardware removal	6 (17.1%)	1 (100%)	1 (7.1%)	4 (20.0%)	0.051

AIS, abbreviated injury scale; HLOS, hospital length of stay; ICU, Intensive Care Unit; ICU LOS, Intensive Care Unit length of stay; ISS, injury severity score; SSRF, surgical stabilization of rib fractures; VATS, video-assisted thoracoscopic surgery.

Data are shown as median (P_{25}-P_{75}) or as n (%); bold p values are considered statistically significant. There were no missing data.

* Mann-Whitney U test for one or two rib fractures versus ≥3 rib fractures: p = 0.003, one or two rib fractures versus flail chest: p = 0.008, ≥3 rib fractures versus a flail chest: p = 0.754.

** Mann-Whitney U test for one or two rib fractures versus ≥3 rib fractures: p < 0.001; one or two rib fractures versus flail chest: p < 0.001; ≥3 rib fractures versus a flail chest: p < 0.001.

† Mann-Whitney U test for one or two rib fractures versus ≥3 rib fractures: p < 0.001; one or two rib fractures versus flail chest: p < 0.001; ≥3 rib fractures versus flail chest: p = 0.001.

‡ Mann-Whitney U test for one or two rib fractures versus ≥3 rib fractures: p = 0.010; one or two rib fractures versus flail chest: p < 0.001; ≥3 rib fractures versus flail chest: p < 0.001.

§ this only accounts for patients who underwent SSRF (n=35).

and ICU admission, had similar ICU LOS, but a significantly longer HLOS than the nonoperative group (Supplemental Table 2). The rate of non-SSRF related thoracic complications was similar across groups. Complications after SSRF were seen in six (18%) patients. One patient had a postoperative bleeding which required a VATS and blood transfusion. Five (15%) patients had their hardware removed after SSRF; two patients because of hardware failure (breakage of one or more plates), and three patients because of subjective complaints or functional disability attributable to the plates. In all patients who underwent hardware removal, the fixated fractures showed full consolidation on thoracic CT.
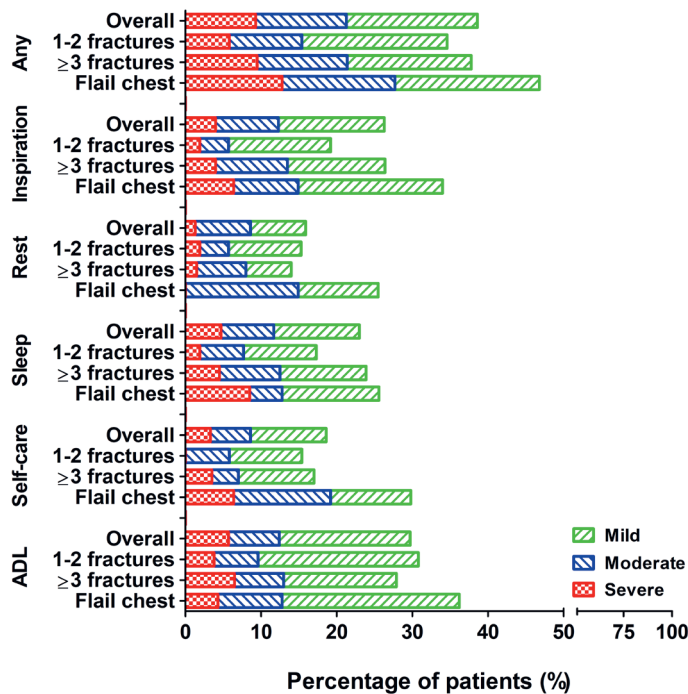
FIGURE 2
Thoracic pain per group for the different moments, stratified by rib fracture severity.
ADL, activities of daily living. Mild pain, NRS 1-3; moderate pain, NRS 4-6; severe pain, NRS 7-10.

In the univariate analysis, the long-term predicted individual's FVC, % and FEV1, %, returned to normal and were similar between the SSRF and nonoperative group (Table 3). The FIVC was higher in the nonoperative group than in the SSRF group (3.2 L [P_{25}-P_{75}, 2.6-4.0] vs. 2.6 L [P_{25}-P_{75}, 2.3-3.3]; p = 0.006). The rate of reported chest tightness, dyspnea, and thoracic pain was equally distributed across both treatment groups (Figure 3; Table 3). In addition, the quality of life was similar across both groups.

After multivariable analysis, the FEV1, L and FIVC, L were significantly lower in the SSRF group in the unadjusted analysis (β, -0.35; 95% CI, -0.68 to -0.03; p = 0.034 and β, -0.49; 95% CI, -0.86 to -0.13; p = 0.008, respectively). The other outcome measures were similar between groups (Table 3).

In the adjusted multivariable analysis, the FEV1, L (β, -0.35; 95% CI, -0.65 to -0.04; p = 0.026), and FIVC, L (β, -0.48; 95% CI, -0.80 to -0.15; p = 0.004), remained significantly lower in the SSRF group. The quality of life and rate of moderate to severe thoracic pain remained similar in both groups (Table 3).

TABLE 2
Long-term pulmonary function, thoracic pain, and quality of life in patients admitted with one or two rib fractures, ≥3 rib fractures, or a flail chest.

	Overall (n=300)		One or Two Rib Fractures (n=52)		≥3 Rib Fractures (n=201)		Flail Chest (n=47)		p
	n*		n*		n*		n*		
Spirometry									
FVC (L)	298	3.8 (3.0-4.6)	52	4.2 (3.7-5.1)	199	3.7 (3.0-4.6)	47	3.7 (3.2-4.5)	**0.014****
FVC (%)	298	84.7 (74.3-93.7)	52	88.2 (75.6-98.6)	199	85.0 (74.0-93.7)	47	81.3 (74.3-93.0)	0.220
FEV1 (L)	298	3.0 (2.5-3.8)	52	3.3 (3.0-4.2)	199	3.0 (2.4-3.8)	47	2.9 (2.6-3.7)	0.051
FEV1 (%)	298	86.3 (75.3-97.0)	52	92.0 (81.0-100.3)	199	86.3 (74.0-96.3)	47	83.0 (75.3-95.3)	0.054
VC (L)	296	1.0 (0.7-1.5)	51	1.2 (0.8-1.6)	198	1.0 (0.7-1.4)	47	0.9 (0.6-1.3)	0.064
FIVC (L)	298	3.3 (2.5-3.9)	52	3.6 (3.0-4.1)	199	3.2 (2.5-3.9)	47	3.0 (2.4-3.8)	**0.039†**
TV (L)	298	0.9 (0.6-1.2)	51	1.0 (0.7-1.5)	200	0.8 (0.6-1.2)	47	0.7 (0.6-1.1)	0.051
Chest tightness	300	48 (16.0%)	52	8 (15.4%)	201	27 (13.4%)	47	13 (27.7%)	0.056
Dyspnea	300	154 (51.3%)	52	22 (42.3%)	201	108 (53.7%)	47	24 (51.1%)	0.340
In rest	154	13 (8.4%)	22	3 (13.6%)	108	8 (7.4%)	24	2 (8.3%)	0.607
Mild effort (*e.g.*, work)	154	57 (37.0%)	22	6 (27.3%)	108	44 (40.7%)	24	7 (29.2%)	
Large effort (*e.g.*, sports)	154	84 (54.5%)	22	13 (59.1%)	108	56 (51.9%)	24	15 (62.5%)	
Pain medication use at FU	300	19 (6.3%)	52	1 (1.9%)	201	13 (6.5%)	47	5 (10.6%)	0.204
Pain (NRS > 0)	300	116 (38.7%)	52	18 (34.6%)	201	76 (37.8%)	47	22 (46.8%)	0.420
SF-12v2									
PCS	300	45 (38-54)	52	467 (42-54)	201	45 (35-54)	47	46 (38-53)	0.417
MCS	300	53 (43-60)	52	51 (43-58)	201	54 (43-60)	47	53 (37-61)	0.713
EQ-5D-5L									
US	300	0.82 (0.66-0.92)	52	0.82 (0.71-0.91)	201	0.82 (0.66-1.00)	47	0.81 (0.64-0.89)	0.808
VAS	300	75 (70-85)	52	75 (66-80)	201	75 (70-85)	47	80 (65-90)	0.643

Data are shown as median (P$_{25}$-P$_{75}$), or as n (%); bold p values are considered statistically significant.
* provides the exact number of patients for which the parameter was known. ** Mann-Whitney *U* test for one or two rib fractures versus ≥3 rib fractures: *p* = 0.006; one or two rib fractures versus flail chest: *p* = 0.011; ≥3 rib fractures versus flail chest: *p* = 0.977. † Mann-Whitney U-test for one or two rib fractures versus ≥3 rib fractures: p=0.023; one or two rib fractures versus flail chest: p=0.021; ≥3 rib fractures versus flail chest: p=0.488. EQ-5D-5L, EuroQol-5D-5L; FEV1, forced expiratory volume at 1 second; FIVC, forced inspiratory vital capacity; FU, follow-up; FVC, forced vital capacity; IC, inspiratory capacity; MCS, mental health component summary; NRS, numeric rating scale; PCS, physical component summary; SF-12v2, Short Form-12 version 2; TV, tidal volume; US, utility score; VAS, visual analog scale.
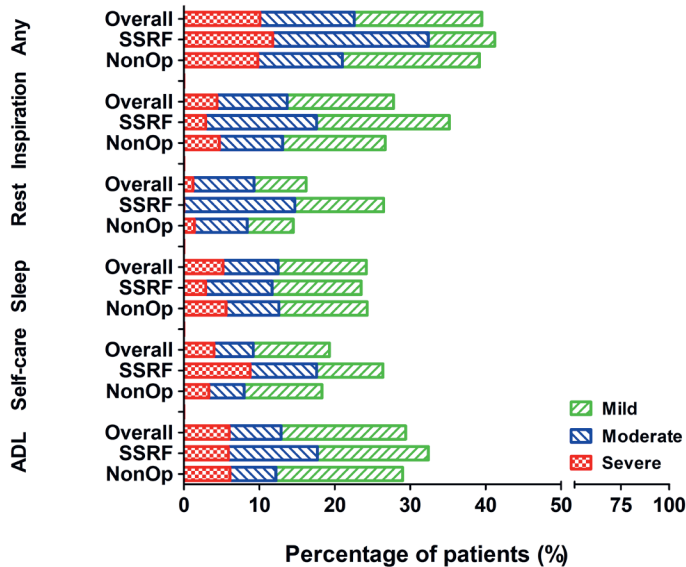
FIGURE 3
Reported thoracic pain scores (for the different moments, stratified for treatment modality.
ADL, activities of daily living. Mild pain, NRS 1-3; moderate pain, NRS 4-6; severe pain, NRS 7-10.

DISCUSSION

This study is the first to combine and evaluate long-term outcomes in patients admitted with rib fractures after blunt thoracic trauma, stratified for chest wall injury severity and treatment modality. In this cohort, pulmonary function recovered to normal values in the long-term, also after stratification for chest wall injury severity or treatment modality. In addition, the median quality of life returned to normal. Nevertheless, long-term debilitating subjective complaints such as moderate to severe thoracic pain (NRS > 3), dyspnea in rest or during mild effort (e.g., work), and chest tightness were experienced by 21%, 23%, and 16% of patients, respectively. While sustaining more severe (intra)thoracic injuries and similar concomitant associated extrathoracic injuries, long-term pulmonary function, thoracic pain, and quality of life did not differ between patients with one or two rib fractures, three or more rib fractures, or a flail chest at a median of 3 years after trauma. Patients treated with SSRF, while older and with more severe thoracic injuries, had similar long-term outcomes as nonoperatively treated patients.

TABLE 3
Univariate and multivariable long-term spirometry, quality of life, and pain after SSRF versus nonoperative treatment in patients with ≥3 rib fractures or a flail chest.

| | Univariate Analysis | | | | | Multivariable Analysis | | | | | |
| | SSRF (n=34) | | Nonoperative (n=214) | | | Crude Analysis | | | Adjusted Analysis | | |
Outcome	n*		n*		p	n*	β or OR (95% CI)	p	n*	β or OR (95% CI)	p
Spirometry											
FVC (L)	34	3.4 (2.6-4.4)	212	3.8 (3.0-4.6)	0.106	245	-0.34 (-0.73 to 0.06)	0.093	245	-0.33 (-0.69 to 0.03)	0.075
FVC (%)	34	83.0 (68.8-93.1)	212	84.3 (74.3-93.6)	0.563	245	-1.67 (-7.12 to 3.79)	0.548	245	-2.65 (-8.27 to 2.99)	0.354
FEV1 (L)	34	2.6 (2.0-3.2)	212	3.0 (2.4-3.8)	**0.044**	245	-0.35 (-0.68 to -0.03)	**0.034**	245	-0.35 (-0.65 to -0.04)	**0.026**
FEV1 (%)	34	83.3 (74.0-93.3)	212	85.8 (75.1-96.3)	0.280	245	-2.85 (-8.82 to 3.13)	0.349	245	-4.44 (-10.51 to 1.62)	0.150
VC (L)	34	0.9 (0.6-1.4)	211	1.0 (0.7-1.4)	0.238	244	0.01 (-0.21 to 0.22)	0.947	244	0.08 (-0.14 to 0.29)	0.484
FIVC (L)	34	2.6 (2.3-3.3)	212	3.2 (2.6-4.0)	**0.006**	245	-0.49 (-0.86 to -0.13)	**0.008**	245	-0.48 (-0.80 to -0.15)	**0.004**
TV (L)	34	0.8 (0.5-1.3)	213	0.8 (0.6-1.2)	0.430	246	0.01 (-0.19 to 0.21)	0.936	246	0.05 (-0.15 to 0.26)	0.604
SF-12v2											
PCS	34	48 (34-55)	214	45 (36-54)	0.733	247	1.03 (-3.05 to 5.11)	0.619	247	2.44 (-1.63 to 6.50)	0.239
MCS	34	56 (39-62)	214	53 (43-60)	0.524	247	0.48 (-3.95 to 4.91)	0.833	247	-0.42 (-4.82 to 3.98)	0.852
EQ-5D-5L											
US	34	0.82 (0.63-0.92)	214	0.81 (0.66-0.94)	0.863	247	-0.01 (-0.11 to 0.09)	0.866	247	0.00 (-0.10 to 0.10)	0.933
VAS	34	80 (70-90)	214	75 (70-85)	0.093	247	4.82 (-1.29 to 10.93)	0.121	247	5.41 (-0.66 to 11.48)	0.080
Moderate to severe thoracic pain (NRS > 3)											
Overall	34	11 (32.4%)	214	45 (21.0%)	0.183	248	1.80 (0.82-3.96)	0.146	248	2.28 (0.95-5.45)	0.064
Inspiration	34	6 (17.6%)	214	28 (13.1%)	0.431	248	1.42 (0.54-3.74)	0.474	248	1.44 (0.63-3.32)	0.381
In rest	34	5 (14.7%)	214	18 (8.4%)	0.334	248	1.88 (0.65-5.45)	0.246	248	1.93 (0.61-6.10)	0.264
At night	34	4 (11.8%)	214	27 (12.6%)	1.000	248	0.92 (0.30-2.83)	0.889	248	1.07 (0.33-3.50)	0.910
Self-care	34	6 (17.6%)	214	17 (7.9%)	0.103	248	2.48 (0.90-6.83)	0.078	248	2.53 (0.84-7.59)	0.099
ADL	34	6 (17.6%)	214	26 (12.1%)	0.408	248	1.55 (0.59-4.10)	0.377	248	2.14 (0.72-6.30)	0.169

ORs and β values are shown with 95% CI; bold p values are considered statistically significant.
*: provides the exact number of patients for which the outcome measure was known.
The multivariable analysis shows the effect of SSRF over nonoperative treatment. In the corrected analysis, sex, smoking status at age of trauma, AIS head score ≥3, thoracic complication during primary hospital stay, and time to follow-up visit (months) were entered as covariate.
ADL, activities of daily living; EQ-5D-5L, EuroQol-5D-5L; FEV1, forced expiratory volume at 1 second; FIVC, forced inspiratory vital capacity; IC, inspiratory capacity; MCS, mental health component summary; NRS, numeric rating scale; PCS, physical component summary; SF-12v2, Short Form-12 version 2; TV, tidal volume; US, utility score; VAS, visual analog scale.

Most literature on pulmonary function after rib fractures focuses on the first six months after trauma or compares SSRF with nonoperative treatment. This study shows recovery of the predicted FVC and FEV1 percentages to normal values on the long-term. This is in line with previously described normalized (>80%) predicted FVC and FEV1, %, values at 12 months to 48 months after sustaining rib fractures [13, 28]. The recovery of pulmonary function does not appear to be impacted by initial chest wall injury severity. Similarly, time to follow up and follow-up within versus over 1 year after trauma did not statistically significantly impact pulmonary function. A previously described reduction of total pulmonary diffusing capacity and pulmonary ventilation impairment due to chest wall injury, precipitating reduced FVC and FEV1, thus appears to recover over time, likely within the first year [29]. Previous literature only evaluating long-term pulmonary function after SSRF showed satisfactory recovery of the corrected FEV1 and FVC to above 83% at 26 months, comparable to the current SSRF cohort's FEV1 and FVC of both 83% at 23 months [30].

Long-term thoracic pain occurs frequently after rib fractures. In the current study, almost 40% still experienced thoracic pain at a median of 3 years after blunt thoracic trauma. This is in line with a previous cohort of 216 patients in which 43% experienced pain at two years [6, 31]. In addition, a positive effect of SSRF on chronic moderate to severe thoracic pain at three years after trauma could not be demonstrated, concurring with current available studies at 1 and 2 years after trauma [13, 17]. Thus, SSRF might be most effective in the treatment of acute thoracic pain [16].

There was no difference in long-term quality of life across the chest wall injury severity groups. The EQ-5D US of 0.82 and VAS score of 75 in the entire cohort is comparable with the population norm for the Dutch and American population [25]. Thus, acute severe thoracic injuries such as a flail chest, pulmonary contusion, or a high ISS do not appear to affect quality of life in the long-term. This was also reflected by the similar PCS and MCS scores of the SF-12 questionnaire for all groups. These scores indicated sufficient recovery of quality of life as a mean score of 50 with a standard deviation of 10 is considered normal. The PCS score of 45 and MCS score of 54 for the total cohort are similar to a previously described cohort with a PCS score of 43 and MCS score of 50 at 2 years after trauma [31]. When stratified for treatment modality, both the SSRF and nonoperative group had similar adequate recovery of quality of life. Quality of life after SSRF has been reported to recover to a status comparable with that of the general population [32-34]. In our study, quality of life did recover to normal, but SSRF was not associated with improved long-term outcomes as compared to nonoperative treatment. This confirms our hypothesis that the use of SSRF might be most beneficial on short-term outcomes.

Hardware removal rates were high (15%), and mainly necessary due to hardware failure and subjective complaints or functional disability. It has been reported before

that the most common implant-related complication after SSRF is implant irritation which is the most common reason for removal [35]. The hardware failure rate in this study of 6% was higher than the previously described 3% [36]. Although the use of SSRF did not lead to improved long-term outcomes as compared to nonoperative treatment, it must be noted that the SSRF group was older with a higher number of ribs fractured and more often intrathoracic injuries.

When interpreting the outcomes of this study, several limitations should be taken into account. First, the groups investigated might not be representative of patients admitted with rib fractures since it was a single-institution study in a Level I trauma center. Also, only 29% of eligible patients could be included in the analysis, but participation rate after invitation was relatively high (51%). Although this might have introduced selection bias, it is the first study to address combined long-term outcomes after rib fractures, stratified for injury severity and treatment modality. Furthermore, all patients had rib fractures diagnosed and delineated on chest CT which made the classification more reliable as CT imaging is more sensitive than chest radiography for detecting rib fractures [37, 38]. Second, due to the retrospective nature of this study with a single follow-up visit, inherent limitations such as missing data or underreporting might have introduced information bias. Whereas underreporting and the effect of unknown variables might have persisted, there was almost no missing data as the highest rate of missing data was less than 2% (VC). Due to the single follow-up visit, these outcomes only provide a one-time overview. Future prospective studies should incorporate standardized follow-up visits to determine the cohort's progress, societal impact, and evaluate whether one returns to outcomes considered normal quicker. This is currently being done for treatment modality in a multicenter randomized controlled trial during the first year after trauma, but could also be done for several years or stratified for chest wall injury severity [39]. Third, the EQ-5D and SF-12 questionnaires do not specify the origin of the reported problems. With these question-naires, it was not possible to adjust for extra thoracic injuries which might have impeded with the perceived quality of life. The chest wall injury severity groups had different ISS but similar extra thoracic AIS, indicating that the ISS difference was most affected by the thoracic AIS. By focusing on pulmonary function, dyspnea, and thoracic pain, this study also evaluated long-term clinically relevant thoracic problems after rib fractures, besides general quality of life. Fourth, the presented logistic and linear regression model included only collected variables. The effect on non-included para-meters remains unknown.

In summary, long-term pulmonary function and quality of life have normalized in patients admitted with rib fractures 3 years after blunt chest trauma. Sustaining rib fractures does however clinically impact the patient's wellbeing in the long-term as subjective complaints such as chest tightness, dyspnea, and thoracic pain remain

frequently present. No effect of initial chest wall injury severity or treatment modality on these outcomes was demonstrated. As this was a retrospective study, no causality could be proven, but rather an association which warrants further prospective investigation of long-term outcomes after rib fractures and the role of SSRF.

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CHAPTER 5

SUPPLEMENTAL DATA

SUPPLEMENTAL TABLE 1
Additional injury characteristics in patients admitted with one or two rib fractures, ≥3 rib fractures, or flail chest.

	Overall (n=300)	One or two rib fractures (n=52)	≥3 rib fractures (n=201)	Flail chest (n=47)	p
Abbreviated Injury Scale ≥3					
Face	7 (2.3%)	1 (1.9%)	5 (2.5%)	1 (2.1%)	0.967
Neck	3 (1.0%)	0 (0.0%)	1 (0.5%)	2 (4.3%)	**0.048**
Spine	40 (13.3%)	6 (11.5%)	30 (14.9%)	4 (8.5%)	0.465
Abdomen	32 (10.7%)	4 (7.7%)	21 (10.4%)	7 (14.9%)	0.503
Upper extremity	17 (5.7%)	3 (5.8%)	10 (5.0%)	4 (8.5%)	0.640
Lower extremity	70 (23.3%)	11 (21.2%)	43 (21.4%)	16 (34.0%)	0.167
External	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	N.A.

Data are shown as median (P_{25}-P_{75}), or as %); bold p-values are considered statistically significant. There were no missing data.

SUPPLEMENTAL TABLE 2
Demographics, injury characteristics, in-hospital outcome, and complications in patients with multiple rib fractures, treated operatively (SSRF) or nonoperatively.

	Overall (n=248)	SSRF (n=34)	Nonoperative (n=214)	p
Patient characteristics				
Age (years)	54 (43-64)	59 (49-70)	54 (42-63)	**0.035**
Sex (male)	187 (75.4%)	24 (70.6%)	163 (76.2%)	0.521
Smoking at age of trauma	49 (19.8%)	4 (11.8%)	45 (21.0%)	0.253
Injury characteristics				
Number of ribs fractured	6 (4-8)	9 (7-11)	5 (4-7)	**<0.001**
Bilateral rib fractures	72 (29.0%)	11 (32.4%)	61 (28.5%)	0.686
Additional thoracic injury				
Flail chest	47 (19.0%)	20 (58.8%)	27 (12.6%)	**<0.001**
Pneumothorax	134 (54.0%)	28 (82.4%)	106 (49.5%)	**<0.001**
Hemothorax	102 (41.1%)	27 (79.4%)	75 (35.0%)	**<0.001**
Pulmonary contusion	141 (57.1%)	25 (75.8%)	116 (54.2%)	**0.023**
Sternal fracture	32 (13.0%)	6 (18.2%)	26 (12.1%)	0.400
Clavicular fracture	66 (26.6%)	9 (26.5%)	57 (26.6%)	1.000
Scapular fracture	48 (19.4%)	10 (30.3%)	28 (17.8%)	0.100
Thoracic vertebral fracture	66 (26.7%)	11 (33.3%)	55 (25.7%)	0.399
ISS	22 (15-29)	23 (17-29)	20 (14-29)	0.115
AIS Head ≥3	73 (29.4%)	8 (23.5%)	65 (30.4%)	0.544
Duration of follow-up (months)	38 (19-62)	23 (15-38)	42 (21-64)	**0.001**
In-hospital outcome				
Mechanical ventilation	65 (26.2%)	17 (50.0%)	48 (22.4%)	**0.001**
ICU admission	99 (39.9%)	24 (70.6%)	75 (25.0%)	**<0.001**
ICLOS (days)	7 (3-11)	8 (4-13)	6 (3-11)	0.249
HLOS (days)	11 (7-21)	20 (13-26)	10 (6-19)	**<0.001**
Complications				
Thoracic complications	42 (16.9%)	9 (26.5%)	33 (15.4%)	0.137
Non-SSRF related	39 (15.7%)	6 (17.6%)	33 (15.4%)	0.800
Pneumonia	24 (9.7%)	4 (11.8%)	20 (9.3%)	0.753
Pleural empyema	7 (2.8%)	1 (2.9%)	6 (2.8%)	1.000
Retained hemothorax	4 (1.6%)	0 (0.0%)	4 (1.9%)	1.000
Pleural effusion	5 (2.0%)	0 (0.0%)	5 (2.3%)	1.000
Nonunion	1 (0.4%)	1 (2.9%)	0 (0.0%)	0.137
Persistent pain	1 (0.4%)	0 (0.0%)	1 (0.5%)	1.000
Surgical re-interventions	26 (10.5%)	7 (20.6%)	19 (8.9%)	0.063
Non-SSRF related	23 (9.3%)	4 (11.8%)	19 (8.9%)	0.533
Chest tube drainage	14 (5.6%)	1 (2.9%)	13 (6.1%)	0.700
Tracheostomy	5 (2.0%)	1 (2.9%)	4 (1.9%)	0.525
VATS	3 (1.2%)	1 (2.9%)	2 (0.9%)	0.359
Thoracotomy	3 (1.2%)	2 (5.9%)	1 (0.5%)	0.050

AIS, abbreviated injury scale; HLOS, hospital length of stay; ICU, Intensive Care Unit; ICU LOS, Intensive Care Unit length of stay; ISS, injury severity score, SSRF, surgical stabilization of rib fractures; VATS, video-assisted thoracoscopic surgery.
Data are shown as median (P_{25}-P_{75}) or as n (%); bold p-values are considered statistically significant. There were no missing data.

SUPPLEMENTAL TABLE 3
Additional injury characteristics in patients with multiple rib fractures, treated operatively (SSRF) or nonoperatively

	Overall (n=248)	SSRF (n=34)	Nonoperative (n=214)	p
Abbreviated Injury Scale ≥3				
Face	6 (2.4%)	0 (0.0%)	65 (30.4%)	1.000
Neck	3 (1.2%)	1 (2.9%)	2 (0.9%)	0.359
Chest	239 (96.4%)	34 (100.0%)	205 (95.8%)	0.615
Spine	34 (13.7%)	5 (14.7%)	29 (13.6%)	0.792
Abdomen	28 (11.3%)	2 (5.9%)	26 (12.1%)	0.389
Upper extremity	14 (5.6%)	2 (5.9%)	12 (5.6%)	1.000
Lower extremity	59 (23.8%)	7 (20.6%)	52 (24.3%)	0.829
External	0 (0.0%)	0 (0.0%)	0 (0.0%)	N.A.

Data are shown as n (%); bold p-values are considered statistically significant. There were no missing data.

PART III

MANAGEMENT

CHAPTER 6

Operative versus nonoperative treatment of
multiple simple rib fractures:
a systematic review and meta-analysis

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ABSTRACT

Background

Surgical rib stabilization in flail chest is proven to be beneficial over nonoperative treatment in terms of rate of pneumonia, Intensive Care (IC) length of stay (ICLOS) and mechanical ventilation days. The aim of this systematic review and meta-analysis was to evaluate the effect of operative versus non- operative treatment on the occurrence of pneumonia and other relevant clinical outcomes in patients with multiple simple rib fractures.

Methods

A search was performed in Embase, Medline Ovid, Cochrane Central, Web of Science, and Google Scholar. The primary outcome was the occurrence of pneumonia. Secondary outcomes were duration of mechanical ventilation, ICLOS, hospital length of stay (HLOS), mortality, and wound infections. Publication bias was assessed using funnel plots for the outcome measures and random-effect models were used when heterogeneity of data on outcome measures was significant ($I^2 \geq 40\%$).

Results

The search resulted in 592 unique records, of which 14 studies on 13 cohorts were included. The 14 studies comprised five prospective and nine retrospective cohort studies with a cumulative total of 4565 patients. Meta-analysis showed a significant decrease of the occurrence of pneumonia (n = 2659 patients; risk ratio, RR = 0.66; 95% confidential interval [CI] 0.49 to 0.90; p = 0.008), mortality (n = 4456 patients; RR = 0.32; 95% CI 0.19 to 0.54; p < 0.001), and HLOS (n = 648 patients; MD = −5.78 days; 95% CI −10.40 to −1.15; p = 0.01) in favor of operative treatment. No effect of operative treatment was found for the duration of mechanical ventilation (n = 113 patients; MD = −6.01 days; 95% CI = 19.61 to 7.59; p = 0.39) or ICLOS (n = 524 patients; MD = −2.93 days; 95% CI −8.65 to 2.80; p = 0.32). The postoperative wound infection rate ranged from 0 to 9.4%.

Conclusion

Surgical treatment of multiple simple rib fractures may result in a significant reduction of pneumonia, mortality, and hospital length of stay. A reducing effect of treatment on the duration of mechanical ventilation and IC length of stay, was not demonstrated. However, due to nonstandard or absent definitions of outcome measures as well as heterogenous patient groups and the observational design of studies, results must be interpreted with caution and high-quality studies are needed.

INTRODUCTION

Rib fractures are common injuries in both trauma- and non-trauma centers and occur in up to 10–35% of patients after sustaining blunt chest trauma [1,2]. Rib fractures are associated with pulmonary morbidity such as pneumonia in 17–77% of patients and a mortality rate around 10%, with increased rates in the elderly and those with a higher number of rib fractures [1,3–9]. Multiple rib fractures can result in a flail chest, which is defined as fracture of three or more consecutive ribs, in two or more places, creating a unstable or flail segment [8,10]. Patients may also suffer from multiple simple rib fractures without a flail segment.

The traditional treatment of multiple rib fractures has a supportive approach, also known as nonoperative treatment. Nonoperative treatment consists of multimodal systemic or locoregional pain management, bronchodilator inhalers, pulmonary physical therapy, oxygen support, and if necessary mechanical ventilation [11]. Nevertheless, 64% of the patients experience thoracic pain and up to 71% develop disabilities long term after nonoperative treatment [9]. Furthermore, there is a prolonged Intensive Care length of stay (ICLOS) and hospital length of stay (HLOS) in patients suffering from three or more rib fractures [6]. This association is also

seen in the prevalence of pneumonia and mortality; the more rib fractures, the greater the risk of pneumonia and mortality [12–14]. The value of the specific types of analgesic therapies such as epidural or intravenous or nerve blocks seems limited in preventing pneumonia [15].

Evidence suggests that surgical stabilization of a flail chest is beneficial with regards to pneumonia rate, ICLOS, and number of ventilation days [16]. The effect of surgical stabilization for multiple simple rib fractures is still a matter of debate since high level of evidence is lacking. Almost all current studies combined patients with and without a flail chest. Therefore, the aim of this systematic review and meta-analysis was to evaluate the effect of operative versus nonoperative treatment on the occurrence of pneumonia, the duration of mechanical ventilation, ICLOS, HLOS, mortality, and wound infections as reported in patients with multiple simple rib fractures.

METHODS

Search strategy

Databases Embase, Medline OVID, Cochrane Central, Web of Science, and Google scholar were searched systematically for cohort studies comparing operatively and nonoperatively treated patients with multiple simple rib fractures. This systematic review was conducted using the Preferred Reporting Items for Systematic Reviews and

Meta-Analyses (PRISMA) guidelines [17]. A protocol was written before initiation of this review. The literature search was performed by a professional librarian on May 7, 2019. The search terminology combined various terms for multiple simple rib fractures, outcomes and different treatments with this type of injury (Table 1).

TABLE 1
Search strategy per data-bank as performed on May 7, 2019.

Database	Total (N=1,023)	Deduplicated (N=592)
Embase.com (Embase, Medline)	364	357
Medline (OVID)	320	135
Cochrane Central	26	14
Web of Science	213	50
Google Scholar	100	36

Embase.com

('rib fracture'/de/mj OR (((rib*) NEAR/3 (fracture*) NEAR/3 (multiple*)) OR 'rib fractures'):ab,ti) AND ('orthopedic surgery'/de OR 'fracture fixation'/exp OR (fixation* OR splint* OR immobili* OR stabili* OR nail*):ab,ti) AND ('treatment outcome'/exp OR 'clinical effectiveness'/de OR 'hospitalization'/de OR 'prospective study'/de OR 'longitudinal study'/exp OR 'retrospective study'/de OR 'cohort analysis'/de OR (outcome* OR effectiv* OR efficacy OR failur* OR hospitali* OR stay* OR cohort* OR prospecti* OR retrospect* OR 'follow up' OR longitudinal):ab,ti)

Medline Ovid SP

("Rib Fractures"[mh] OR multiple rib fracture*[tiab] OR "rib fractures"[tiab]) AND ("Orthopedic Procedures"[mh] OR Fracture Fixation[mh] OR fixation*[tiab] OR splint*[tiab] OR immobili*[tiab] OR stabili*[tiab] OR nail*[tiab]) AND ("Treatment Outcome"[mh] OR "Hospitalization"[mh] OR "Length of Stay"[mh] OR "Cohort Studies"[mh] OR outcome*[tiab] OR effectiv*[tiab] OR efficacy[tiab] OR failur*[tiab] OR hospitali*[tiab] OR stay*[tiab] OR cohort*[tiab] OR prospecti*[tiab] OR retrospect*[tiab] OR "follow up"[tiab] OR longitudinal[tiab])

Cochrane Central (trials)

(((((rib*) NEAR/3 (fracture*) NEAR/3 (multiple*)) OR 'rib fractures'):ab,ti) AND ((fixation* OR splint* OR immobili* OR stabili* OR nail*):ab,ti) AND ((outcome* OR effectiv* OR efficacy OR failur* OR hospitali* OR stay* OR cohort* OR prospecti* OR retrospect* OR 'follow up' OR longitudinal):ab,ti)

Web of Science

TS=(((((rib*) NEAR/2 (fracture*) NEAR/2 (multiple*)) OR "rib fractures")) AND ((fixation* OR splint* OR immobili* OR stabili* OR nail*)) AND (outcome* OR effectiv* OR efficacy OR failur* OR hospitali* OR stay* OR cohort* OR prospecti* OR retrospect* OR "follow up" OR longitudinal))

Google Scholar

"multiple rib fracture|fractures" fixation|splint|immobilization|stabilization outcomes|effectiveness|efficacy|failure|hospitalization|"length of stay"|cohort|prospective

Study selection, inclusion and exclusion criteria

For inclusion, studies had to compare operative with nonoperative treatment, and report on pneumonia, duration of mechanical ventilation, HLOS, ICLOS, mortality, or occurrence of wound infections in patients with multiple simple rib fractures. Multiple rib fractures was defined as having sustained three or more fractured ribs of ribs 1-12, regardless of side, site, adjacentness, dislocation or level of the fractured rib (1st, 2nd, etc.). Exclusion criteria were studies describing populations in which 50% or more of patients had a flail chest (as evidence is already available showing the beneficial effect of operative treatment regarding pneumonia rate, ICLOS, and mechanical ventilation days over nonoperative treatment [16]), studies that did not compare operative with nonoperative treatment of multiple simple rib fractures, studies that did not report on any of the outcomes of interest, studies in pediatric patients, animal studies, meta-analyses or literature reviews, and manuscripts that were not available to us in full text as no outcome measures or study characteristics could be collected. No language criterion was used. The titles and abstracts of the records were screened independently by three authors for eligibility and any disagreement was resolved by consensus. When an author used the same population in multiple publications, the population was only used once in this review, unless the manuscripts reported different outcome measures. The same authors used the same procedure when reviewing the full text manuscripts. Finally, a manual search of the reference lists of all included studies was performed, in order to avoid any missing relevant publication.

Quality assessment and evaluation of publication bias

The methodological quality of the included studies was assessed using a modified quality assessment for cohort studies derived from the Newcastle-Ottawa Scale (NOS) [18]. Studies were scored for various items by three authors independently and scored 0 when not reported, 1 when reported but inadequate, and 2 adequately reported. This then results in a score ranging from zero to 16 points, with a higher score indicating better quality. Any disagreement was resolved by consensus. Publication bias was determined based upon funnel plots.

Outcomes measures

The primary outcome was the occurrence of pneumonia. Secondary outcome measures were duration of mechanical ventilation, ICLOS, HLOS, mortality, and the occurrence of wound infections.

Data collection

Three authors independently extracted the following data from the included studies: author name, publication year, study period, study design, sample size for operative and nonoperative group, number of patients without a flail chest, number of male patients, age, number of rib fractures, duration of follow-up, surgical technique, and time to surgery. The corresponding authors of the manuscripts were contacted by e-mail and requested for raw data on the subgroup of patients without a flail chest, when the provided data were inadequate for meta-analysis. If they did not respond after two weeks a final reminder was sent.

Data analysis

Meta-analysis of the primary and secondary outcomes was performed using Review-Manager (Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Pooled risk ratio's and mean differences were calculated for binary and continuous variables, respectively. Both are reported with their 95% confidence intervals (CI) and p-value. Subgroup analysis on the outcome measures was performed for different cut-off values of the percentage of patients with multiple simple rib fractures per study (i.e., studies with 60% or more, 70% or more, or 85% of patients without a flail chest). Heterogeneity was quantified with Cochran's Q test and I^2 statistic, a fixed effects model was used when the I^2 was < 40%. A random-effects model was used for the pooled analysis when the I^2 was ≥ 40%. A p-value <0.05 was considered statistically significant.

RESULTS

Search results

A total of 1023 records were retrieved (364 from EMBASE, 320 from Medline Ovid, 26 from Cochrane Central, 216 from Web of Science, and 100 from Google Scholar; Figure 1). After removal of duplicate records (n=431), 592 unique records were screened for eligibility. The most common reasons for exclusion of records was because they did not compare operative with nonoperative treatment of multiple rib fractures (n=400) or because over 50% of the population had a flail chest (n=129). Two studies did not report the rate of patients with a flail chest [19,20]. The corresponding authors were

contacted, and one author confirmed they excluded patients with a flail chest [19]. Finally, 14 manuscripts reporting on 13 different cohorts with a total of 4565 patients fulfilled the inclusion criteria [21–27,19,28–33]. Two publications were written on the same study, but reported on complementary data [24,25].
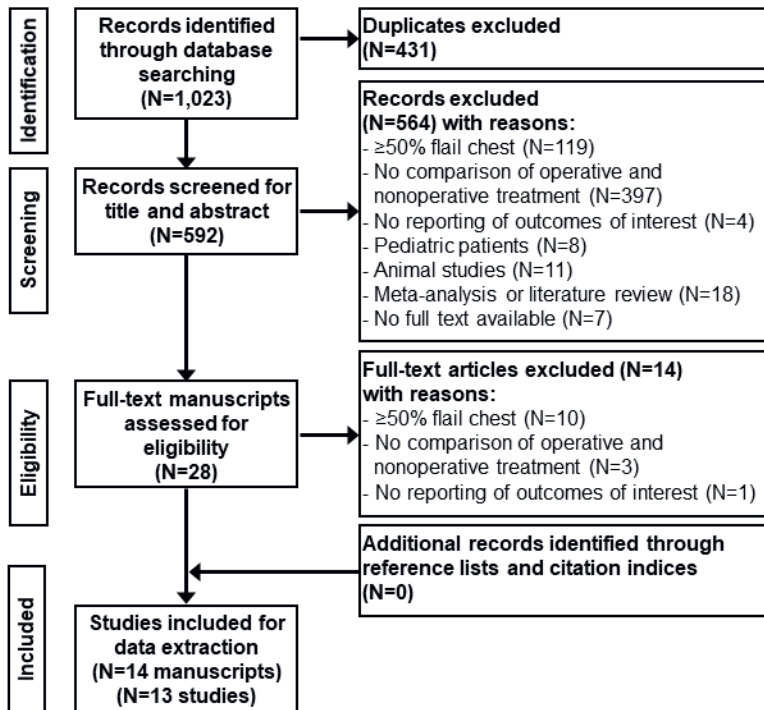
FIGURE 1
Study flow chart.

Study characteristics

Study characteristics are shown in Table 2. From the included manuscripts, five studies were prospective cohort studies [22,23,27,30,32], nine were retrospective studies on eight different cohorts [21,24–26,19,28,29,31,33]. The mean age per study varied from 37 years to 73 years [26,19]. The mean ISS per study varied from 16 to 31 [23,29].The mean number of rib fractures varied from 3 to 8 [21,22]. The percentage of patients without a flail chest per study varied from 54% to 100% [24–26,19]. The percentage operatively treated patients per study varied from 4.5% to 52.5% [22,32]. Most studies used plates for rib fixation (Table 2).

TABLE 2
Overview of included studies comparing operative versus nonoperative treatment.

Author (year)	Study period	Study design	Sample size operated	Sample size not operated	Nr. of patients with simple MRF	Nr. of male patients
			n	n	n (%)	n (%)
De Moya *et al.* (2011) [21]	July 2009 - June 2010	Retrospective cohort	16	32	28 (58)	40(83)
Khandelwal *et al.* (2011) [22]	July 2009 - June 2010	Prospective cohort	32	29	59 (97)	40 (66)
Granhed *et al.* (2014) [23]	September 2010 - July 2012	Prospective cohort	60	153	157 (74)	NA
Majercik *et al.* (2015) [24,25]*	January 2009 - June 2013	Retrospective cohort	137	274	223 (54)	328 (80)
Qiu *et al*. (2016) [26]	January 2006 - May 2013	Retrospective cohort	65	59	124 (100)	88 (70.9)
Tarng *et al.* (2016) [27]	January 2010 - December 2012	Prospective cohort	12	53	56 (86)	64 (98)
Fitzgerald *et al.* (2017) [19]	2003 - 2015	Retrospective cohort	23	50	73 (100)	NA
Uchida *et al*, (2017) [28]	April 2007 - March 2015	Retrospective cohort	10	10	14 (70)	14 (70)
Kane *et al*. (2018) [29]	2007 - 2016	Retrospective cohort	116	1000	1041 (93)	NA
Majeed *et al.* (2018) [30]	January 2017 - March 2018	Prospective cohort	21	22	32 (74)	37 (86)
Fokin *et al.* (2019) [31]	2011 - 2017	Retrospective cohort	87	87	122 (70)	129 (74)
Marasco *et al.* (2019) [32]	January 2012 - April 2015	Prospective cohort	67	1,415	1,309 (88)	1,098 (74)
Shibahashi *et al.* (2019) [33]	2004 - 2015	Retrospective cohort	147	588	456 (62)	536 (73)

ISS, injury severity score; MRF, multiple rib fractures; NA, not available; NO, nonoperative group; O, operative group; SD, standard deviation; TEN, titanium elastic nails. *, these are two studies reporting on the same cohort.

Quality Assessment and evaluation of publication bias

The detailed outcome of the methodological quality assessment, based on the Newcastle-Ottawa Quality assessment scale is shown in Table 3. The average score of the quality assessment was 9 points (range 5-12). The funnel plots did not raise substantial concern for publication bias (Supplemental Figure S1).

Mean age in years (SD/range)	Mean ISS (SD/range)	Mean Nr. of rib fractures (SD/range)	Mean Follow-up (range)	Surgical technique	Mean time to surgery (SD/range)
46 (14.7)	O=24 (7) NO=25 (9)	8 (3.4)	29 days	plates	5 days (1-10)
46.4	NA	3.2	30 days	plates	12 days
57 (19-86)	O=21.7 (10.8) NO=30.9 (13.3)	7.5 (2-14)	1 year	plates and intramedullary splints	median 4 days (1-59)
55 (18.4)	O=21 (10.7) NO=22 (11.8)	5.2 (2)	2 years	plates	NA
37.03	NA	3.34	6 months	plates	NA
47.3 (14.4)	O=21.2 (4.1) NO=26.1 (6.0)	7.33 (1.15)	21 months (18-24)	TEN	4 days
72.8	O=20.7 (15.7-25.7) NO=18.5 (14.3-22.7)	3.5	4 months	plates	NA
O=63 (51-72), NO=57 (53-75)	NA	O=5 (4-6.5), NO=4 (2-7)	NA	plates	4 days (1-7.5)
48.08	O=20.9 (11.4) NO=15.9 (11.5)	NA	NA	plates	NA
51.35 (13.75)	NA	NA	3 months	plates	NA
O=55.9 NO=55.4	O=19.9 NA=19.9	O=7 NO=6.4	NA	plates	4.5 days
53.6 (19.2)	O=17 (13-24) NA=24 (14-30)	NA	24 months	NA	NA
O=59.57 (17.13) NO=60.31 (18.22)	O=26.2 (11.7) NA=26.4 (12.7)	NA	NA	NA	NA

Pneumonia

Pneumonia was reported for both treatment groups in eight studies, totaling 2659 patients [21,23,25,19,28-30,33]. Only one study diagnosed pneumonia based upon a standardized definition, namely of the Center for Disease Control and Prevention [21,34]. Overall, 41 out of 530 patients (7.7%) in the operative group and 189 out of 2129 (8.9%) in the nonoperative group developed pneumonia. The forest plot of the meta-analysis comparing operative and nonoperative treatment for studies including

50% or more patients with multiple simple rib fractures is shown in Figure 2A. The plot showed moderate heterogeneity between the studies (I^2=38%). A significant difference between groups was found in favor of the operative group (risk ratio [RR] 0.66, 95% confidential interval [CI] 0.49 to 0.90; p=0.008). Subgroup analysis of studies with an increasing proportion of patients with multiple simple rib fractures showed a persistent pooled risk ratio below 1, but an increase of the confidence interval with loss of statistical significance due to the small number of available studies (Figures 2B-D).

Mechanical ventilation days

The duration of mechanical ventilation was reported in eight studies (n = 2456 patients) [21, 23, 25, 27, 28,30–32]. This outcome measure was expressed in days by all studies without further elaboration. Six of these studies could not be included in the meta-analysis, because they did not provide the means and standard deviation for the two treatment groups separately [23,25,28,30–32]. This resulted in complete data for 113 patients. The forest plot of the meta-analysis of mechanical ventilation comparing operative and nonoperative treatment is shown in Figure 2E. The plot shows much

TABLE 3
Quality assessment scores of the included studies

Author (year)	Aim stated	Consecutive enrolment	Prospective data collection	Appropriate endpoints	Unbiased assessment	Appropriate FU time	Loss-to-FU <5%	Sample size	Totaal score
De Moya (2011) [21]	2	1	1	2	0	0	2	1	9
Khandelwal *et al.* (2011) [22]	1	1	2	1	2	1	2	0	10
Granhed *et al.* (2014) [23]	2	1	2	2	0	1	0	0	8
Majercik *et al.* (2015) [24,25]	2	1	0	2	0	0	2	0	7
Qiu *et al.* (2016) [26]	1	0	0	2	2	2	2	0	9
Tarng *et al.* (2016) [27]	1	2	2	2	0	1	2	0	10
Fitzgerald *et al.* (2017) [19]	2	2	2	2	0	2	0	0	10
Uchida *et al.* (2017) [28]	1	0	0	2	2	2	2	0	9
Kane *et al.* (2018) [29]	1	1	2	2	2	2	2	0	12
Majeed *et al.* (2018) [30]	2	0	1	1	0	1	0	0	5
Fokin *et al.* (2019) [31]	2	1	0	2	0	1	0	0	6
Marasco *et al.* (2019) [32]	2	2	2	2	0	2	1	0	11
Shibahashi*et al.* (2019) [33]	1	2	1	1	0	0	0	2	7

heterogeneity of effects between studies (I^2 = 94%). The pooled mean difference (MD) across the two studies was −6.01 days (95% CI −19.61 to 7.59) for the overall effect, which was not statistically significant (p = 0.39). Subgroup analysis of studies with an increasing proportion of patients with multiple simple rib fractures, made pooling impossible as only one study remained available, with statistically significant shorter duration of mechanical ventilation in the operative group (Figures 2F–H).

ICLOS

The ICLOS was reported in eight studies (n = 3389 patients) [21,24,27,19,28,29,31,32]. This outcome measure was expressed in days by all studies without further elaboration. Five of these studies could not be included in the meta-analysis due to incomplete data reporting, resulting in complete data for 524 patients [19,28,29,31,32]. The forest plot of the meta-analysis of ICLOS comparing operative and nonoperative treatment is shown in Figure 3A. The plot shows much heterogeneity of effects across the studies (I^2 = 93%). One of the three studies in the meta-analysis showed a statistically significantly shorter ICLOS in the operative group with a mean difference of −8.70 days [27]. The pooled MD across the three studies was −2.93 days (95% CI −8.65 to 2.80) for the overall effect, which was not statistically significant (p = 0.32). Subgroup analysis of studies with an increasing proportion of patients with multiple simple rib fractures made pooling impossible as only one study remained available, with statistically significant shorter ICLOS for the operative group (Figures 3B–D).

HLOS

The HLOS was reported in nine studies (n = 2267 patients) [21,23,24 ,26,27,19,29–31]. This outcome measure was expressed in days by all studies without further elaboration. Five of these studies could not be included in the meta-analysis due to incomplete data reporting, resulting in complete data for 648 patients [23,19,29–31]. The forest plot of the meta-analysis of HLOS comparing operative and nonoperative treatment is shown in Figure 3E. The plot shows much heterogeneity of effects across the studies (I^2 = 95%). Two of the four studies in the meta-analysis showed a statistically significantly shorter hospital length of stay in the operative group with a mean difference ranging from −4.84 to −20.38 days [26,27]. The pooled MD across the four studies was −5.78 days (95% CI −10.40 to −1.15) for the overall effect, which was statistically significant (p = 0.01). Subgroup analysis of studies with an increasing proportion of patients with multiple simple rib fractures showed a persistent shorter HLOS. With only two studies available for pooling, significant difference in HLOS was lost from 60% or more patients with multiple simple rib fractures (Figures 3F–H).
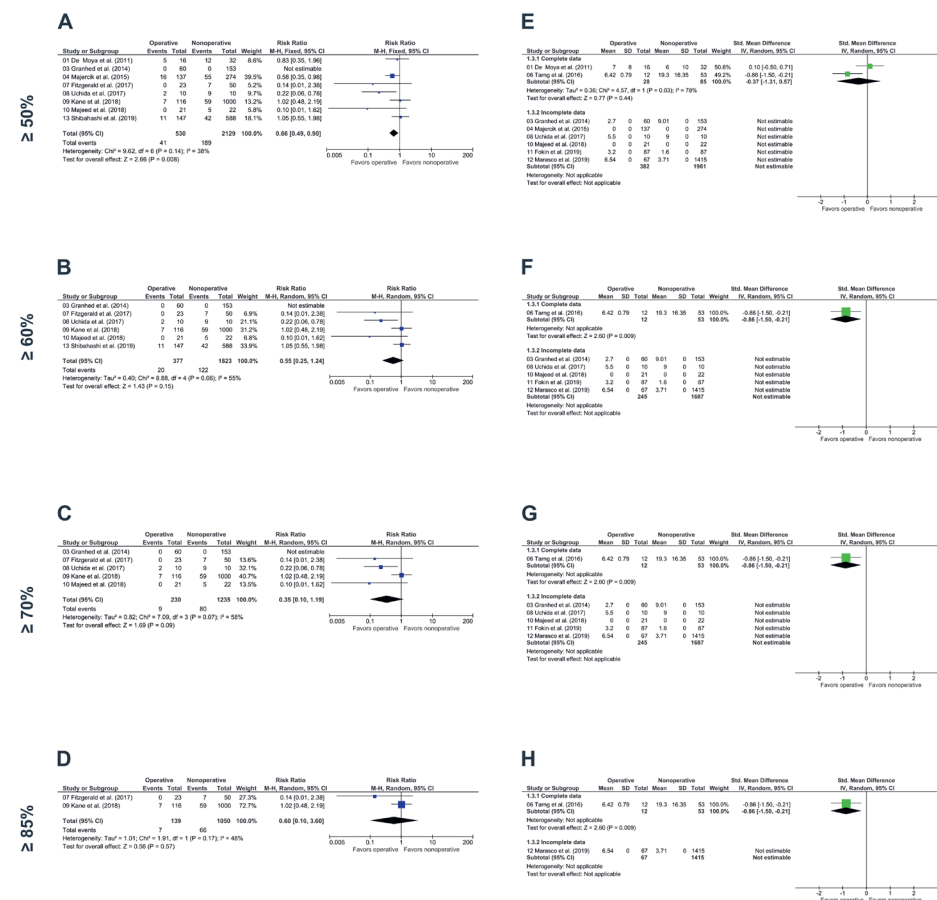
FIGURE 2

Forest plots detailing the risk ratio for pneumonia (A-D) and the mean difference for duration of mechanical ventilation (E-H) for operative versus nonoperative treatment of multiple simple rib fractures.

Forest plots are shown for increasing cut-offvalues for multiple simple rib fractures, i.e., ≥50% (A, E), ≥60% (B, F), ≥70% (C, G), and ≥85% (D, H). CI, Confidence Interval; IV, Inverse Variance; M-H, Mantel-Haenszel; SD, Standard Deviation.

Mortality

Mortality was reported in 11 studies (n=,456 patients) [23,25-27,19,28-33]. Three studies elaborated on the reason and timing of their mortality rate [23,26,30]. The forest plot of the meta-analysis of mortality comparing operative and nonoperative treatment is shown in Figure 4A. Overall mortality was 13 out of 745 (1.7%) in the operative group and 194 out of 3711 (5.2%) in the nonoperative group. The plot shows slight heterogeneity of effects across the studies (I²=22%). The pooled risk ratio (RR) across the 11 studies showed statistically significantly less mortality in the operative group (RR 0.32; 95%
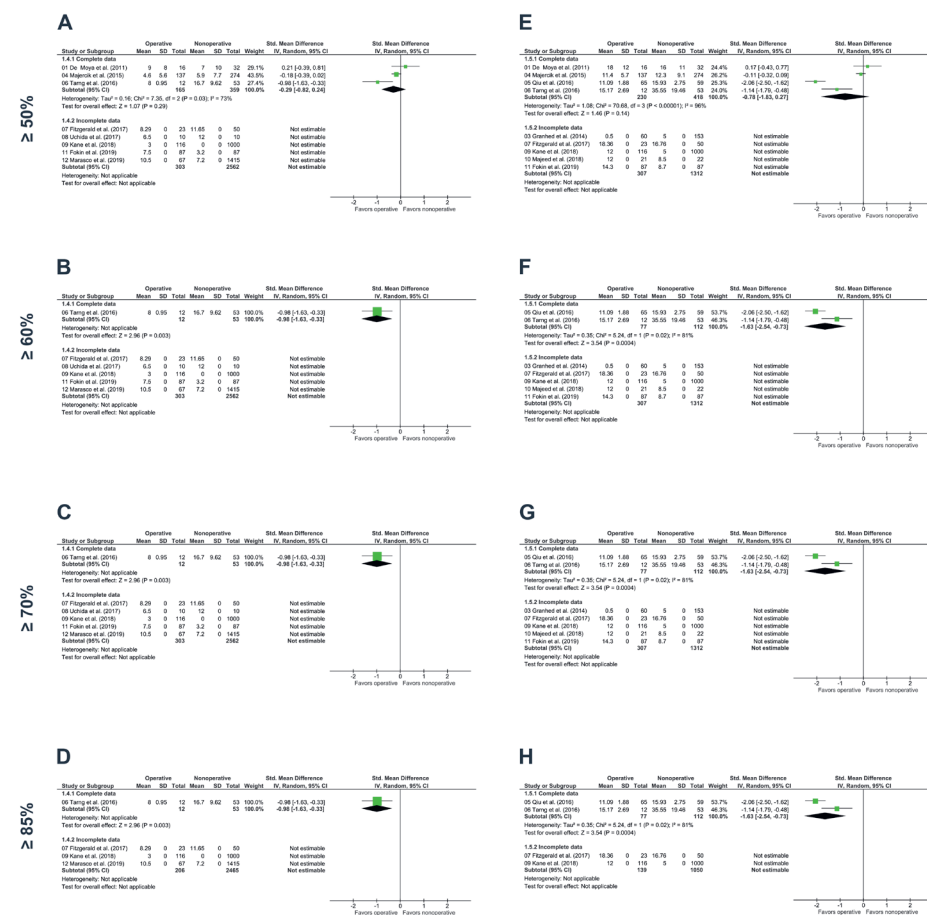
FIGURE 3

Forest plots detailing the mean difference for ICLOS (A-D) and HLOS (E-H) for operative versus nonoperative treatment of multiple simple rib fractures.

Forest plots are shown for increasing cut-offvalues for multiple simple rib fractures, i.e., ≥50% (A, E), ≥60% (B, F), ≥70% (C, G), and ≥85% (D, H). CI, Confidence Interval; IV, Inverse Variance; SD, Standard Deviation.

0.19 to 0.54; P<0.001). Subgroup analysis of studies with higher percentages of patients without a flail chest, showed a significant pooled risk ratio of around 0.32, up to studies including 85% of patients without a flail chest (Figures 4B-D).

Wound infections

Wound infections was reported as outcome measure in four studies (n=123 operatively treated patients), ranging from 0 to 9.4% (Table 4) [22,23,28,30]. Two studies reported
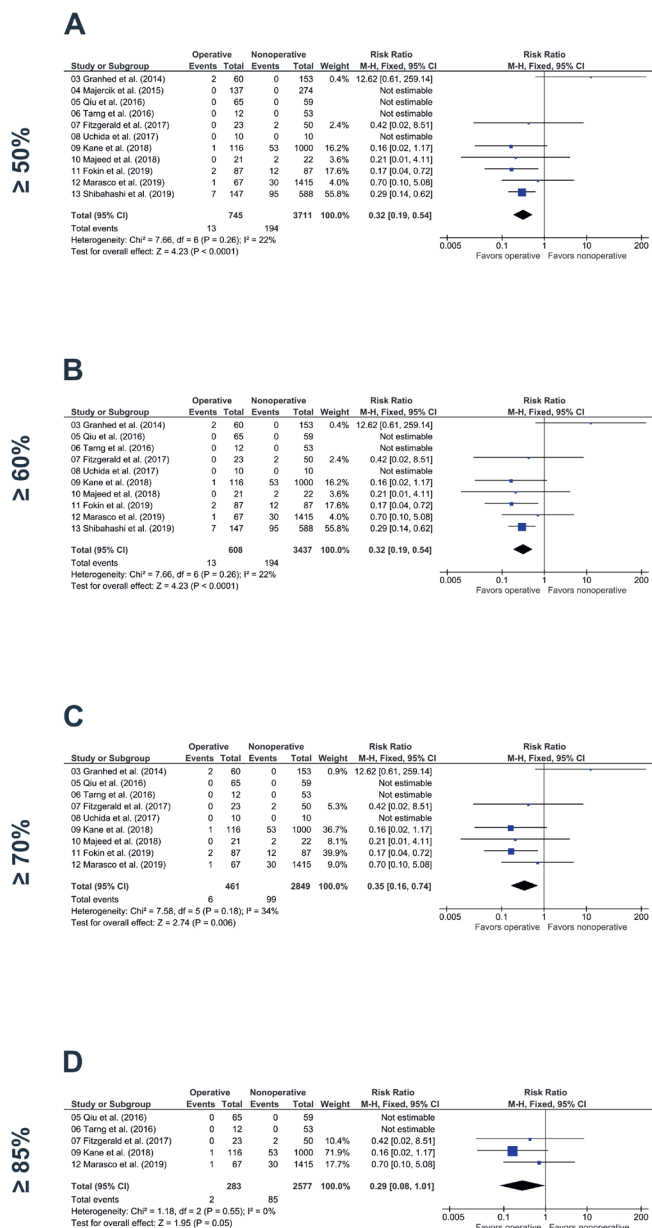
FIGURE 4

Forest plots detailing the risk ratio for mortality for operative versus nonoperative treatment of multiple simple rib fractures.

Forest plots are shown for increasing cut-off values for multiple simple rib fractures, i.e., ≥50%(A), ≥60% (B), ≥70% (C),and ≥85% (D).CI, Confidence Interval; M-H, Mantel-Haenszel.

wound infections. One study only mentioned three superficial wound infections without any further information on treatment and outcome [22]. The other study reported one deep infection resulting in a fracture related infection which was treated with a reoperation at seven months after initial trauma and antibiotics for three months after which the infection resolved [23].

TABLE 4
Occurrence of wound infections after operative treatment of multiple simple rib fractures.

Author (year)	Sample size	Wound infection	
		(N)	(%)
Khandelwal *et al.* (2011) [22]	32	3	9.4%
Granhed *et al.* (2014) [23]	60	1	1.7%
Uchida *et al.* (2017) [28]	10	0	0.0%
Majeed *et al.* (2018) [30]	21	0	0.0%

DISCUSSION

This study showed that operative fixation of multiple simple rib fractures may lead to a reduced risk of pneumonia, mortality, and hospital length of stay. No significant difference in the duration of mechanical ventilation and, IC length of stay was demonstrated. As the included studies had observational study designs with heterogenous populations and different or absent definitions of the outcome measures, the data should be interpreted with caution and might not be viewed in terms of causality. The occurrence of pneumonia is of critical importance for the outcome after rib fractures. Battle et al. showed in a meta-analysis that pneumonia is one of the significant risk factors for mortality in blunt chest wall trauma patients [12]. The assumed pathomechanism is that pain due to the fractures results in inadequate ventilation and mucus retention concordant to pulmonary contusion resulting in an increased risk of pneumonia. Theoretically, less pain would enable the patient to normalize ventilation and mucus clearance, resulting in a reduced risk of pneumonia. Therefore, adequate pain treatment is mandatory.

Epidural catheters are used most frequently as a mean to control pain and appear superior over other systemic pain management modalities [35,36]. Although thoracic epidural catheters may reduce the mechanical ventilation duration, any benefit in mortality, ICLOS, or HLOS has not been proven [37]. This stresses the need for other pain reducing treatment modalities. Since immobilization of rib fractures prevents the periosteum from movement at the fracture site, surgical fixation might reduce pain significantly. However, studies comparing pain in operatively versus nonoperatively

treated patients are rare. They are often retrospective and the results are contradicting [21,22,38,39].

Differences in occurrence of pneumoniae between included studies can be based on differences in or lack of definition. For example, six of the eight studies that reported the outcome of occurrence of pneumonia did not describe their definition of pneumonia [23,19,28-30,33]. In their retrospective study, Majercik et al. based their definition of pneumonia on microbiological data but provide no further specification [25]. The definition by DeMoya et al. was according to the Center for Disease Control and Prevention's definition and included chest radiographical findings, positive biochemical blood samples, and clinical symptoms [21]. The two studies [21,25] which provided a definition of pneumonia, reported almost half of pneumoniae of all studies combined for the operatively treated group and almost a third of the nonoperatively treated group. These differing and absent definitions of the primary outcome measure might influence the effect of the treatment in these patients.

Although multivariable analysis or metaregression analysis has not been done, the reduction of occurrence of pneumonia and mortality did not result in a reduction in duration of mechanical ventilation and ICLOS. The fact that pneumonia occurred statistically significantly more often in the nonoperative group stresses the possibility that the mechanical ventilation is less often the cause of pneumonia in patients with multiple rib fractures. The effect of treatment on mechanical ventilation, ICLOS, and HLOS must be interpreted with caution regarding the heterogeneity of up to 96% of the meta-analyses. The results for pneumonia and mortality displayed much less heterogeneity (I^2 38 and 22%, respectively) and appear more reliable. The nonstandard definitions of pneumonia might have confounded outcome in these two treatment groups. In addition, of the 11 studies that determined mortality rate, seven studies reported one or more deaths within the treatment groups and only three studies elaborated on the cause of the mortality [23,26,30]. These three studies reported a total of seven deaths of which five had a pulmonary cause such as respiratory failure, pneumonia, or acute respiratory distress syndrome (ARDS). The lack of insight into the causes of mortality in the larger part of the studies potentially introduced bias for this outcome measure and hinders interpretation of causality.

One of the main problems in evaluation of surgical rib fixation is the variety in injury characteristics of the patient population. Multitraumatized patients are often evaluated together with patients with isolated rib fractures. Most studies included multitrauma patients defined as ISS of >16 with mean ISS ranging from 16 to 31 (Table 2) [21,23-25,27,19,29,31-33]. Only five studies also reported the abbreviated injury score (AIS) as specification of the thoracic trauma [21,27,28,32,33]. As a result, it remains unclear in the larger part of the studies if the rib fractures contributed most to the ISS. Also, the number of rib fractures per patient was not available in four studies which only

stated including patients with three or more fractured ribs in the Methods section [29,30,32,33]. As the number of rib fractures is a risk factor for pulmonary complications such as pneumonia and mortality, the lack of these data might have influenced these outcome measures [6,8,12,40]. Therefore, ICLOS and HLOS might be influenced by other main contributors of the high ISS. In order to further clarify the outcome of patients with multiple rib fractures, future studies should include patients with isolated rib fractures solely or provide detailed AIS and ISS scores to enable stratification for the body-regional AIS score.

In addition, while this study we only included studies with a majority (≥50%) of patients without a flail chest, nine studies did not specify the distribution of these patients into the two treatment groups [22-24,26,27,19,28-30]. Five studies did report this population distribution. Four studies found significantly more patients with a flail chest in the operatively treated group [25,32,31,33]. Only De Moya et al. had similar numbers of patients with and without a flail chest in both groups [21]. Significant variability in the thoracic injuries with the more seriously injured patients being in the operative treatment group could have also affected ICLOS and HLOS. Differences in outcome between the two groups must therefore be interpreted with caution. Also, only two studies consisted of 100% patients with multiple non-flail rib fractures.[26,19].

In order to correct for the arbitrary cut-off value of including studies with at least 50% of patients with multiple simple rib fractures, subgroup analyses were performed for studies with increasing cut-off values up to 85% of patients with multiple simple rib fractures. This showed the lack of available studies reporting on various outcome parameters. Duration of mechanical ventilation and ICLOS could not be pooled if more than 50% of the patients had multiple simple rib fractures, and outcome measure HLOS could only be assessed in two studies with 60% or more patients with multiple simple rib fractures. The lower risk ratio of mortality in the operative fixation group remained significant up to the cut-off value of 85%. While showing a persistent pooled risk ratio below 1 for the outcome measure of pneumonia when performing subgroup analysis in studies with higher cut-off values, statistical significance was lost due to the increased confidence intervals. This highlights the need for high quality (randomized) studies in order to assess the true effect of operative rib fixation in patients with multiple simple rib fractures with similar patient and injury characteristics.

Published operative rib fixation guidelines and consensus statements advocate surgery within 72 h post-trauma [41-43]. For example, every additional hospital day before surgery is associated with a 31% increased likelihood of pneumonia [44]. While all surgeries were performed at index admission, only six studies mentioned the time to surgery which ranged from 4 to 12 days [21-23,27,28,31]. As a result, the effect of early operative rib fixation on ICLOS, HLOS, and pneumonia rate might have been influenced and could not be distilled.

CHAPTER 6

This study has several limitations. First, this study was unable to extract data for patients with multiple simple rib fractures only. In order to diminish the influence of patients with a flail chest on the outcome measurements, we excluded studies with ≥50% of patients with a flail chest. However, with patients without a flail chest accounting for 54-100% of the study population, the influence of patients with a flail chest can not be estimated exactly.

Second, this meta-analysis is mainly based on comparative observational studies, often retrospective (Table 2). With nonstandard or absent definitions of pneumonia and mostly no elaboration on the cause of mortality, the precise effect of both treatment options for multiple simple rib fractures could be less accurately measured. Randomized controlled trials are currently absent for patients with multiple simple rib fractures. In addition, for the duration of mechanical ventilation, ICLOS and HLOS, up to over 75% of the included studies did not provide all data that were needed to include them in the meta-analysis. Also, results from case series that enrolled one type of treatment only were excluded, which may have caused inclusion bias. Third, the included studies had variable methodological strength, follow-up, and outcome parameters. As there was no exclusion of studies after quality assessment, this may influence the outcome in an unknown way. Finally, the pooled risk ratio's and mean differences could not be adjusted for potential confounders, such as the number of rib fractures or ISS. The unadjusted pooled estimates reported in this review should therefore be interpreted with caution. Von Hippel et al. showed that I^2 should be presented and interpreted with caution in small meta-analyses [45]. Therefore, the heterogeneity that was found may be considered as imprecise and biased. The random-effects model was used because the effect size varied from study to study and this model was more likely to fit the actual sampling distribution [46]. The true effect size might be higher or lower due to differences in case mix.

Correction for most of these flaws in methodology was impossible since the authors of the included studies did not response to the request for missing data and data for patients with multiple isolated rib fractures only. Despite these shortcomings, the presented data suggest a favorable outcome on occurrence of pneumonia and mortality rate comparing operatively with nonoperatively treatment in patients with multiple simple rib fractures. Including only studies in which the majority of patients did not have a flail chest suggest some positive effects, but the exact effect remains to be studied in randomized homogenous populations consisting of patients with multiple simple rib fractures only.

This systematic review and meta-analysis shows that operative treatment of multiple simple rib fractures may result in a significant reduction of pneumonia, mortality, and hospital length of stay. However, a reducing effect of treatment on the duration of mechanical ventilation and IC length of stay. The wound infection rate which should

be kept in mind as a complication following operative treatment ranges from 0 to 9.4%. The results must be interpreted with caution due to the limitations such as non- standard definitions of outcome measures, heterogeneous patient groups, and low-quality observational studies. These limitations, in combination with the promising results, stress the need for randomized controlled trials evaluating outcome after nonoperative and operative treatment in patients with multiple simple rib fractures.

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CHAPTER 6
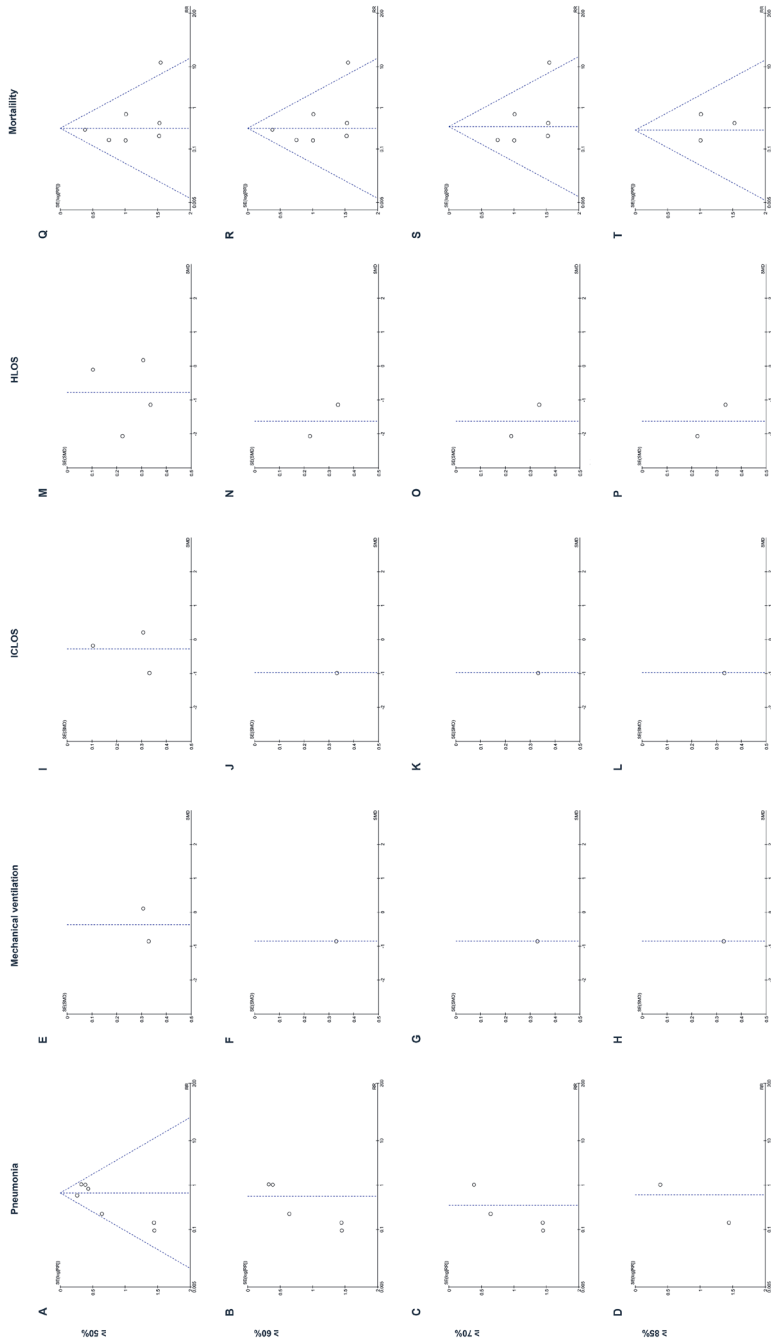
SUPPLEMENTAL DATA

SUPPLEMENTAL FIGURE S1
Funnel plots detailing the risk of publication bias for pneumonia (A-D), duration of mechanical ventilation (E-H), ICLOS (I-L), HLOS (M-P), and mortality (Q-T) for operative versus nonoperative treatment of multiple simple rib fractures. Forest plots are shown for increasing cut-off values for multiple simple rib fractures, i.e., ≥ 50% (A, E, I, M, Q), 60% (B, F, J, N, R), 70% (C, G, K, O, S), 85% (D, H, L, P, T).
CI, Confidence Interval; IV, Inverse Variance; M-H, Mantel-Haenszel; SD, Standard Deviation.

CHAPTER 7

Early fixation versus conservative therapy of multiple, simple rib fractures (FixCon):
protocol for a multicenter randomized controlled trial

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ABSTRACT

Background
Multiple rib fractures are common injuries in both the young and elderly. Rib fractures account for 10% of all trauma admissions and are seen in up to 39% of patients after thoracic trauma. With morbidity and mortality rates increasing with the number of rib fractures as well as poor quality of life at long-term follow-up, multiple rib fractures pose a serious health hazard. Operative fixation of flail chest is beneficial over nonoperative treatment regarding, among others, pneumonia and both Intensive Care Unit (ICU) and hospital length of stay. With no high-quality evidence on the effects of multiple simple rib fracture treatment, the optimal treatment modality remains unknown. This study sets out to investigate outcome of operative fixation versus nonoperative treatment of multiple simple rib fractures.

Methods
The proposed study is a multicenter randomized controlled trial. Patients will be eligible if they have three or more multiple simple rib fractures of which at least one is dislocated over one shaft width or with unbearable pain (Visual Analog Scale (VAS) or Numeric Rating Scale (NRS) >6). Patients in the intervention group will be treated with open reduction and internal fixation. Pre- and postoperative care equals treatment in the control group. The control group will receive nonoperative treatment, consisting of pain management, bronchodilator inhalers, oxygen support or mechanical ventilation if needed, and pulmonary physical therapy. The primary outcome measure will be occurrence of pneumonia within 30 days after trauma. Secondary outcome measures are the need and duration of mechanical ventilation, thoracic pain and analgesics use, (recovery of) pulmonary function, hospital and ICU length of stay, thoracic injury-related and surgery-related complications and mortality, secondary interventions, quality of life, and cost-effectiveness comprising health care consumption and productivity loss. Follow-up visits will be standardized and daily during hospital admission, at 14 days, one, three, six, and 12 months.

Discussion
With favorable results in flail chest patients, operative treatment may also be beneficial in patients with multiple simple rib fractures. The FixCon trial will be the first study to compare clinical, functional, and economic outcome between operative fixation and nonoperative treatment for multiple simple rib fractures.

INTRODUCTION

Rib fractures are common injuries in both trauma and non-trauma centers, occurring in up to 10-39% of patients with blunt chest trauma and accounting for 10% of all trauma admissions (1-4). With an estimated 25% of all traumatic deaths, chest trauma ranks second after head injury (3, 4). Rib fractures are caused by high-energy trauma (HET) in the younger patients, often with concomitant injuries and in the elderly as a result of low energy trauma (LET) (5-7). Sustaining multiple rib fractures can result in a flail chest, defined as fracture of three or more consecutive ribs in two or more places, creating a flail segment (8, 9). Patients may also have multiple simple rib fractures or a combination of both.

While open surgical fixation of rib fractures dates back to the 1940s, multiple rib fractures are routinely treated nonoperatively (10). Nonoperative treatment includes pain management, oxygen support or mechanical ventilation, bronchodilator inhalers, and pulmonary physical therapy. Despite this treatment strategy, mortality and complications such as pulmonary contusion, hemopneumothorax, and pneumonia is seen in up to 34% and in 35-77% of patients, respectively (1, 2, 5, 6, 11-15). Various studies have identified risk factors that increase mortality such as age and number of rib fractures (3, 6, 7, 11, 16-18).

Furthermore, at two years post-injury up to 29% of patients have not yet returned full-time to their pre-injury job and 64% of patients with isolated multiple rib fractures still experiences chest wall pain (19, 20). With incapacitating pain often accompanying traumatic rib fractures, epidural analgesics are suggested as the optimal analgesic for patients with multiple rib fractures. Two meta-analysis have shown that epidural use results in significant less pain but has no benefit regarding length of both Intensive Care Unit (ICU) and hospital stay, mortality and complication rate, indicating the necessity of an optimized analgesic modality for rib fracture patients (21, 22).

Rib fractures may show the same pattern as a restrictive pulmonary disease, resulting in loss of total lung capacity which precipitates inadequate oxygenation and ventilation. Patients with rib fractures and reduced pulmonary function are more susceptible to pulmonary complications and longer length of hospital stay (23-25). With contradicting studies on the difference in spirometry between operatively and nonoperatively treated patients with rib fractures, additional research is needed (12-14, 26-29). While surgical treatment of flail chest patients appears to be cost-effective over nonoperative treatment, but for multiple simple rib fractures the most cost-effective treatment modality is still unknown (30, 31).

Over the last decade, there has been an increasing number of studies suggesting superior results of open reduction and fixation (ORIF) for the stabilization of multiple rib fractures due to profitable results in traumatic flail chests compared with nonoperative

management (31-34). Several studies with flail and non-flail chest patients combined have shown promising effects of ORIF with less pneumonia, less hemo- and pneumo-thorax, shorter need for mechanical ventilation, lower mortality, shorter length of hospital and IC stay, and quicker return to normal activity (15, 28, 35-38).

As only two studies, both retrospective cohort studies with small sample sizes and short follow-up, have singularly focused on operative versus nonoperative management of multiple simple rib fractures, definitive proof for the optimal treatment of multiple simple rib fractures is not achieved yet (9, 14, 39-41).

Therefore, the aim of this multicenter randomized controlled trial is to investigate the effect of ORIF versus nonoperative treatment in patients who sustained multiple simple fractured ribs.

METHODS

Objective
The primary aim of this trial is to investigate the effect of ORIF versus nonoperative treatment on the occurrence of pneumonia within 30 days after trauma in adult patients who sustained multiple simple fractured ribs. The secondary aims are to investigate the effect of treatment on the need for and duration of mechanical ventilation, level of thoracic pain and analgesics use, (recovery of) pulmonary function, hospital and ICU length of stay, thoracic injury-related and surgery-related complications and mortality, secondary interventions, quality of life, and total costs (in-hospital and socio-economic) of treatment, health care consumption, and work absence. At the end, a cost-effectiveness analysis will be done.

Trial design and setting
The FixCon trial is a multicenter randomized controlled trial, with a parallel group design. The following 12 hospitals in The Netherlands will participate; Amphia Ziekenhuis (Breda), Catharina Ziekenhuis (Eindhoven), Deventer Ziekenhuis (Deventer), Erasmus MC (Rotterdam), Haga Ziekenhuis (The Hague), Ikazia Ziekenhuis (Rotterdam), Isala (Zwolle), Maasstad Ziekenhuis (Rotterdam), Maastricht UMC+ (Maastricht), Rijnstate (Arnhem), Spaarne Gasthuis (Haarlem), and Zuyderland Medisch Centrum (Heerlen).

Inclusion and exclusion criteria
The study population will consist of adults with three or more simple rib fractures after blunt force trauma. The fracture pattern will be diagnosed and delineated with a CT-scan of the thorax, at least 64-slice and preferable including 3D reconstruction.

In order to be eligible to participate in this study, a patient must meet all of the following inclusion criteria:

1. Age 18 years or older
2. For any of the ribs number 4 to 10, three simple fracture ribs with either A) at least one fracture dislocated over one shaft-width; or B) unbearable pain (VAS or Numeric Rating Scale (NRS) >6 points)
3. Blunt force trauma
4. Hospital presentation within 72 h after trauma
5. Provision of informed consent by patient or proxy

A patient who meets any of the following criteria will be excluded from participation:

1. Neurotraumatic changes leading to mechanical ventilation (GCS ≤ 8 at 48 h post injury. If unable to assess full GCS due to intubation or other causes, GCS motor ≤ 4 at 48 h post-injury)
2. Rib fractures due to cardiopulmonary resuscitation
3. Surgical rib fixation not possible due to additional traumatic injuries (hemodynamically or pulmonary unstable, for example based on parenchymal lung trauma) or patient is unfit for surgery; to be decided by an ICU-doctor, trauma surgeon, or anesthesiologist
4. Flail chest, based on radiological or clinical findings
5. Decreased sensory or motor function due to (previous) cervical or thoracic spine failure
6. Previous rib fractures or pulmonary problems, requiring continuous oxygen use at home pre-trauma
7. Congenital thoracic deformity (pectus excavatum, pectus carinatum, severe scoliosis, or kyphosis)
8. Inhalation trauma or severe burns close to or inside the mouth or neck
9. Surgical fixation of the ribs not feasible within seven days after trauma
10. Patient unwilling or unable to comply with the intervention or follow-up visit schedule
11. Insufficient comprehension of Dutch language to understand the rehabilitation program and other treatment information in the judgement of the attending physician
12. Participation in another surgical intervention or drug study that might influence any of the outcome parameters

Recruitment and randomization

Eligible persons presenting to the Emergency Department (ED) or referred from another hospital, with multiple, simple rib fractures will be informed about the trial at the ED or at the surgical ward after admission. After explanation of the study, eligible patients will receive written information and a consent form from the attending physician, the

clinical investigator, or a research assistant. Patients meeting all eligibility criteria will be recruited within one day after hospital admission. As surgical rib fixation appears to be most beneficial when performed within 72 h after trauma, patients are stimulated to decide within this period. However, informed consent can be given by the patient as long as rib fixation can be carried out within one week after trauma. Should patients not be able to sign informed consent themselves, a legal representative will receive oral and written information about the study, in the hospital, by the attending physician, the clinical investigator, or a research assistant, and will be asked to consent with participation of the patient.

After signing informed consent by patient or proxy, participants are allocated to one of the two study arms (surgical stabilization or nonoperative treatment) using a web-based randomization program that will be available 24 h a day. Allocation will be at random and concealed, in a 1:1 ratio, and will be stratified by site. Variable block sizes will be used; in each block both treatments will be represented equally. As the intervention cannot be blinded it will in no case be necessary to break the randomization code.

As with many surgical trials, patients and surgeons cannot be blinded for the intervention. In order to reduce bias as much as possible, a research physician or research assistant will perform the follow up measurements using a standardized protocol. Also, the treating surgeon or ICU doctor will identify the primary outcome (*i.e.*, pneumonia) based on the definition as mentioned under Outcome measures.

Participation is on a voluntary basis and participants are allowed to withdraw from the study at any time without specifying why. The general practitioner will be informed about the patients' participation.

Nonoperative allocation

Nonoperative treatment will consist of optimal pain treatment, supportive oxygen or ventilation if needed, early mobilization, Salbutamol/Atrovent spray, and physical therapy for optimizing ventilation. Without definitive proof for the best protocol, each participating center is allowed to use its local protocol for interpleural drainage use, mechanical ventilation, and pain control. Although this may introduce some heterogeneity across hospitals, it benefits extrapolation of the results. Critical elements of the nonoperative treatment will be recorded.

Operative allocation

Preoperative treatment is the same as in the nonoperative treatment group. ORIF should be preferably carried out within 72 h after trauma, but fixation within one week will not lead to exclusion. The surgical fixation will be conducted by a senior fracture management surgeon who has participated in at least five rib fracture fixation procedures. A surgeon in training with limited experience in rib fixation is allowed to work under supervision of an experienced surgeon.

Patients allocated to the surgical group will undergo ORIF using plates and/or splints. The decision on what rib fixation system to use is to the discretion of the treating surgeon, provided that the fixation system is CE-mark approved for rib fixation. Each system will be used according to the supplier's protocol. The patient will receive an intravenous single prophylactic dose of a third-generation cephalosporin preoperatively. The incision will be planned, based preferably on a preoperative 3D reconstruction of the thoracic cage. The positioning of the patient and number of ribs fixated will be left to the preference of the operating surgeon. A minimally invasive technique will not lead to exclusion of the study. The ribs will be visualized using a muscle-sparing approach. After removing interpositioning tissue, fracture reduction will be carried out and the rib fixation device will be positioned and fixated. The use of interpleural space rinsing with warmed NaCl 0.9% or thoracoscopic visualization during rib fixation will be left to the judgement of the surgeon. If indicated, an interpleural drain is percutaneously placed in dorsocaudal direction, apart from the surgical wound. The wound is closed, using a wound drain if needed.

After surgery, the patient will be admitted to the ward or ICU depending on his/her clinical state. Participating hospitals are allowed to use their local protocol for interpleural and wound drainage. Postoperative physical therapy and supportive treatment may be prolonged if needed. Postoperative care and preoperative treatment are the same as for nonoperative management. Critical elements of the operative treatment will be recorded.

Outcome measures
Primary outcome measure
The primary outcome measure is pneumonia within 30 days after trauma. In order to define pneumonia, the flow-chart of the Centers of Disease control and Prevention, based on imaging, clinical and laboratory criteria, will be followed (Figure 1) (42). Temperature (T) will be measured daily during admission. If T>38.0°C intra-auricular (or T>39°C rectal), bladder, central or a sputum culture will be done. Also the wound will be checked (if applicable) and a radiograph of the thorax will be made. If patients are suffering from fever at home, they will be advised to visit the outpatient clinic or Emergency Department. The temperature will be measured on arrival at the outpatient clinic or Emergency Department and the same additional examinations will be performed. A monitor will independently review the patient's medical files in order to ensure that the pneumonia was actually present.

Secondary outcome measures
The secondary outcome measures are:
1. Need and duration of mechanical ventilation in days. The number of days of invasive mechanical ventilation (by endotracheal tube or tracheostomy) from intubation

until successful weaning will be determined. The need for mechanical ventilation will be evaluated based on arterial blood gas analysis and clinical performance of the patient. The duration of mechanical ventilation will be calculated from the dates of intubation and extubation. Re-intubation within 30 days will be recorded as well.
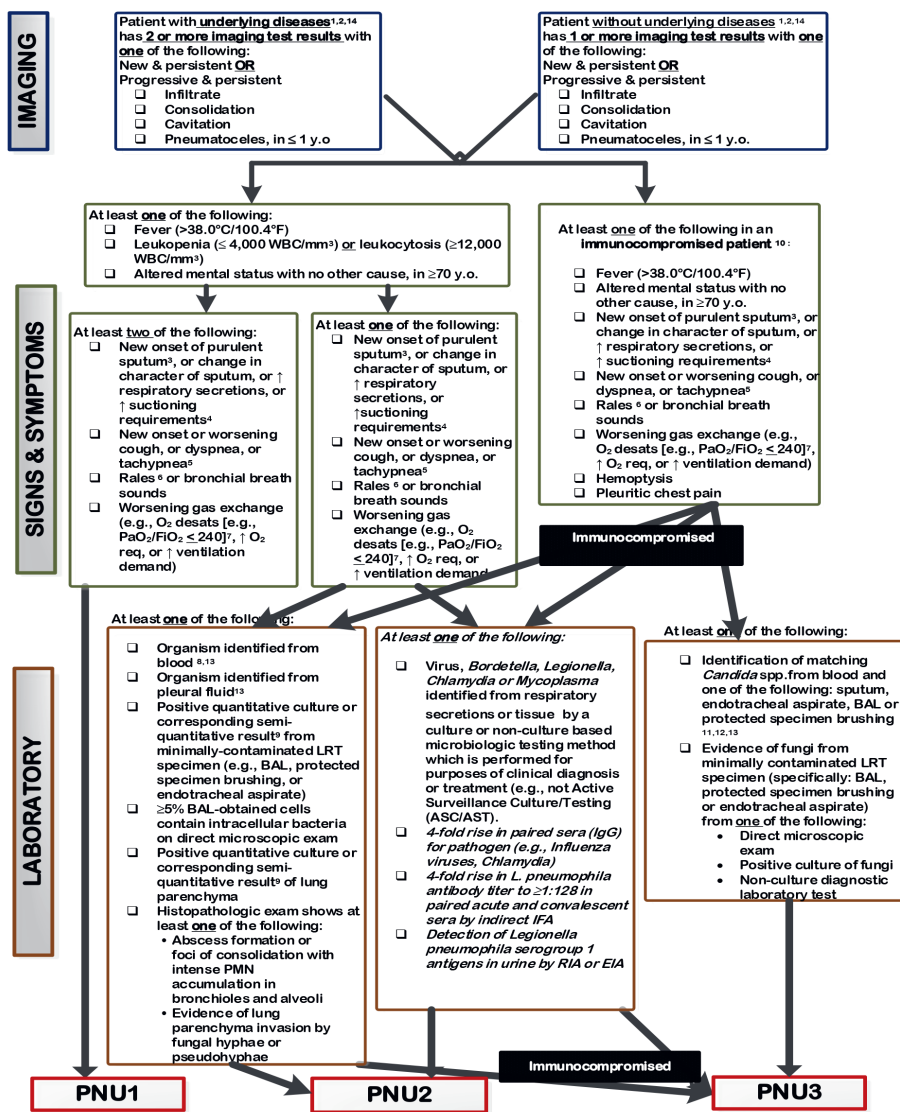
FIGURE 1
Pneumonia flow diagram, as designed by the CDC (42).
For further details of the flow chart, see the website of the CDC (42)

2. Level of thoracic pain (NRS) and analgesics use. Thoracic pain will be determined using a 11-point Numeric Rating Scale (NRS) in which 0 implicates no pain and 10 the worst possible pain. Five thoracic pain levels will be analyzed: pain in rest, at night, during daily activities (*e.g.*, work or hobbies), during maximal inspiration, and during self-care. Analgesics use during admission will be extracted from the medical files. After discharge, analgesics use will be asked for during the follow-up visits. Daily narcotic requirement will be calculated using an equivalence scale for 30 mg/day oral morphine.

3. (Recovery of) pulmonary function. The parameters tidal volume (TV), forced vital capacity (FVC), inspiratory capacity (IC_{lung}), and forced expiratory volume at 1 second (FEV_1) will be determined using spirometry. Spirometry will be done by a member of the research team. During the spirometry the patient has to inhale actively and exhale with maximum force possible. The mean of three tests will be calculated.

4. Hospital length of stay expressed in days. This will be calculated as the time between admission and discharge from the hospital. Re-admission within 30 days will be added. Re-admission for thoracic reasons after 30 days and up to 12 months will be counted separately.

5. ICU length of stay expressed in days. This will be calculated similar as the hospital length of stay.

6. Thoracic injury-related complications and mortality. The occurrence of thoracic injury-related complications will be recorded from the medical charts during clinical admission and each follow-up visit. Complications will be categorized for level of severity and treatment necessity according to the Clavien-Dindo classification (43). Complications will include empyema (as diagnosed on CT-scan, in presence of fever or positive cultures in the drained fluid), (retained) hydrothorax (a heterogeneous fluid collection with Hounsfield Units readings of 35-70 and evidence of pleural thickening) (44), nonunion (diagnosed on CT-scan or operatively, at least six months after trauma) (45) and other (all other complications as judged by the treating physician). If mortality is caused by the thoracic injury or complication of thoracic injury, it will be counted in rates of mortality. Death caused by other reasons will be noted but excluded in this calculation.

7. Surgery-related complications. The ORIF group can also develop hardware-related complications or failure. Hardware-related complication are superficial and deep wound infection which is defined as redness, tenderness and warmth surrounding and in direct contact with the postoperative wound. Superficial infection leads to oral or IV-antibiotics and deep infection leads to surgical activity such as stitch removal of exploration of the wound. Hardware failure is defined as loosening of the plate, secondary dislocation of fixation material, malposition of hardware, and broken plates or splints.

CHAPTER 7

8. Secondary interventions to resolve complications. Secondary interventions within 12 months after trauma to relieve pain, treat infection or other rib fracture related problems will include the following; antibiotic therapy (both oral and intravenous), additional surgical interventions (*e.g.*, surgical stabilization of nonunion, evacuation of hematoma, evacuation of empyema, removal of failed hardware, symptomatic hardware removal, and treatment of infection), and additional percutaneous interventions (*e.g.*. for persistent bleeding intercostal artery, intraparenchymal bleeding, drainage of infection, and drainage of pleural fluid).

9. Health-related quality of life measured using the Short Form-12 (SF-12) and EuroQoL-5D (EQ-5D) questionnaires. The SF-12 analyzes global health status, functional scale, and symptom scale. The score will be calculated based on eight domains and summarized into a Physical Component Summary (PCS) and Mental Component Summary (MCS). Data will be reported as utility score, ranging from 0 to 1 with a higher value indicating better quality of life. As a reference the US population of 1998 will be used (46). The EQ-5D is the most commonly used quality of life instrument for (rib) fracture patients (47, 48). The EQ-5D is recommended for assessment of quality of life in trauma patients, especially for economic evaluation (49, 50). The EQ-5D-5L descriptive system consists of five dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each with five possible answers. The patients' health states will be converted into a utility score using the Dutch tariff (51). Utility scores range from zero to one with lower scores indicating poorer quality of life.

10. Cost-effectiveness and health care consumption. Economic evaluations will be done from a societal perspective. The validated Medical Consumption Questionnaire (iMCQ) and Production Consumption Questionnaire (iPCQ) will be used. iMCQ details medical specialist care, physical therapy, hospitalization, nursing home, home care, and other costs directly associated with diagnosis, treatment, and rehabilitation. iPCQ comprises work resumption and production losses. Health care costs and lost productivity until one year after trauma will be measured in accordance with economic guidelines (52).

Other data collected

In addition to the outcome measures, the following data will be collected in order to assess similarity between the treatment groups.

a) Intrinsic variables (baseline characteristics): age, gender, body mass index (BMI), American Society of Anesthesiologists (ASA) grade, tobacco consumption, comorbidities, and medication use.

b) Injury-related variables: injury mechanism, pleura drain placed, number and location of rib fractures, affected side, presence of sternum fracture, additional injuries

represented by the Abbreviated Injury Score (AIS) (53), and injury severity score (ISS).

c) Intervention-related variables: surgical approach, number of plates and splints used and for which ribs, surgical delay, primary and secondary surgeon (resident or staff surgeon), wound drain, intra-operatively placed interpleural drain including duration of drainage, and duration of surgery.

Study procedures

Patients will be followed until 12 months after trauma. Clinical evaluation will occur daily during hospital admission. After discharge, outpatient clinic evaluation will occur at two weeks (window 7-21 days), one month (window 21-39 days), three months (window 11-15 weeks), six months (window 24-28 weeks), and 12 months (window 12-14 months). These visits are standard of care for the targeted patient group. A schedule of events is shown in Table 1. Baseline data and perioperative data will be collected from the patients' medical files as soon as possible, but no later than the first outpatient department visit. At the 12-month follow-up contact, the surgeon or research assistant will document any secondary intervention that may be planned for the patient. After six months a thoracic CT scan is repeated. Pulmonary function will be tested during the outpatient clinic visits at one, three, six, and 12 months. At each follow-up visit, the coordinating researcher or research assistant will ascertain patient status (*i.e.*, adverse events/complications or secondary interventions) and will verify information within the medical records. At each visit, patients will be asked to complete questionnaires relating to their pain (NRS), analgesics use, Quality of Life (QoL) (SF-12 and EQ-5D), and health care use (iPCQ and iMCQ).

Sample size calculation

Calculation of the required sample size for the primary analysis is based on data from a Cochrane review and a large retrospective analysis (7, 32). These studies suggest a pneumonia rate of 35% in nonoperatively treated patients and 15% in operatively treated patients with multiple rib fractures. This difference is considered clinically relevant. A two-sided test with an α level of 0.05 and a β level of 0.2 requires 72 patients in each group. In order to account for 25% loss of patients to follow-up and mortality, a sample size of 90 patients per group is needed. In total 180 patients will be included and randomized.

Statistical analyses

Data will be analyzed using the Statistical Package for the Social Sciences (SPSS), version 24.0 or higher (SPSS, Chicago, Ill., USA), and reported following the Consolidated Standards of Reporting Trials (CONSORT) guidelines. Normality of continuous data will

be tested with the Shapiro-Wilk test. Homogeneity of variances will be tested using the Levene's test. The analysis will be performed on an intention to treat basis. A two-sided p-value <0.05 will be taken as threshold of statistical significance in all statistical tests. Procedures will be implemented to reduce missing data. In previous studies of the principal investigator's department, these procedures led to <5% missing data (54). If necessary, missing values will be replaced using multiple imputation following the predictive mean matching method, using ten imputations.

TABLE 1
Schedule of Events (duration after trauma).

Radiographs & Event forms	Screening	Enrolment	Pre-surgery	Surgery	Post-surgery (until day 7*)	2 weeks (7-21 days)	30 days (21-39 days)	3 months (11-15 weeks)	6 months (24-28 weeks)	12 months$ (12-14 months)
CT-scan	X								X	
Screening	X									
Informed Consent		X								
Randomization		X								
Baseline Data			X	X						
Intervention/Surgical Report Form				X	X					
Outpatient Clinic FU						X	X	X	X	X
Spirometry							X	X	X	X
Analgesic use			Daily, afternoon		Daily, afternoon	X	X	X	X	X
Pain (NRS-rest and inspiration)			Daily, afternoon		Daily, afternoon	X**	X	X	X	X
Pain (NRS-night, daily, and care)						X**	X	X	X	X
QoL (EQ-5D and SF-12)						X**	X	X	X	X
Complications			X	X	X	X	X	X	X	X
(Secondary) Interventions			X		X	X	X	X	X	X
iPCQ and iMCQ questionnaire						X***	X	X	X	X
Early Withdrawal						****	****	****	****	****

* Post surgery, $ may be planned at the patients residency; ** Asking for current and pre-trauma status; *** Asking for pre-trauma situation; **** Only if applicable.

Descriptive analysis will be performed in order to report the outcome measures for both treatment arms. For categorical data, numbers and frequencies will be reported. For continuous data, the mean and SD (parametric data) or the mean and percentiles (non-parametric data) will be reported.

Next, univariate analysis will be performed in order to test for statistical significance of differences between the primary and secondary outcome measures across the two groups. A Chi-squared analysis or Fisher's Exact test will be used for statistical testing of categorical data (*e.g.*, the primary outcome, pneumonia). Continuous data (*i.e.*, hospital length of stay) will be tested using a Student's t-test (parametric data; with equal variance or unequal variance whichever applies according to the Levene's test) or a Mann-Whitney U-test (non-parametric data).

Multivariable analysis will be done as secondary analysis. A logistic regression model will be developed, with pneumonia as dependent variable and treatment as covariate. Nonoperative treatment will serve as reference category. Baseline and injury-related variables that may potentially confound the association between treatment and outcome will be included in this model as covariate. These will be selected from literature and from data of this study (see Other data collected). Known potential confounders according to literature data are the number of rib fractures and age. Other potential confounders collected as part of this study are gender, ASA, COPD, osteoporosis, and additional injuries (ISS≥16 versus ISS <16, and presence versus absence of severe injuries (AIS ≥3) for any body region). Variables that produce a p-value <0.2 in the univariate analysis will be included in the regression model. Odds ratio's will be reported with their 95% confidence interval and p-value.

Continuous outcomes repeatedly measured over time will be compared between treatment groups using linear mixed-effects regression models (with fixed effects for treatment and other covariates like gender, and age, if applicable). The interaction between treatment and time will be included to test for differences between groups over time. For each follow-up moment, the estimated marginal mean will be computed per treatment group and compared post hoc with a Bonferroni test in order to correct for multiple testing.

Other continuous and binomial variables will be tested with multivariable linear and binary logistic regression models, respectively. The outcome measure will be entered as dependent variable and treatment as covariate. Nonoperative treatment will serve as the reference group. Baseline and injury-related variables that may potentially confound the association between treatment and outcome will be included in the models as covariate. Coefficients will be reported with their 95% confidence interval and p-value.

Economic evaluation will be done from a societal perspective with iMCQ and iPCQ questionnaires. Health care costs and lost productivity until one year after trauma will

be measured. Cost prices of the standardized referral strategy will be determined by a bottom-up micro-costing method. The incremental cost-effectiveness ratio of ORIF versus nonoperative treatment will be expressed as costs per pneumonia prevented, with confidence ellipses and acceptability curves. A cost-utility analysis, with QALY (based on the EQ-5D summary score) as outcome measure, will also be done.

Ethical concerns

The study will be conducted according to the principles of the Declaration of Helsinki (64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO). This study has been approved by the Medical Research Ethics Committee (MREC); in Dutch: Medisch Ethische Toetsings Commissie (METC). The MREC Erasmus MC has given dispensation from the statutory obligation to provide insurance for subjects participating in medical research (article 7 of the WMO and Medical Research (Human Subjects) Compulsory Insurance Decree of 23 June 2003) as participation involves no risks.

Participants can leave the study at any time for any reason if they wish to do so without having to give a reason. No replacement will take place. Anticipated loss-to-follow up is included in the sample size calculation. Reasons for non-participation will be documented.

Data management and monitoring

Data will be encoded and stored in a password protected database (Data Management, The Research Manager, Deventer, The Netherlands) with restricted access to the researchers only. Data will be entered once. Quality of the entered data will be monitored by checking entry for a random sample of patients prior to database locking.

Trial status

The trial is registered at the Netherlands Trial Register (NTR) (NTR7248), registration date May 31, 2018. Inclusion of patients has started January 1, 2019 and the planned recruitment period will be three years. With a follow-up of one year, data presentation is expected in the beginning of 2022.

DISCUSSION

The FixCon trial studies outcome after operative versus nonoperative treatment of multiple simple rib fractures. With high rates of morbidity and low quality of life at long-term follow-up, multiple simple rib fractures cause a serious health hazard. With favorable results in flail chest patients, operative treatment might also result in better clinical and functional recovery of patients with multiple simple rib fractures. Improved outcome could translate into less pulmonary complications, shorter hospital stay, less pain, improved quality of life and quicker return to normal activities or work compared with nonoperative treatment. Operative treatment, while initially yielding higher economic costs, could then result in less financial needs, due to less health care use and less productivity loss. As a result, primarily performing surgery could be both improving patient outcome as well as being the most cost-effective treatment modality. To the best of our knowledge, this is the first multicenter randomized controlled trial to evaluate outcome from patient, medical, and economic perspectives in patients suffering from multiple simple rib fractures. Twelve hospitals in the Netherlands will participate in this trial.

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CHAPTER 8

A decade of surgical stabilization of rib fractures: the effect of study year on patient selection, operative characteristics, and in-hospital outcome

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ABSTRACT

Background

Many centers now perform surgical stabilization of rib fractures (SSRF). This single center study aimed to investigate temporal trends by year in patient selection, operative characteristics, and in-hospital outcomes We hypothesized that, over time, patient selection, time to SSRF, operative time, and in-hospital outcomes varied significantly.

Methods

A retrospective review of a prospectively maintained SSRF database (2010 to 2020) was performed. Patients were stratified by year in which they underwent SSRF. The primary outcome was operative time, defined in minutes from incision to closure. Secondary outcomes were patient and operative characteristics, and in-hospital outcomes. Multivariable regression analyses were performed to assess for temporal trends, corrected for confounders. The outcomes ventilator-, Intensive Care Unit-, and hospital-free days (VFD, IFD, and HFD, respectively) were categorized based on the group's medians, and complications were combined into a composite outcome.

Results

In total, 222 patients underwent SSRF on a median of one day after admission (P_{25}-P_{75}, 0-2). Patients had a median age of 54 years (P_{25}-P_{75}, 42-63), ISS of 19 (P_{25}-P_{75}, 13-26), RibScore of 3 (P_{25}-P_{75}, 2-5), and sustained a median of 8 fractured ribs (P_{25}-P_{75}, 6-11). In multivariable analysis, increasing study year was associated with an increase in operative time ($p<0.0001$). In addition, study year was associated with a significantly reduced odds of complications (Odds ratio [OR], 0.76; 95% Confidence Interval [95% CI], 0.63-0.92; $p=0.005$), VFD < 28 days (OR, 0.77; 95% CI, 0.65-0.92; $p=0.003$), IFD < 24 days (OR, 0.77; 95% CI, 0.66-0.91; $p=0.002$), and HFD < 18 days (OR, 0.64; 95% CI, 0.53-0.76; $p<0.0001$).

Conclusion

In-hospital outcomes after SSRF improved over time. Unexpectedly, operative time increased. The reason for this finding is likely multifactorial and may be related to patient selection, onboarding of new surgeons, fracture characteristics, and minimally invasive exposures. Due to potential for confounding, study year should be accounted for when evaluating outcomes of SSRF.

INTRODUCTION

Over the last decade, the practice of surgical stabilization of rib fractures (SSRF) has increased exponentially, and with this increase has come an evolution in practice patterns. The use of SSRF as compared to nonoperative management has been associated with fewer pulmonary complications, improved in-hospital outcomes, and lower costs [1-3]. Although flail chest is the traditional indication for surgery, multiple bicortically displaced fractures, failure of early nonoperative management, and chronic pain following rib fracture nonunion have now become accepted indications for SSRF [4, 5]. Additionally, indications precluding SSRF have changed and narrowed over time. Traditional contraindications, largely based on expert opinions rather than high quality studies, include age, as well as concomitant pulmonary contusion or traumatic brain injury (TBI), but recently SSRF has shown to be safe in these patients and has even been associated with improved outcomes in select patient cohorts [5-10]. Finally, the ideal time from injury to surgery is debated but, in general, believed to be as early as possible [11-15].

While present literature has established the overall effectiveness of SSRF in a broadening group of patients with rib fractures, little is known regarding how a SSRF program evolves over time. For example, outcomes such as operative time and complication rate have been shown to be affected by case volume or years after implementation for cardiothoracic or vascular procedures [16]. To our knowledge, there is no literature available concerning the effect of study year on patient selection, intra-operative characteristics, and in-hospital outcomes after SSRF.

Our SSRF program began in 2010, at which time it was at a low volume and lacked institutional familiarity. Furthermore, case selection favored patients with severe thoracic injuries. Over the years, experience has accumulated through increased case volume, additional resources, and standardized management pathways. The primary objective of this study was to evaluate the evolution of our SSRF program over time, defined by patient selection, procedural characteristics, and in-hospital outcome. We hypothesized that with increasing years of SSRF performance, patient selection changed, time to SSRF and operative time decreased, and in-hospital outcomes improved.

METHODS

Design and participants
This was a retrospective study of a prospectively maintained SSRF database from a Level 1 Trauma Center (Denver Health Medical Center, Denver, CO) of patients who underwent SSRF between January 1st, 2010 and December 31st, 2020. Institutional

review board approval was obtained. Inclusion criteria were: 1) age 18 years or older at the time of SSRF; 2) SSRF performed between January 1st, 2010 and December 31st, 2020. Patients with any of the following criteria were excluded: 1) SSRF performed for chronic indication (>30 days after trauma) such as nonunion or chronic chest wall deformity; 2) no information on operative time; 3) imprisoned at time of SSRF; 4) known pregnancy at time of SSRF.

Indications for surgery were ≥1 of the following: 1) flail segment (2 or more consecutive ribs fractured in ≥2 locations on chest CT) or clinical flail chest (paradoxical breathing); 2) ≥ 3 ipsilateral, severely displaced rib fractures, defined as no cortical contact between fracture ends on axial chest CT; 3) ≥30% volume loss of hemithorax, as quantified on chest CT; 4) failure of optimal nonoperative management. Contraindications for SSRF were hemodynamic instability, intracranial hypertension, pleural empyema, and severe chest wall tissue loss. There was no age or BMI cutoff for SSRF.

During the study period, one implant system was available and SSRF was performed exclusively by Trauma and Acute Care Surgeons. All fractures of ribs three to 10, with at least three centimeters from the vertebral column for posterior fractures, were considered amenable to SSRF. The implanted pre-contoured plate's length was chosen to allow for fixation with three screws on each fracture end. If possible, both fractures were repaired in case of a flail segment. The SSRF procedure was standardized to include general anesthesia, fiberoptic bronchoscopy, muscle sparring incisions, video-assisted thoracoscopic surgery (VATS)-inspection of the thorax, evacuation of retained hemothorax, pleural irrigation, and chest tube placement. Non-standardized intra-operative procedures included intercostal nerve blockade during VATS or pain catheter placement. Post-operatively, all patients were prescribed pulmonary toilet regimens implemented by certified respiratory therapists and received locoregional pain control as well as scheduled acetaminophen, ibuprofen, gabapentin, oxycodone, or intravenous narcotics as needed. Follow-up included outpatient visits at four, eight, and 12 weeks postoperatively including physical examination and chest radiography.

Data collection and outcome measures

Data were collected from the local SSRF database or extracted from the patient's electronic medical file. The independent variable was the year in which SSRF was performed. This variable was operationalized as categorical in which the years 2010-2013 were combined due to the low volume of SSRF. The primary dependent variable was operative time (minutes), defined as the time of incision to closure of the SSRF surgical site.

Additional operative characteristics were time from admission to SSRF (days), time per plate fixated (minutes), concurrent surgery during SSRF, proportion with multiple patient positioning (e.g., lateral decubitus to address lateral fractures followed by prone

positioning to address posterior fractures), number of ribs plated, number of fractures plated, subscapular fracture fixation, first or second rib fixation [17, 18], and intra-operative locoregional analgesia (i.e., intercostal nerve blockade or pain catheter). In-hospital outcomes included mechanical ventilation requirement and duration (days), HLOS and ICU-LOS, complication rates (rate of tracheostomy, pneumonia [19], and mortality), and additional required thoracic operative procedures (e.g., acute takeback <30 days, chest tube placement, hardware explant).

In addition, the following baseline characteristics were collected: age (years), sex, body mass index (BMI, kg/m2), smoking at age of trauma, and presence of asthma or chronic obstructive pulmonary disease (COPD). Injury-related variables included Injury Severity Scale (ISS), admission Glasgow Coma Scale (GCS), presence of blunt cerebrovascular injury (BCVI), intracranial hemorrhage (ICH), degree of pulmonary contusion, as measured by the Blunt Pulmonary Contusion 18 (BPC-18) score [20], and presence of hemo- or pneumothorax on admission, clavicle fracture, scapula fracture, spine fracture, pelvic fracture, long bone fracture, and solid organ injury. Rib fracture severity was captured through the number of rib fractures, presence of a flail segment, ≥3 displaced rib fractures, and the RibScore [21]. Additional required major procedures during primary admission that were collected were pelvic, spine, or long bone operation, laparotomy, thoracotomy pre-SSRF, vascular intervention (i.e., endovascular repair or embolization), and craniotomy.

Statistical analysis

Data were analyzed using SAS 9.4 (SAS Institute, Cary, NC). Descriptive analysis was performed to report data for the entire study population and stratified by study year. Because of the low sample sizes per study year and skew distributions, continuous variables were reported as median and percentiles and analyzed using non-parametric tests of significance. Categorical data were reported as numbers and frequencies. Statistical significance between groups was determined using Kruskal-Wallis test (≥2 groups) for continuous data and Chi-squared or Fisher's Exact test for categorical data as applicable. A p-value lower than 0.05 was considered statistically significant and all tests were two-sided.

In multivariable analysis, all collected variables found to be associated with study year at the p<0.25 level by univariate analysis were entered into regression models to determine independent predictors to correct for. In linear models, an automated selection procedure based on the Schwarz Bayesian information criterion (SBC) was used to reduce the number of confounders in categories pre-operative and intra-operative variables while keeping all confounders of similar importance in univariate analysis. In this selection procedure, if removing any effect yields a model with a lower SBC statistic than the current model, then the effect producing the smallest SBC statistic

is removed. If removing an effect increases the SBC statistic, the effect producing the model with the lowest SBC is added (provided that adding it lowers the SBC statistic). In logistic models, calibration of the model was assessed via Hosmer-Lemeshow (H-L) with higher p-values indicating better calibration. Discrimination of the model was evaluated via area under the receiver-operating characteristics curve (AUROC) with 95% confidence interval (CI). Patients with concomitant extra-thoracic procedures (e.g., long bone or pelvic repair) performed during SSRF were excluded for all outcomes.

Due to the study year group's medians which were too skewed to be used as continuous variables with no transformation approximating normality, the outcomes ventilator-free days (days of hospital admission without assisted breathing requirement), ICU-free days (days outside of the ICU during hospital stay), and hospital-free days (days spent outside of the hospital after SSRF) were categorized. The outcome-free days were fixed at 28 days as recommended [22]. The definition for the outcome-free days was: if outcome >28 days or the patient died, then outcome-free days was set to 0, otherwise outcome-free-days = 28-outcome.The outcome complication rate was combined into a composite outcome (rate of pneumonia, tracheostomy requirement, additional chest tube requirement or acute takeback <30 days). The final unadjusted model included the outcome measure as the dependent variable, and study year as covariate. In the adjusted analysis, the covariates in the final model were added. For logistic regression analysis, the OR per study year is reported with 95% CI and p-values. For linear regression analysis, the beta value per study year is reported with standard error (SE) and p-values.

RESULTS

In total, 222 patients underwent SSRF on a median of one day (P_{25}-P_{75}, 0-2 days) after admission. Of the total cohort, 162 (73%) were male, the median age was 54 years (P_{25}-P_{75}, 42-63 years) with a BMI of 26 kg/m^2 (P_{25}-P_{75}, 23-30 kg/m^2) and an ISS of 19 (P_{25}-P_{75}, 13-26) (Table 1). Patients had a median RibScore of 3 (P_{25}-P_{75}, 2-5) with 8 (P_{25}-P_{75}, 6-11) fractured ribs and 12 (P_{25}-P_{75}, 7-15) rib fractures. A radiographic flail segment was present in 138 (62%) patients and 154 (69%) required a chest tube at admission (Table 1). In univariate analysis, the number of rib fractures, the proportion of patients requiring a chest tube at admission or with a hemothorax, was significantly different across study years (Table 1). Except for BCVI, the extra-thoracic injuries and required interventions were similar throughout the years (Table 1). Age, ISS, and proportion of patients with a radiographic flail segment, ≥3 displaced rib fractures or subscapular rib fractures were similar (Table 1).

Over the years, the time to SSRF shortened from 2 days (P_{25}-P_{75}, 0-5 days) to 0 days (P_{25}-P_{75}, 0-1 days; p=0.032). The operative time varied significantly during the study

years, ranging from 116 (P_{25}-P_{75}, 91-189) to 178 minutes (P_{25}-P_{75}, 149-268; p<0.001; Table 2). In addition, time per plate was significantly different over the study years, ranging from 24 minutes (P_{25}-P_{75}, 20-28) in 2015 to 38 minutes (P_{25}-P_{75}, 30-59) in 2019 (p<0.001). While the median number of ribs plated (4, P_{25}-P_{75}, 3-6) and ratio of fractures plated to fractures sustained (0.4, P_{25}-P_{75}, 0.3-0.6) did not change over the years, the median number of plates used (5, P_{25}-P_{75}, 4-6; p=0.005) and median ratio of fractures plated to ribs plated (1.0, P_{25}-P_{75}, 1.0-1.0; p=0.018) were significantly different (Table 2). Concurrent surgeries during SSRF were more common in the later study years and included spine repair in 6 patients (3%), orthopedic clavicle or long bone repair in 4 (2%), pelvic repair in 2 (0.9%), diagnostic laparoscopy in 2 (0.9%), bladder repair in 1 (0.5%), and laparotomy in 1 (0.5%).

In-hospital outcomes showed a significant difference in ICU-LOS, HLOS, ventilator days, pneumonia, and tracheostomy rate throughout study years (Table 2). In total, 13 (6%) patients required an acute takeback within 30 days of which 6 (3%) were due to post-operative bleeding, 2 (0.9%) due to empyema, 2 (0.9%) due to pulmonary herniation, 2 (0.9%) due to additional SSRF, and 1 (0.5%) due to scapular hardware removal. Seven (3%) patients required an additional chest tube post-SSRF due to empyema (n=1, 0.9%), pleural effusion (n=4, 2%), or a pneumothorax (n=2, 0.9%). In-hospital mortality occurred in 3 (1%) patients, due to a myocardial infarction (n=1, 0.5%), pulmonary embolism (n=1, 0.5%), and sepsis (n=1, 0.5%) following colitis. In seven (3%) patients, hardware was explanted because of hardware infection (n=4, 2%), scapular grinding complaints (n=2, 0.9%), and hardware displacement (n=1, 0.5%). Two (0.9%) patients required operative repair of a symptomatic non-fixated rib fracture nonunion. There were no patients with osteomyelitis or neuropathic pain during follow-up.

In the unadjusted multivariable regression analysis both operative time and time per plate increased significantly (p<0.0001; Figure 1). In multivariable regression analysis, adjusted for confounding covariates, both operative time (beta, 9.0 minutes per study year, SE 1.9) and time per plate (beta, 2.2 minutes per study year, SE 0.5) increased significantly over the years (both p<0.0001; Figure 2). An alternative regression model including all confounders showed similar results for both outcomes (results not shown). Increasing study year was a significant predictor of no complications and associated with a reduction in odds of 0.76 per study year (95% CI, 0.63-0.92, p=0.005). Also, study year emerged as a significant predictor of ventilator-free days ≥28, Intensive Care Unit-free days ≥24, and hospital-free days ≥18. There was a reduction in odds of ventilator-free days <28 of 0.77 per study year (95% CI, 0.65-0.92, p=0.003). Per study year, there was a reduction in odds of Intensive Care Unit-free days <24 of 0.77 (95% CI, 0.66-0.91, p=0.002). Per study year, there was a reduction in odds of hospital-free days <18 of 0.64 (95% CI, 0.53-0.76, p<0.0001). All models had acceptable to excellent calibration and discrimination (Table 3).

TABLE 1
Demographics, injury-related, and non-SSRF treatment-related characteristics in patients who underwent surgical stabilization of rib fractures from 2010-2020.

	Overall (n=222)	2010-2013 (n=9)	2014 (n=33)	2015 (n=32)
Demographics				
Age (years)	54 (42-63)	40 (24-52)	51 (37-60)	59 (45-67)
Sex (male)	162 (73%)	5 (56%)	28 (85%)	24 (75%)
Smoking at age of trauma	70 (32%)	2 (22%)	13 (39%)	13 (41%)
COPD or asthma	27 (12%)	1 (11%)	2 (6%)	3 (9%)
BMI (kg/m^2)	26 (23-30)	26 (22-31)	28 (23-32)	27 (23-31)
Injury characteristics				
ISS*	19 (13-26)	22 (16-24)	22 (17-26)	21 (13-29)
Admission GCS score	15 (14-15)	14 (11-15)	15 (14-15)	15 (11-15)
ICH	35 (16%)	3 (33%)	2 (6%)	7 (22%)
BCVI	15 (7%)	0 (0%)	0 (0%)	0 (0%)
Spine fracture	83 (37%)	6 (67%)	13 (39%)	11 (34%)
Pelvic fracture	40 (18%)	2 (22%)	8 (24%)	7 (22%)
Long bone fracture	33 (15%)	1 (11%)	2 (6%)	7 (22%)
Solid organ injury	56 (25%)	2 (22%)	10 (30%)	3 (9%)
Chest injury characteristics				
Number of fractured ribs	8 (6-11)	10 (8-17)	8 (7-9)	8 (6-11)
Number of rib fractures	12 (7-15)	15 (12-22)	13 (11-15)	11 (7-17)
Flail segment	138 (62%)	9 (100%)	22 (67%)	23 (72%)
≥3 displaced rib fractures	217 (98%)	9 (100%)	33 (100%)	31 (97%)
≥1 SS rib fractures	156 (70%)	9 (100%)	26 (79%)	20 (63%)
RibScore	3 (2-5)	5 (4-6)	3 (3-5)	4 (2-5)
BPC18*	4 (3-5)	5 (3-9)	4 (2-7)	4 (1-5)
Hemothorax	136 (61%)	5 (56%)	19 (58%)	9 (28%)
Pneumothorax	167 (75%)	6 (67%)	27 (82%)	25 (78%)
Chest tube pre-SSRF	154 (69%)	8 (89%)	22 (67%)	22 (69%)
Clavicle fracture	48 (22%)	3 (33%)	7 (21%)	9 (28%)
Sternum fracture	20 (9%)	0 (0%)	2 (6%)	3 (9%)
Scapula fracture	51 (23%)	6 (67%)	7 (21%)	5 (16%)
Treatment characteristics				
Exploratory laparotomy	19 (9%)	0 (0%)	3 (9%)	2 (6%)
Emergency thoracotomy pre-SSRF	4 (2%)	1 (11%)	0 (0%)	0 (0%)
Craniotomy	1 (0.5%)	0 (0%)	0 (0%)	1 (3%)
Pelvic operation	23 (10%)	1 (11%)	5 (15%)	2 (6%)
Spine operation	17 (8%)	0 (0%)	1 (3%)	2 (6%)
Vascular intervention	11 (5%)	0 (0%)	1 (3%)	1 (3%)
Long bone operation	32 (14%)	2 (22%)	7 (21%)	7 (22%)

*: the parameter ISS was available for 214 patients and BPC18 for 219 patients. Data on all other parameters were complete for all patients.
a: Chi-squared test; b: Kruskal-Wallis test. Data are shown as median (P25-P75) or as N (%); bold p-values are considered statistically significant.
BCVI, blunt cerebrovascular injury; BMI, body mass index; BPC18, blunt pulmonary contusion 18-score; COPD, Chronic Obstructive Pulmonary Disease; GCS, Glasgow Coma Scale; ICH, intracranial hemorrhage; ISS, injury severity score; MCC, motorcycle collision; MVC, motor vehicle collision; SS, subscapular; SSRF, surgical stabilization of rib fractures.

	2016 (n=24)	2017 (n=24)	2018 (n=29)	2019 (n=31)	2020 (n=40)	p
	56 (48-63)	54 (42-61)	59 (43-68)	55 (41-72)	50 (42-60)	0.061
	16 (67%)	16 (67%)	21 (72%)	25 (81%)	27 (68%)	0.503
	9 (38%)	7 (29%)	4 (14%)	8 (26%)	14 (35%)	0.341
	3 (13%)	5 (21%)	3 (10%)	4 (13%)	6 (15%)	0.836
	26 (23-30)	27 (23-30)	26 (24-29)	25 (22-29)	26 (23-31)	0.677
	17 (14-26)	18 (10-25)	15 (10-22)	18 (9-25)	22 (16-38)	0.066
	15 (10-15)	15 (9-15)	15 (15-15)	15 (14-15)	15 (13-15)	0.277
	3 (13%)	4 (17%)	3 (10%)	5 (16%)	8 (20%)	0.458
	0 (0%)	1 (4%)	3 (10%)	3 (10%)	8 (20%)	**0.007[a]**
	10 (42%)	7 (29%)	8 (28%)	11 (36%)	17 (43%)	0.535
	3 (13%)	3 (13%)	2 (7%)	5 (16%)	10 (25%)	0.527
	2 (8%)	3 (13%)	3 (10%)	6 (19%)	9 (23%)	0.420
	2 (8%)	6 (25%)	9 (31%)	10 (32%)	14 (35%)	0.109
	8 (5-12)	6 (5-8)	8 (7-12)	9 (6-12)	8 (6-11)	0.212
	11 (6-15)	9 (6-12)	12 (9-16)	12 (7-18)	12 (7-16)	**0.040[b]**
	14 (58)	12 (50%)	19 (66%)	16 (52%)	23 (58%)	0.153
	24 (100%)	23 (96%)	27 (93%)	31 (100%)	39 (98%)	0.587
	19 (79%)	16 (67%)	20 (69%)	21 (68%)	25 (63%)	0.314
	3 (2-5)	2 (1-4)	4 (3-4)	4 (2-5)	4 (2-4)	0.100
	6 (3-9)	4 (3-5)	4 (2-6)	4 (3-6)	3 (2-6)	0.221
	20 (83%)	13 (54%)	16 (55%)	26 (84%)	28 (70%)	**<0.001[a]**
	21 (88%)	20 (83%)	24 (83%)	22 (71%)	22 (55%)	0.051
	21 (88%)	23 (96%)	24 (83%)	15 (48%)	19 (48%)	**<0.001[a]**
	6 (25%)	6 (25%)	1 (3%)	8 (26%)	8 (20%)	0.343
	5 (21%)	1 (4%)	4 (14%)	2 (7%)	3 (8%)	0.409
	4 (17%)	3 (13%)	7 (24%)	7 (23%)	12 (30%)	0.053
	2 (8%)	4 (17%)	2 (7%)	2 (7%)	4 (10%)	0.838
	1 (4%)	0 (0%)	0 (0%)	0 (0%)	2 (2%)	0.177
	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.544
	2 (8%)	3 (13%)	0 (0%)	3 (10%)	7 (18%)	0.409
	5 (21%)	2 (8%)	2 (7%)	1 (3%)	4 (10%)	0.257
	0 (0%)	2 (8%)	1 (3%)	3 (10%)	3 (8%)	0.666
	2 (8%)	2 (8%)	2 (7%)	5 (16%)	5 (13%)	0.530

CHAPTER 8

TABLE 2
Intra-operative characteristics of surgical stabilization of rib fractures (SSRF) and in-hospital outcome in patients who underwent SSRF from 2010 to 2020

	Overall (n=222)	2010-2013 (n=9)	2014 (n=33)	2015 (n=32)
Intra-operative characteristics				
Time to SSRF (days)	1 (0-2)	2 (0-5)	1 (0-2)	1 (0-2)
Operative time (minutes)	143 (113-187)	147 (115-162)	137 (112-177)	117 (92-147)
Concurrent surgery during SSRF	16 (7%)	0 (0%)	1 (3%)	1 (3%)
Multiple positions/dressing	17 (8%)	0 (0%)	0 (0%)	0 (0%)
Locoregional analgesia				
VATS ICNB	70 (31.5%)	0 (0%)	0 (0%)	0 (0%)
Pain catheter placement	106 (48%)	4 (44%)	28 (85%)	22 (69%)
Number of ribs plated	4 (3-6)	5 (4-5)	5 (4-6)	4 (3-6)
Number of fractures plated	5 (4-6)	5 (4-5)	6 (5-7)	5 (3-6)
Fractures plated : ribs plated ratio	1.0 (1.0-1.0)	1.0 (1.0-1.1)	1.0 (1.0-1.3)	1.0 (1.0-1.0)
Fractures plated : total fractures	0.4 (0.3-0.6)	0.3 (0.2-0.4)	0.4 (0.4-0.6)	0.5 (0.4-0.7)
Time per plate (minutes)	30 (25-40)	29 (25-39)	26 (21-30)	24 (20-28)
Subscapular fracture fixation	104 (47%)	7 (78%)	18 (55%)	13 (41%)
Posterior fracture fixation	106 (48%)	6 (67%)	19 (58%)	15 (47%)
First or second rib fixation	8 (4%)	1 (11%)	0 (0%)	2 (6%)
In-hospital outcome				
Acute takeback (<30 days)	13 (6%)	0 (0%)	0 (0%)	3 (9%)
Additional chest tube post-SSRF	7 (3%)	0 (0%)	2 (6%)	1 (3%)
ICU-LOS	4 (2-8)	11 (2-14)	7 (3-11)	4 (2-9)
HLOS	10 (6-16)	19 (9-24)	15 (10-21)	11 (11-18)
MV requirement	84 (38%)	7 (78%)	17 (52%)	12 (38%)
Ventilator days	8 (4-16)	11 (2-16)	9 (5-23)	9 (6-17)
Pneumonia	27 (12%)	2 (22%)	7 (21%)	7 (22%)
Tracheostomy	40 (18%)	4 (44%)	9 (27%)	9 (28%)
Mortality	3 (1%)	0 (0%)	0 (0%)	0 (0%)
Hardware explant	7 (3%)	0 (0%)	2 (6%)	3 (9%)

Data was complete for all parameters. [a]: Kruskal-Wallis test; [b]: Chi-squared test. Data are shown as median (P_{25}-P_{75}) or as N (%); bold p-values are considered statistically significant.
HLOS, hospital length of stay; ICNB, intercostal nerve blockade; ICU-LOS, Intensive Care Unit length of stay; MV, mechanical ventilation; SSRF, surgical stabilization of rib fractures; VATS, Video-Assisted Thoracoscopic Surgery.

	2016 (n=24)	2017 (n=24)	2018 (n=29)	2019 (n=31)	2020 (n=40)	p
	1 (0-2)	0 (0-2)	0 (0-1)	0 (0-1)	1 (0-2)	**0.032[a]**
	121 (98-135)	116 (91-189)	155 (116-201)	178 (149-268)	162 (137-232)	**<0.001[a]**
	1 (4%)	0 (0%)	1 (3%)	4 (13%)	8 (20%)	**0.021[b]**
	0 (0%)	1 (4%)	3 (10%)	5 (16%)	8 (20%)	**0.004[b]**
	0 (0%)	8 (33.3%)	17 (58.6%)	21 (67.7%)	24 (60.0%)	**<0.001[b]**
	21 (88%)	12 (50%)	5 (17%)	5 (16%)	9 (23%)	**<0.001[b]**
	4 (3-6)	4 (2-4)	5 (3-6)	5 (3-6)	5 (3-6)	0.087
	5 (3-6)	4 (2-4)	5 (3-6)	5 (3-6)	5 (3-8)	**0.005[a]**
	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.2)	1.0 (1.0-1.0)	1.0 (1.0-1.3)	**0.018[a]**
	0.4 (0.3-0.7)	0.4 (0.3-0.6)	0.4 (0.3-0.5)	0.4 (0.3-0.7)	0.5 (0.3-0.7)	0.251
	26 (22-33)	35 (27-49)	34 (25-43)	38 (30-59)	37 (29-45)	**<0.001[a]**
	10 (42%)	6 (25%)	15 (52%)	17 (55%)	18 (45%)	0.151
	11 (46%)	6 (25%)	14 (48%)	13 (42%)	22 (55%)	0.263
	1 (4%)	1 (4%)	0 (0%)	1 (3%)	2 (5%)	0.696
	2 (8%)	1 (4%)	3 (10%)	1 (3%)	3 (8%)	0.615
	1 (4%)	0 (0%)	0 (0%)	2 (7%)	1 (3%)	0.763
	6 (2-11)	4 (2-6)	2 (1-3)	3 (1-6)	4 (2-7)	**<0.001[a]**
	12 (8-19)	8 (5-10)	6 (4-10)	9 (4-11)	9 (6-16)	**<0.001[a]**
	12 (50%)	10 (42%)	4 (14%)	10 (32%)	12 (30%)	**0.008[b]**
	7 (3-15)	3 (1-11)	3 (1-4)	5 (4-9)	14 (5-36)	**0.015[a]**
	3 (13%)	1 (4%)	0 (0%)	1 (3%)	6 (15%)	**0.046[b]**
	5 (21%)	3 (13%)	0 (0%)	2 (7%)	8 (20%)	**0.011[b]**
	1 (4%)	1 (4%)	0 (0%)	1 (3%)	0 (0%)	0.584
	1 (4%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)	0.276

TABLE 3
Adjusted effect of study year on secondary outcomes and included covariates per final regression model

Outcome	Occurrence	Covariates included in regression model	H-L (p)	AUROC (95% CI)	Odds ratio (95% CI)	p
Complications	47 (24%)	Age, ISS, RibScore, hemothorax at admission, and time to SSRF	0.810	0.828 (0.758-0.900)	0.762 (0.629-0.922)	**0.005**
Ventilator-free days < 28	71 (35%)	Age, ISS, chest tube at admission, and time to SSRF	0.260	0.826 (0.766-0.886)	0.771 (0.650-0.915)	**0.003**
Intensive Care Unit-free days < 24	95 (46%)	Age, ISS, time to SSRF	0.970	0.858 (0.805-0.910)	0.772 (0.655-0.909)	**0.002**
Hospital-free days <18	86 (42%)	Age, ISS, time to SSRF	0.980	0.856 (0.804-0.908)	0.638 (0.534-0.762)	**<.0001**

AUROC, area under the receiver-operating characteristics curve; CI, confidence interval; H-L, Hosmer Lemeshow; ISS, injury severity scale; SSRF, surgical stabilization of rib fracture.
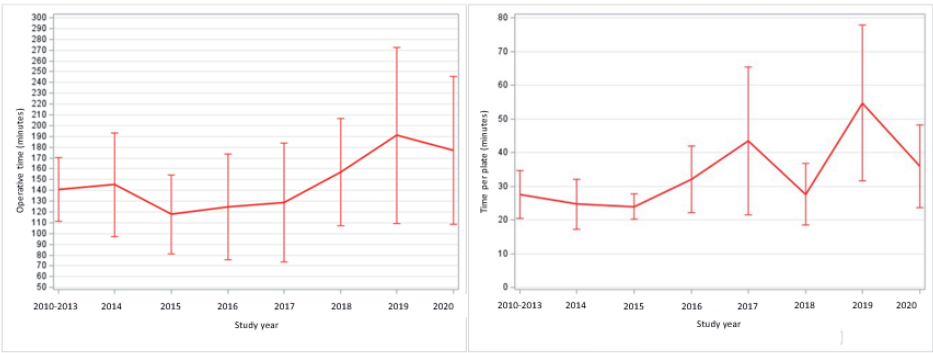
FIGURE 1
Unadjusted temporal trends in operative time (OR) and time per plate over the study period.
Data are presented as mean ± standard deviation.
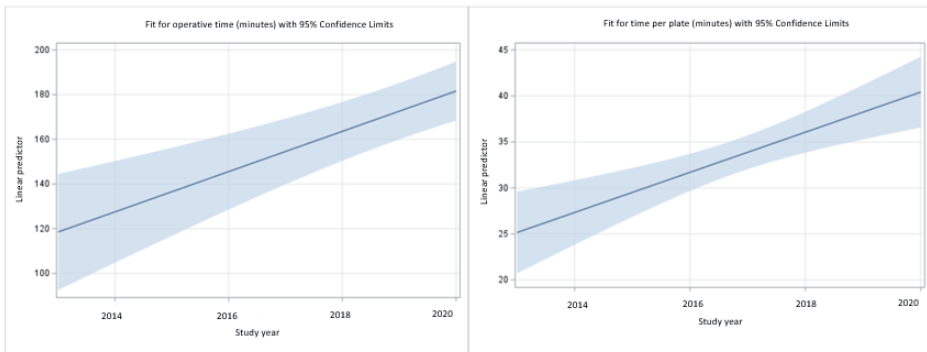
FIGURE 2

Adjusted temporal trends in operative time (OR) and time per plate over the study years.
The final regression model for operative time included RibScore, hemothorax at admission, number of plates used, intra-operative locoregional intercostal nerve blockade. The final regression model for time per plate included age, number of rib fractures, hemothorax at admission, number of plates used, and intra-operative locoregional intercostal nerve blockade.

DISCUSSION

This retrospective review assessed patient selection, procedural characteristics, and in-hospital outcome over a decade of SSRF at a single institution. Over time, operative time increased, time to SSRF decreased, patient selection remained similar, and in-hospital outcomes improved. Even after correcting for confounders, operative time increased significantly over the years. For in-hospital outcome, every additional year of experience with SSRF was associated with a 24% reduction in odds of complications, a 23% reduction of both ventilator-free days <28 days and Intensive Care Unit-free days <24 days, and a reduction of 36% of hospital-free days <18 days.

Literature addressing SSRF has increased ten-fold over the last decade, and SSRF has been implemented internationally in most Trauma Centers [23-27]. Due to SSRF being a relatively novel technique and because of recently broadening indications in specific patients or injury patterns, studies on outcomes following this procedure often cover multiple study years [8, 28, 29]. This approach could be limited as it may not account for changes in both practice and outcomes over time. Our study suggests that important differences exist over time and thus study year should be accounted for in multi-year investigations of SSRF.

One unexpected finding was that operative time increased over the years. When learning a new procedure, performance tends to improve with experience [30]. While other clinical outcomes might be of at least equal clinical importance, these might not be as directly linked to the specific procedure itself as operative time. In cardiothoracic

surgery, the effect of time and case volume on operative time and complication rate has been studied previously and has been referred to as a "learning curve" for a new procedure [16]. A learning curve is typically described by the starting point at which the performance begins, the learning plateau at which the performance stabilizes, and the rate of learning which is the speed at which a defined level of performance is reached [31]. In this previous review on learning curves in cardiothoracic and vascular surgeries, all studies reported similar or decreased operative time and complications over time or with an increasing number of cases [16].

Our study did not find decreased operative time with experience. One potential explanation for this finding is an increased complexity of cases. For example, although the number of both ribs and fractures fixed remained relatively constant over time, we did note an increase over time of two specific variables: (1) the number of cases utilizing multiple positions/exposures and (2) the number of cases in which additional surgeries (e.g., clavicle fixation) took place. These findings suggest that, as familiarity with SSRF increases, new practice patterns are employed that may increase operative time, but ultimately are beneficial to the patient. However, the increased operative time over the years persisted even after controlling for the above variables. One additional explanation for the increasing operative time could be the onboarding of new surgeons, amount of supervision and mentorship given during SSRF, or operative characteristics and case selection bias not captured in the collected variables. In this study, the attending thoracic surgeon and senior author was present at over 80% of SSRF cases, but due to the retrospective nature and lengthy study period, it could not be distilled to what extent other surgeons or residents participated in the approach, rib stabilization, or wound closure. Finally, it is possible that size of incisions and muscle dissection lessened over time, resulting in increased time to fixate fractures through a smaller "window" of exposure. It was not possible to capture this variable with only the time of incision and of surgical site closure available in the medical record. Other operative characteristics such as subscapular or posterior fracture fixation and the ratios of rib fractures fixated over ribs fixated and fractures fixated over fractures sustained did not significantly impact operative time. On the other hand, the currently collected variables might not be adequate parameters in defining case complexity while uncaptured injury characteristics (e.g., oblique rib fractures) or other operative characteristics (e.g., fixating two rib fractures with one long plate instead of two shorter plates to increase minimally invasiveness) might have impacted this outcome more strongly.

This study highlights another important aspect which has not previously been described when evaluating SSRF, namely the effect of study year on outcomes. Not only did more experience with SSRF result in quicker time to SSRF and reduced odds of complications, each additional year of SSRF performance was associated with reduced

odds of lengthy hospital and ICU stay and ventilator days of over 20%. Also, the variability in outcomes over the years identifies a possible new covariate which might need accounting for when presenting outcome after SSRF. In multicenter studies, study center is a known confounder [32]. Based on the findings of this study, adjusting for study year or time frame since implementation of SSRF when presenting outcomes over multiple years, might be necessary.

The decreased time from admission to SSRF observed over the years was also likely multifactorial. This finding could be partially explained by surgeons evolving practice pattern to incorporate data suggesting clinical benefit to early SSRF [12, 13, 33]. However, it is also our contention that, as case volume and experience with SSRF increases, there is an increased familiarity with the procedure by operating room staff. Indeed, operative room access for SSRF remained relatively constant at our institution over the 10-year study period in the form of a single urgent/emergent room that was shared with multiple other services. However, as staff became more familiar with the operation and specific aspects such as bronchoscopy, there may have been a subtle shift in allowing operative room access for a known service.

Although this study is the first to evaluate the effect of study year on characteristics of and outcome after SSRF, several limitations should be considered when interpreting these findings. First, this was a retrospective single-center trial which might have introduced information and treatment bias. Information bias through missing data was eliminated by extensive chart review and excluding patients with no information on the primary outcome. This resulted in only two variables (ISS and BPC-18) having missing data, but both <5%. Also, follow-up was relatively short (three months) and patients might have presented with SSRF-related complications to other hospitals, resulting in unclear follow-up time and an underestimation of the true rate of adverse events. The single-center design of this study might have introduced treatment effect, with single center trials tending to overestimate treatment effect [34]. However, indications for SSRF and perioperative management protocols have been standardized over the years and are similar in international Trauma Centers following previous multicenter studies, guidelines or collaboratives such as that of the Chest Wall Injury Society [8, 9, 12, 35]. Second, due to the large number of subgroups stratified by study year, the sample sizes of these groups might have been too low to detect small but clinically meaningful differences in outcome between study years. These yearly numbers do however mimic daily practice. Third, the presented regression models only included confounders which were identified from the available data. The confounding effect of non-included parameters was therefore not known. For example, no information was available on whether the registered surgeon completed the entire SSRF or whether it (partially) was a less experienced resident or surgeon. In addition, other variables that were not captured such as the specific lengths of the implanted plates, Abbreviated

Injury Scale (AIS) scores or day-to-day physiologic parameters might have impacted outcomes while not in the regression model. To correct for the missing AIS scores, all operative procedures and additional extra-thoracic injuries were collected, and these were, besides BCVI, similar across the subgroups. Last, it was not possible to capture or correct for general developments in this center's trauma care. The improved in-hospital outcomes might have been influenced by a significant overall improvement in trauma care.

Intra-operative characteristics of and in-hospital outcomes after SSRF appear to be associated with study year as they changed considerably throughout the study period. Patient selection remained similar and while time to SSRF decreased, the corrected operative time and time per plate both increased over the years. This is likely multifactorial and might be related to uncaptured patient selection, onboarding of new surgeons, and minimally invasive exposures. After controlling for available covariates, the odds of poor in-hospital outcomes decreased signficantly over the years, showing improved outcomes the longer a center performs SSRF. Due to the differences observed in this study, controlling for study year is recommended when evaluating outcomes after SSRF.

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CHAPTER 9

What is the optimal timing to perform surgical stabilization of rib fractures?

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ABSTRACT

The practice of surgical stabilization of rib fractures (SSRF) for severe chest wall injury has exponentially increased over the last decade due to improved outcomes as compared to nonoperative management. However, regarding in-hospital outcomes, the ideal time from injury to SSRF remains a matter of debate. This review aims to evaluate and summarize currently available literature related to timing of SSRF. Nine studies on the effect of time to SSRF were identified. All were retrospective comparative studies with no detailed information on why patients underwent early or later SSRF. Patients underwent SSRF most often for a flail chest or ≥3 displaced rib fractures. Early SSRF (≤48-72 hours after admission) was associated with shorter hospital and intensive care unit length of stay, duration of mechanical ventilation, and lower rates of pneumonia, and tracheostomy as well as lower hospitalization costs. No difference between early or late SSRF was demonstrated for mortality rate. As compared to nonoperative management, late SSRF (>3 days after admission), was associated with similar or worse in-hospital outcomes. The optimal time to perform SSRF in patients with severe chest wall injury is early (≤48-72 hours after admission) and associated with improved in-hospital outcomes as compared to either late salvage or nonoperative management. These data must however be cautiously interpreted due the retrospective nature of the studies and potential selection and attrition bias. Future research should focus on both factors and pathways that allow patients to undergo early SSRF.

INTRODUCTION

Thoracic trauma is the second leading cause of mortality after head trauma and accounts for 25% of injury-related deaths annually (1, 2). Rib fractures are common and present in 10% of trauma admissions and with rates up to 40% the most common injury following thoracic trauma (2-5). In addition, rib fractures are a marker of severe injury (6, 7). The gold standard for diagnoses and delineation of rib fractures is chest computed tomography (CT) which finds on average three additional rib fractures as compared to traditional chest radiography (8-11). Traumatic rib fractures often occur following high-energy trauma in younger patients, whereas more than half of elderly patients (≥65 years) sustain rib fractures after low-energy trauma such as a ground level fall (12, 13). There is a clear association between rib fractures and adverse outcomes. Not only the presence of rib fractures but also an increasing number of rib fractures is associated with mortality and pulmonary complications such as pneumonia (4, 14-18). In elderly patients this effect is even more prominent with two- to fivefold higher mortality rates as compared to younger patients with rib fractures and an increase in the mortality rate of 19% for each additionally fractured rib (12, 19, 20).

Furthermore, the degree of rib fracture dislocation has been associated with more severe concurrent thoracic trauma such as parenchymal injuries or pneumohemothorax, pulmonary complications and opioid requirement (21-23). In the long-term, sustaining rib fractures has been associated with chronic pain, disability, and decreased quality of life (24-28). Historically, rib fractures have been managed nonoperatively. Nonoperative treatment includes multimodal pain management, oxygen support or mechanical ventilation if required, and pulmonary physical therapy such as incentive spirometry (29). Even with improved critical care technology and widespread adoption of adjunctive pain management techniques, outcomes after multiple severe rib fractures have not significantly improved over the past 15 years (30). To date, the practice of rib fixation or surgical stabilization of rib fractures (SSRF) has increased exponentially and is now implemented in most international Trauma Centers (31-35). Despite increased use, many controversies within the field of SSRF remain. One such controversy surrounds the optimal time from injury to surgery. Two practice management guidelines for SSRF suggest early operative fixation to improve in-hospital outcomes (36, 37). However, literature on the optimal timing to SSRF is scarce. This review aimed to evaluate and summarize current available evidence related to timing of SSRF.

SSRF

The effect of SSRF has been studied using a variety of techniques, including wire cerclages, absorbable plates or Judet struts, but, to date, plating the outer cortex of

the rib with bicortical screws is the most commonly employed technique (38, 39). This procedure often comprises standardized components such as, but not limited to, muscle sparing or minimally invasive incisions, fiberoptic bronchoscopy, video-assisted thoracoscopic surgery (VATS), pleural irrigation, and chest tube placement (40, 41). Simultaneously, an evolution in practice patterns has come with the increase of the practice of SSRF. More recently, implementation of intra-operative cryoablation of the intercostal nerves or complete thoracoscopic SSRF have been described (42-44).

In trauma, the use of SSRF first established ground in the treatment of patients with a flail chest. Several randomized controlled trials and multiple systematic reviews and meta-analysis have demonstrated a benefit of SSRF as compared to nonoperative management in terms of pneumonia rate, duration of mechanical ventilation (DMV), hospital and intensive care unit length of stay (HLOS and ICU-LOS, respectively), and cost-effectiveness (45-54). As a result, consensus guidelines by among others the Eastern Association for the Surgery of Trauma (EAST) and the Chest Wall Injury Society (CWIS) now recommend SSRF in patients with a flail chest (36, 37). Over the last years, the indications for SSRF extended. For example, literature on patients with non-flail fracture patterns shows improved short-term outcomes associated with SSRF in these patients with for example multiple severely dislocated rib fractures (40, 55-58). In addition, traditional contraindications for SSRF, such as traumatic brain injury (TBI), age, or severe pulmonary contusion, are narrowing as SSRF has been shown to be a safe procedure in these patients and has even been correlated with improved outcomes in select patients (59-61). Long-term outcomes following SSRF have been studied less commonly with studies showing long-term pulmonary function and quality of life to recover to values within normal, but no significant benefit has been demonstrated compared to nonoperative management (62-66).

Theoretical Rationale

In orthopedics, data supports early fracture fixation (24 to 48 hours after admission) with improved in-hospital outcomes as compared to late fixation cohorts (67-69). In case of hip fractures, early fixation is associated with shorter HLOS, lower mortality, pain, and complications such as pneumonia, pressure ulcers, and infection, which might be partially due to earlier out of bed mobilization (68, 69). In patients with open fractures of the tibia and femur, early stabilization is paramount to restore alignment of the limb, eliminate movement and fracture overlap, diminish further soft-tissue damage, and decrease the risk of bacterial spread (70). For polytraumatized patients with pelvic, acetabulum, femur or spine fractures, early fixation is advocated because of a lower risk of pulmonary complications and multiple organ failure as compared to late surgery (71). When severe head trauma (Glasgow Coma Scale, GCS, <9) is present in patients with major orthopedic fractures, early aggressive stabilization of these

fractures is recommended if sufficient cerebral perfusion pressure can be maintained as this might prevent additional secondary brain injury due to hypotension, but available studies are of low quality (72).

The optimal timing to perform SSRF is debated, but, in general, believed to be rather early than late in patients without contra-indications who are deemed stable for surgery (Table 1). Because the ribs are intimately associated with respiration, it is impossible to immobilize them in an effective, nonoperative fashion without impacting pulmonary mechanics. Furthermore, rib fracture pain during respiration results in splinting and ineffective secretion clearance, both of which begin immediately following the injury and, over time, act in a cumulative fashion to place patients at a possibly increased risk for respiratory failure. The earlier these factors can be mitigated by stabilization, the earlier this risk is theoretically minimized.

One traditional SSRF indication is the failure of nonoperative management or the development of progressive pain or respiratory insufficiency. Advocates of this indication believe that primary nonoperative treatment avoids an unnecessary surgery. However, as mentioned, debilitating pulmonary morbidity rates including pneumonia, retained hemothorax, or empyema remain high in these patients and possibly precede this nonoperative management failure, whereas SSRF might have potentially prevented these complications (55, 73, 74). In addition, early SSRF creates an opportunity to clear the pleural space and place guided loco-regional anaesthesia. Furthermore, tissue inflammation and edema of both lung parenchyma and thoracic wall soft tissue peak at approximately 72 hours after injury with dissection often being bloodier and more challenging as compared to early SSRF (75). Also, hardware implantation in patients who have had recent pneumonia or empyema might lead to infected hardware, often requiring an additional operative procedure of implant removal (76, 77). Practice patterns and consensus statements appear to be shifting towards early SSRF.

TABLE 1
Contraindications to early SSRF

1.	Hemodynamic Instability
2.	Other high priority injuries (e.g. spine fractures)*
3.	Intracranial hypertension
4.	Inability to properly position patient (e.g. open abdomen, pelvic fixator)
5.	Pleural empyema
6.	Severe chest wall tissue loss

* The CWIS practice management guidelines advocate for a combined approach with a spine team in those patients with spine fractures that require operative fixation (59).
SSRF, surgical stabilization of rib fractures; CWIS, Chest Wall Injury Society.

Literature Review

Currently, there have been nine studies specifically addressing the effect of timing on outcomes after SSRF (Table 2).The earliest of these studies was a retrospective single center cohort study comparing patients who underwent SSRF (n=22) with a matched cohort of nonoperatively managed patients (n=28) (78). Indications for SSRF were a radiographic or clinical flail chest, and pulmonary hernia. The SSRF group consisted of 17 (77.3%) male patients with a mean age of 48 years with a mean ISS of 25 and 6 rib fractures. Patients underwent SSRF with 2.7-mm locking reconstruction plates and mean operative time of 55 minutes at a mean of 2.3 (range, 1-5) days after injury. The total cohort had a follow-up time of 17.8 (range, 13-22) months during which no cases of hardware failure, surgical site infection, or nonunion were reported. In regression analysis, Shorter time to SSRF was associated with decreased HLOS, ICU-LOS and DMV. The following study was a retrospective single center cohort study of 102 patients, stratified by time to SSRF (early, ≤48 hours or late, >48 hours) (79). Patients with a flail chest or ≥3 displaced rib fractures were considered for SSRF, but patients with chest wall deformity, inadequate analgesia, hemopneumothorax, or increasing ventilatory support when intubated, were also assessed for SSRF candidacy. A multidisciplinary team decided if patients should require SSRF and aimed to perform the procedure as soon as possible. Patients underwent SSRF with precontoured titanium rib fracture plates at 2 (range, 0-16 days) days after admission. The groups had similar sex, ISS, and presence of flail chest, hemopneumothorax, and additional non-chest injuries, but the early SSRF group was younger. The early SSRF group had significantly shorter HLOS (11.5 versus 17.3 days; p=0.008), ICU-LOS (3.3 versus 7.1 days; p=0.01), and DMV (4.8 versus 2.0 days; p=0.03), and decreased rate of pneumonia (n=11, 17% versus n=18, 49%; p=0.001), and tracheostomy (n=4, 6% versus n=8, 22%; p=0.02). The mortality rate was similar between groups.

The third study was a multicenter retrospective cohort study of 551 patients who underwent SSRF, stratified by timing to SSRF as early (day 0, ≤24 hours), mid (day 1-2), or late (days 3-10) (75). The choice of rib fixation system was left to the discretion of the surgeon and operative time varied significantly by group and was shortest in the mid group (median, 122 minutes) and longest for the late group (median, 201 minutes; p<0.01). Time to SSRF was significantly associated with study site, year of surgery, age, body mass index (BMI), and mechanism of injury. On univariate analysis, patients who underwent early SSRF had shorter HLOS, ICU-LOS and lower rate of DMV >24 hours. Rate of mortality, pneumonia, and tracheostomy did not differ between groups. Multivariable logistic regression showed that each additional day to SSRF was associated with an increased likelihood of 31% for pneumonia, 27% for DMV >24 hours, and 26% for tracheostomy.

The fourth study was a single center retrospective cohort study of 33 patients who underwent SSRF, stratified as early (≤3 days) or late (>3 days) (80). The two groups had similar age, BMI, sex, comorbidities, ISS, presence of flail chest, and associated injuries. Patients underwent SSRF with non-precontoured 2.4- or 3.5-mm metal locking plates between 0 and 14 days after injury. Operative time was similar between groups. The early SSRF group had significantly shorter HLOS (12 versus 18 days; p=0.005), ICU-LOS (123 versus 230 hours; p=0.005), and DMV (36 versus 90 hours; p=0.03). The rate of pneumonia, mortality, and total hospital costs were similar between groups. Multivariable regression analysis showed that time to SSRF was positively associated with shorter HLOS, ICU-LOS, DMV, and national health insurance costs.

The following study was a single center retrospective cohort study of 95 patients who underwent SSRF, stratified by number of hospital days to SSRF (0-2, 3-4, 5-6, and >6 days) (81). These SSRF groups were compared to patients who were treated nonoperatively, matched in a 1:2 ratio by age, ISS, AIS chest and head. Patients underwent SSRF with a non-specified fixation system with a mean operative time of 147 minutes on hospital day 5.5 (range, day 1-25). Over 35% of patients underwent SSRF for other indications than flail chest such as pain and rib displacement which were not further defined. As compared to the nonoperative group, the SSRF group had a significant higher number of rib fractures, pulmonary contusion, presence of flail chest, and history of smoking. Within the SSRF groups, patients who underwent early SSRF (0-2 days) had shorter HLOS than the other groups (11.8 days versus 3-4 days: 12.6 days versus 5-6 days: 13.4 days versus >6 days: 19.6 days; p=0.003). As compared to nonoperative management, patients who underwent SSRF after day 2 had longer HLOS and ICU-LOS.

The sixth study was a retrospective national database study of 162 patients with rib fractures who required mechanical ventilation within 1 day of admission and underwent SSRF within 3, 6, or 10 days after admission (82). There was no information on rib fracture severity or operative characteristics. These SSRF groups were compared to patients who were treated nonoperatively, based on "overlap weighting", a propensity scoring method. After overlap weighting, there were no differences between groups in baseline and injury characteristics. On adjusted analysis, patients who underwent SSRF within 3 days had shorter HLOS and DMV than nonoperatively treated patients. The rates of pneumonia, tracheostomy, and mortality were similar. There were no significant differences in all outcomes between patients who underwent nonoperative management and those who underwent SSRF within 6 or 10 days after admission.

The next study was a retrospective national database study of the same time period and patient population as the previous study (83). In this study (n=211), patients who underwent SSRF were stratified based on the median time to SSRF in ≤6 days and >6 days (no range given) following admission. There was no information on rib fracture

severity or operative characteristics. Patients in the ≤6 days group were more often male, and more often had a higher GCS score, and flail chest. Propensity score matching was performed to compare outcomes between the two groups. On adjusted analysis, patients who underwent SSRF within 6 days had shorter HLOS (percent difference, -27.1, 95% CI, -40.0 to -11.5; p=0.001), DMV (-34.1, 95% CI, -53.8 to -6.2; p=0.02, and lower total hospitalization costs (-28.4, 95% CI, -38.4 to -16.9; p<0.001). The rates of tracheostomy, pneumonia, and mortality were similar between groups.

The eighth study on timing to SSRF was a retrospective study of the Trauma Quality Improvement Program database comparing patients ≥65 years who underwent SSRF to nonoperatively treated elderly patients (84). A subgroup analysis was performed of 741 patients who underwent SSRF, stratified as early (≤3 days) or late (>3 days). While injury characteristics such as ISS and chest AIS were known, no detailed information on rib fracture severity or SSRF characteristics was available. The early SSRF group had a higher rate of male patients and lower rate of intubation on ED arrival. After propensity score matching, the early SSRF group had lower rates of tracheostomy (6.6% versus 15.5%; p<0.001) and ventilator-associated pneumonia (0.8% versus 4.8%; p<0.001) and shorter HLOS (10 versus 15 days; p<0.001), ICU-LOS (6 versus 10 days; p<0.001), and DMV (4 versus 8 days; p<0.001) as compared to the late SSRF group. There was no difference in mortality rate.

The most recent study is by the senior author of this review (85). This was a retrospective multicenter study comparing patients aged 80 years or older who underwent SSRF (n=133) with a matched cohort of nonoperatively managed patients (n=227). Indications for SSRF were radiographic flail segment and/or ≥3 ipsilateral, displaced rib fractures. The choice of rib fixation system was left to the discretion of the surgeon. Patients underwent SSRF at a median of 3 days after injury and operative time was 115 (range, 92-161) minutes. Chest wall injury severity and likelihood of additional urgent procedures were similar between groups. On multivariable logistic regression, early SSRF was associated with lower mortality but also associated with a higher risk of pneumonia and ICU-LOS ≥3 days, as compared to late SSRF or nonoperative management. This was hypothesized to be attributable to survivor bias, inadequate control of associated injuries, variability in practice across centers, and invasive impact of intubation and tissue trauma of SSRF in this frail population. Subgroup analysis was performed for patients who underwent SSRF <72 hours versus ≥72 hours. The early SSRF group was older, more likely to be women, and had a lower BMI. In this analysis, there was no observed benefit to early vs. late surgery.

Logistical Considerations

While some studies were able to correct for patient- and injury characteristics when analyzing outcomes, many other factors might also confound time from admission to the operative room (OR). In these retrospective studies, it is difficult to grasp what affects getting the patient to the OR besides characteristics available on chart review. The time to theatre might for example be delayed by associated comorbidities including cardiac problems, medication use such as anticoagulation, or higher priority injuries requiring immediate operative or invasive repair (86) .

In addition to the hypothesized patient- and injury characteristics which might preclude SSRF, logistical considerations might also be of significance. For example, admission delay from emergency department to hospitalization due to shortage of beds, delayed diagnosis, or operative room availability might affect time to surgery and negatively affect outcome (87). It is possible that the shift to earlier SSRF over the years might have to do with increased familiarity with this procedure. Whereas operative room access might have been limited in the first years of implementation, a subtle shift might occur over the years, allowing operative room access at a lower threshold for a known service. In line with implementation of a new procedure, there might not be a trained surgeon available to perform SSRF at any moment during the night or weekends. Furthermore, a relatively novel practice such as SSRF or aspects of it (e.g., bronchoscopy) might not be considered standard of care in its early years. As a result of this unfamiliarity, it might be more difficult to gain approval from Institutional Review Boards to conduct high quality research such as randomized controlled trials to strengthen the benefit of a new procedure or get informed consent from the patient or family to perform SSRF (88).

COMMENTS

Current practice management guidelines for SSRF both advocate early operative fixation (≤72 hours, once other life-threatening injuries have been identified and stabilized) to reduce HLOS, ICU-LOS, duration of mechanical ventilation, and rate of mechanical ventilation requirement, pneumonia, and tracheostomy (36, 37). While only the first study was available at the time of developing these guidelines, the more recently published studies corroborate this consensus of early SSRF benefit (75, 78-80, 82-84, 89). In addition, early SSRF appears to be safe and also beneficial in elderly patients for all outcomes and is associated with lower hospitalization costs (80, 83, 84). Interestingly, recent studies have also suggested that while early fixation within 2-3 days after admission is associated with improved in-hospital outcomes, performing SSRF after this time period might actually correlate with outcomes inferior to nonoperative

TABLE 2
Overview of studies addressing timing to surgical stabilization of rib fractures (SSRF).

Author (year)	Study period	Study design	Indication for SSRF	Time to SSRF
Althausen *et al.* (2011) (78)	01-2005 to 01-2010	Single center retrospective cohort	Flail chest and pulmonary hernia	Mean 2.3 d (range, 1-5 d)
Iqbal *et al.* (2018) (79)	03-2015 to 05-2016	Single center retrospective cohort	Flail chest and ≥3 displaced rib fractures	Early (≤48 h) Late (>48 h)
Pieracci *et al.* (2018) (75)	01-2006 to 01-2017	Multicenter retrospective cohort	Flail chest, ≥3 displaced rib fractures, ≥30% volume loss of hemithorax, failing nonoperative management	Early (≤24 h) Mid (1-2 d) Late (3-10 d)
Su *et al.* (2019) (80)	Not specified	Single center retrospective cohort	Flail chest, ≥4 displaced rib fractures, respiratory failure, intractable pain after nonoperative management	Early (≤3 d) Late (>3 d)
Harrell *et al.* (2020) (81)	01-2007 to 01-2018	Single center retrospective cohort	Flail chest, rib displacement, respiratory failure, pain, flail sternum, pulmonary hernia	Early (0-2 d) Mid (3-4 d) Later (5-6 d) Latest (>6 d)
Otaka *et al.* (2020) (82)	07-2010 to 04-2018	Retrospective national database study	Flail chest or multiple rib fractures requiring mechanical ventilation ≤1 day of admission	Early (≤3 d) Mid (≤6 d) Late (≤10 d)
Otaka *et al.* (2020) (83)	07-2010 to 04-2018	Retrospective national database study	Flail chest or multiple rib fractures requiring mechanical ventilation ≤1 day of admission	Early (≤6 d) Late (>6 d)
Zhu *et al.* (2020) (84)	01-2016 to 01-2018	Retrospective national database study	Flail chest or multiple rib fractures in patients ≥65 years	Early (≤3 d) Late (>3 d)
Pieracci *et al.* (2021) (85)	01-2015 to 04-2020	Multicenter retrospective cohort	Flail chest, ≥3 ipsilateral displaced rib fractures	Early (<3 d) Late (≥3 d)

SSRF, surgical stabilization of rib fractures; HLOS, hospital length of stay; ICU-LOS, intensive care unit length of stay; DMV, duration of mechanical ventilation; FU, follow-up; NOM, nonoperative management; UK, United Kingdom; US, United States of America.

Sample size SSRF	Follow-up time	Major outcomes	Limitations
22	Mean, 17.8 (range, 13-22 months)	Shorter time to SSRF was associated with shorter HLOS, ICU-LOS, and DMV.	Retrospective, single center study, small sample size and no insight in reason for timing of SSRF.
Early (n=65) Late (n=37)	3 months	Early SSRF group had shorter HLOS, ICU-LOS, DMV, and lower rates of pneumonia and tracheostomy.	Retrospective, single center study, short FU, and no insight in stratification reason in SSRF groups.
Early (n=207) Mid (n=168) Late (n=176)	Not specified	Early SSRF group had shorter HLOS, ICU-LOS and DMV >24 h. Each additional day was associated with increase in pneumonia, tracheostomy, and DMV>24h likelihood.	Retrospective study with short FU and no insight in stratification reason in SSRF groups.
Early (n=16) Late (n=17)	Not specified	Early SSRF had shorter HLOS, ICU-LOS, and DMV. Time to SSRF was positively associated with shorter HLOS, ICU-LOS, DMV, and costs.	Retrospective, single center study, small sample size, short FU, and no insight in stratification reason in SSRF groups.
Early (n=8) Mid (n=34) Later (n=31) Latest (n=22)	Not specified	Early SSRF had shorter HLOS. As compared to NOM, patients who underwent SSRF after 2 days had longer HLOS and ICU-LOS.	Retrospective, single center study, small sample size, short FU, and no insight in stratification reason in SSRF groups.
Early (n=62) Mid (n=113) Late (n=162)	Not specified	As compared to NOM, early SSRF was associated with shorter HLOS and DMV. The mid and late SSRF groups had similar outcomes to patients who underwent NOM.	Retrospective study, no details on chest wall injury severity, and no insight in stratification reason in SSRF groups.
Early (n=113) Late (n=98)	Not specified	The early SSRF group had shorter HLOS, DMV, and lower total costs. These results were similar in a subgroup analysis of patients without a flail chest.	Retrospective study, no details on chest wall injury severity, and no insight in stratification reason in SSRF groups.
Early (n=366) Late (n=375)	Not specified	The early SSRF group had lower rates of tracheostomy and pneumonia as well as shorter HLOS, ICU-LOS, and DMV.	Retrospective study, no details on chest wall injury severity, and no insight in stratification reason in SSRF groups.
Early (n=63) Late (n=70)	Not specified	As compared to late SSRF or NOM, early SSRF was associated with lower mortality risk, but higher risk of pneumonia and ICU-LOS ≥3 d	Retrospective study with short FU and no insight in stratification reason in SSRF groups.

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management (81, 82). This might be associated to exposing the patient to the risks of surgery without the benefit of early fixation such as improving chest wall stability, evacuation of hemothorax or trans positioned chest wall tissue, and possible prevention of pneumonia and a lengthy hospitalization. Furthermore, no association between time to SSRF and mortality rate was demonstrated in any of the studies.

There are several methodologic considerations when interpreting this data addressing optimal timing of SSRF. The first is selection bias. While most studies tried to adjust for covariates, in general, patients who are selected for early SSRF are often less severely injured. Thus, any observed improved outcomes might be due to the patient's associated injuries or lack thereof. A second limitation is attrition bias. This comprises patients who are initially considered for surgery but improve after observation and are discharged following nonoperative treatment. By contrast, patients who deteriorate after an uncomplicated period of observation might ultimately undergo SSRF late in their hospitalization and represent the late SSRF group. While the first example of attrition bias results might affect the nonoperative group which was studied in two of the abovementioned studies (81, 82), the second example possibly affects the late SSRF groups in all studies. The missing piece of information in all reviewed studies to overcome this bias is an overview of the reasons for stratification of these patients in either the early or later SSRF groups. Hypothetical reasons can be injury severity, logistic reasons as surgeon, operating room, and fixation system availability, and patient or surgeon preference. Furthermore, all studies were retrospective with most follow-up time limited to index hospitalization, and often either small sample sizes or no insight in chest wall injury severity. Also, only one study controlled for study year which could confound outcomes as complication rates or other in-hospital outcomes tend to improve over time after implementation of a relatively novel procedure such as SSRF (75, 90).

FIGURE 1
Initial chest radiography (A) of a 55-year old male who sustained left 4-9 rib fractures which were nondisplaced. Chest radiography of the same patient 24 hours after ICU admission (B) showing interval rib fracture displacement. Chest radiography after SSRF (C) during which this patient received 11 plates to restore chest wall stability ICU, intensive care unit; SSRF, surgical stabilization of rib fractures.
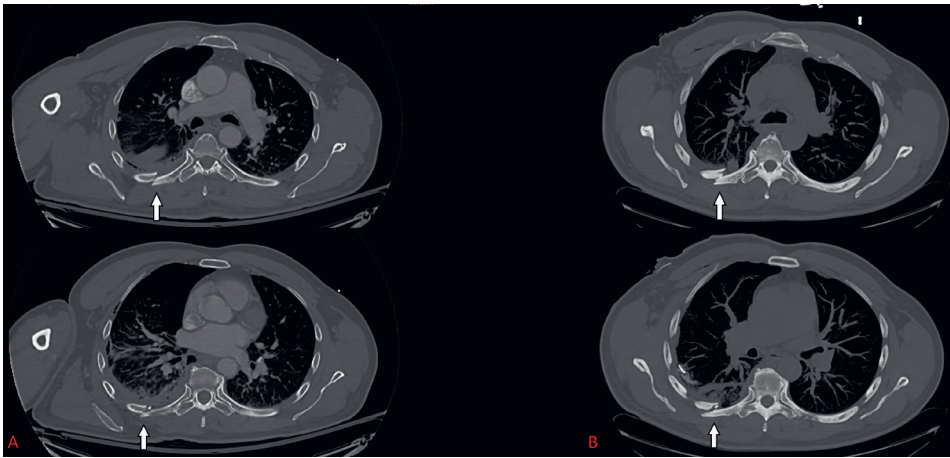
FIGURE 2
Initial chest CT displaying two offset posterior fractures of rib six and seven (A). After two days, a repeat chest CT showed interval rib fracture displacement of these same fractures (B).
CT, computed tomography.

The authors' practice pattern is derived from the study by the senior author and includes early performance of SSRF, ideally within 24 hours of admission if there are no contra-indications present (Table 1) (75). The SSRF procedure has been standardized to include general anesthesia, fiberoptic bronchoscopy, muscle sparing incisions, video-assisted thoracoscopic surgery (VATS)-inspection of the thorax, evacuation of retained hemothorax, pleural irrigation, chest tube placement, and lately, an injection of locoregional intercostal nerve analgesia. It is believed that these adjunctive maneuvers positively impact the patients' recovery, pain level, and decrease the likelihood of the development of pneumonia, retained hemothorax or empyema, and respiratory failure. Also, interval rib fracture displacement has been previously described in the rib fracture literature and incidentally experienced by the authors in patients who were initially not deemed SSRF candidates but developed severe interval rib fracture displacement along fracture lines which thus increased chest wall instability, pain, and risk for pulmonary morbidity (91). This interval displacement can be discovered by comparing sequential chest radiography, but it is unclear in how many patients this occurs following trauma or which patients are at risk (Figure 1). A prospective study on the rate of interval rib fracture displacement in terms of rib fracture taxonomy and impact on in-hospital outcomes is now being conducted at the authors' institution (Figure 2).

Over the decade of implementation of this procedure, average time from admission to SSRF in the senior author's center has decreased from 2 days to within 24 hours, which is most likely multifactorial. First, the aforementioned studies and guidelines

have advocated a clinical benefit to early SSRF. Second, the contention is that, as case volume and experience with SSRF increases, there is an increased familiarity with the procedure by operating room staff. Third, as staff becomes more familiar with the operation, a subtle shift may occur, allowing quicker operative room access for a known instead of novel service.

CONCLUSION

In line with current guidelines and consensus, increasing amounts of data support the benefit of early (≤48-72 hours after admission) SSRF in properly selected stable patients as compared to late salvage SSRF. Performing early SSRF is associated with reduced HLOS, ICU-LOS, and DMV, as well as lower hospitalization costs and rates of pneumonia and tracheostomy. These data must however be interpreted with caution and attention to potential selection and attrition bias. The current studies are all retrospective with often small sample sizes and short follow-up. The authors' practices aim to perform SSRF as soon as possible and ideally within the first 24 hours after injury. The current exponential increase in number of SSRF cases performed and international collaborations should accommodate the possibility to perform sufficiently powered analyses of the effect of timing of SSRF on both acute and long-term outcomes.

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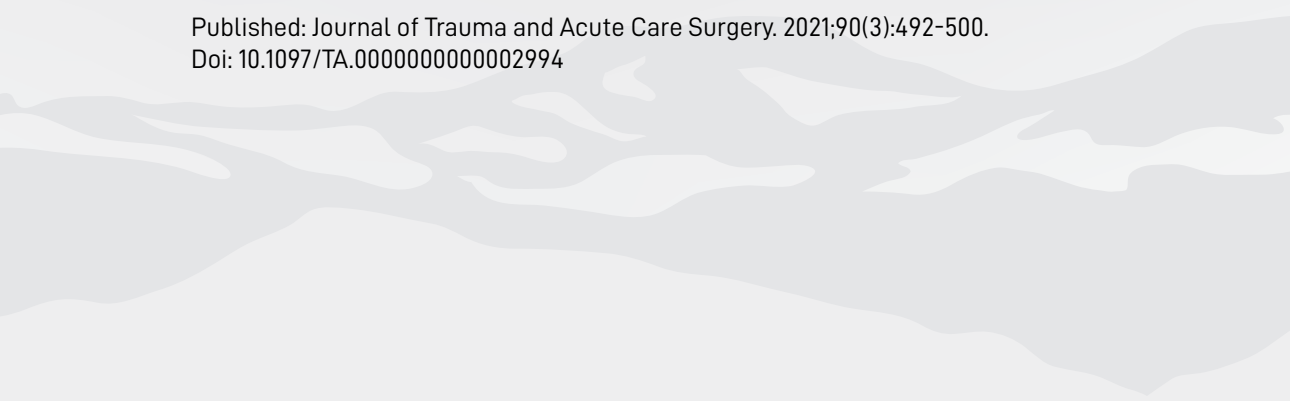
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CHAPTER 10

Outcome after surgical stabilization of rib fractures versus nonoperative treatment in patients with multiple rib fractures and moderate to severe traumatic brain injury (CWIS-TBI)

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ABSTRACT

Background
Outcomes after surgical stabilization of rib fractures (SSRF) have not been studied in patients with multiple rib fractures and traumatic brain injury (TBI). We hypothesized that SSRF, as compared to nonoperative management, is associated with favorable outcomes in patients with TBI.

Methods
A multicenter, retrospective cohort study was performed in patients with rib fractures and TBI between January 2012 and July 2019. Patients who underwent SSRF were compared to those managed nonoperatively. The primary outcome was mechanical ventilation-free days. Secondary outcomes were Intensive Care Unit (ICU-LOS) and hospital length of stay (HLOS), tracheostomy, occurrence of complications, neurologic outcome, and mortality. Patients were further stratified into moderate (GCS score, 9-12) and severe (GCS score, ≤8) TBI.

Results
The study cohort consisted of 456 patients of which 111 (24.3%) underwent SSRF. SSRF was performed at a median of 3 days and SSRF-related complication rate was 3.6%. In multivariable analyses, there was no difference in mechanical ventilation-free days between the SSRF and nonoperative groups. The odds of developing pneumonia (OR [OR], 0.59; 95% CI [95% CI], 0.38-0.98; p=0.043) and 30-day mortality (OR, 0.32; 95% CI, 0.11-0.91; p=0.032) were significantly lower in the SSRF group. Patients with moderate TBI had similar outcome in both groups. In patients with severe TBI, the odds of 30-day mortality was significantly lower after SSRF (OR, 0.19; 95% CI, 0.04-0.88; p=0.034).

Conclusions
In patients with multiple rib fractures and TBI, the mechanical ventilation-free days did not differ between the two treatment groups. In addition, SSRF was associated with a significantly lower risk of pneumonia and 30-day mortality. In patients with moderate TBI, outcome was similar. In patients with severe TBI a lower 30-day mortality was observed. There was a low SSRF-related complication risk. These data suggest a potential role for SSRF in select patients with TBI.

INTRODUCTION

Over 15% of polytraumatized patients have both severe thoracic trauma and traumatic brain injury (TBI) [1]. In the intensive care unit (ICU), rib fractures (42%) and TBI (39%) are the injuries with the highest prevalence [2]. While TBI is the leading cause of mortality, thoracic trauma is listed second and accounts for 25% of injury-related deaths annually [3, 4]. In patients with multiple rib fractures, 15-26% have concurrent TBI; the presence of both injuries is associated with poor outcomes including longer mechanical ventilation and prolonged ICU length of stay [4, 5]. Rib fractures are seen in up to 39% of patients who have sustained blunt thoracic trauma and a debilitation and lethal complication is pneumonia [3]. Rib fractures are associated with pneumonia rates of 17-77%, with increased rates in elderly patients and patients with more rib fractures [6-10]. In addition, the combination of severe thoracic trauma and severe TBI (i.e., an Abbreviated Injury Score (AIS) of 3 or higher) are risk factors for the development of pneumonia which is one of the strongest independent predictors of in-hospital mortality in polytraumatized patients [1].

Due to proven beneficial outcomes in patients with severely displaced rib fractures or flail chest, the use of surgical stabilization of rib fractures (SSRF) has increased considerably over the last decade and has become an important modality in rib fracture management [11-13]. As patients with TBI might confound outcome measures due to an increased risk of prolonged duration of mechanical ventilation, high mortality rate, and complications such as pneumonia, these patients are typically excluded in studies on outcome of SSRF in patients with multiple rib fractures [7, 9, 13, 14]. Also, the unclear prognosis of TBI patients, irrespective of their underlying thoracic injury, has historically been an exclusion criteria among various studies on the outcome of SSRF. One theoretical concern is that patients with TBI might deteriorate perioperatively due to an increase in intracranial pressure secondary to patient positioning and anesthetics. A survey among thoracic, orthopedic, and trauma surgeons showed that even patients with moderate TBI (Glasgow Coma Scale [GCS] score at admission of 9 to 12) were the least likely to be recommended for SSRF, regardless of abnormal pulmonary variables [15]. Thus, while SSRF may be less frequently offered to patients with TBI, the possible benefit of SSRF in this type of patient has not been studied. Specifically, the respiratory benefits achieved by SSRF in the setting of severe chest wall injuries may be of sufficient magnitude to mitigate the negative effects of TBI and ultimately still improve outcomes in this specific patient population.

The primary aim of this study was to determine the effect of SSRF versus nonoperative treatment of rib fractures on the number of ventilator-free days in adults who sustained both multiple severe rib fractures and moderate or severe TBI. Secondary aims were to determine the effect of treatment on the ICU length of stay (ICU-LOS), hospital length

of stay (HLOS), tracheostomy rate, occurrence of complications, neurological outcome, and (in-hospital and 30-day) mortality. We hypothesized that SSRF is associated with favorable outcomes vs. nonoperative management in patients with co-existing moderate to severe TBI.

METHODS

Design and participants

The Chest Wall Injury Society TBI study (CWIS-TBI) was a multicenter, retrospective cohort study conducted by CWIS and involved 19 trauma centers. The Chest Wall Injury Society is an international surgical society founded in 2016 and comprised of approximately 250 trauma, thoracic, and orthopedic surgeons with a specific interest in the management of chest wall trauma (www.cwisociety.org). Members of CWIS were invited for participation if they expressed interest based on information on the CWIS website and a personal e-mail consisting of a short and full-length study protocol. After approval for each individual participating center by the local Medical Research Ethics Committee (MREC) or Institutional Review Board (IRB), local investigators identified patients. This was done by searching the hospital's electronic patient files which were registered with specific diagnosis treatment combinations and by searching the national/regional/state trauma registry for admitted patients with a registered AIS for rib or sternum fractures in combination with an AIS ≥3 of the head. Each hospital used the best local option to identify eligible patients.

Inclusion criteria were: 1) age 18 years or older at time of index trauma; 2) three or more fractures of ribs 3-10 with either a flail chest or bicortical displacement of at least three fractured ribs, as diagnosed on CT-scan; 3) moderate or severe TBI (GCS score ≤12 at admission with posttraumatic intracranial changes, as diagnosed on CT-scan); 4) trauma sustained between January 1, 2012 and July 1, 2019; 5) blunt force thoracic trauma; 6) admission to participating hospital within seven days after trauma with documented GCS at first presentation.

Patients with any of the following criteria were excluded: 1) rib fractures due to cardiopulmonary resuscitation; 2) patient unfit for surgery due to hemodynamic instability or patient is moribund; 3) previous rib fractures or pulmonary problems, requiring continuous oxygen use at home pre-trauma; 4) rib fixation device in situ pre-trauma; 5) pre-existing neurological deficit (i.e., GCS ≤12); 6) congenital thoracic deformity; 7) imprisoned at time of trauma; 8) known pregnancy at time of trauma; 9) clinically transferred to other hospital during primary admission; 10) no post-traumatic intracranial changes on brain CT.

Given the exploratory nature of this study and the lack of data on ventilator-free days in the targeted population, a formal sample size calculation was not made.

Data collection and outcome measures

Data were extracted from the patients' electronic medical files. The primary outcome measure was the number of ventilator-free days during primary hospital admission, defined as the number of days where the patient breathed without assisted breathing.

Secondary outcome measures were ICU-LOS during primary hospital admission, HLOS for the primary admission, rate of and time to tracheostomy performed, the occurrence of complications (e.g., pneumonia within 30 days after trauma as defined according to the Centers for Disease Control and Prevention (CDC) guidelines [16], pleural empyema as diagnosed on CT-scan within 30 days after trauma and/or pus evacuation [17], and SSRF-related complications such as thoracic bleeding or wound infection), neurological outcome (i.e., if motor GCS [mGCS] score = 6 was achieved and number of days recovery since it was first <6), and in-hospital and 30-day mortality (including cause of death).

In addition to the outcome measures, the following data were collected: patient characteristics (i.e., age, sex, Body Mass Index (BMI) (kg/m2), smoking at age of trauma, Chronic Obstructive Pulmonary Disease (COPD), and diabetes mellitus) and injury-related variables (i.e., mechanism of injury (high energy (HET) or low energy trauma (LET), type of TBI (epidural hematoma, subdural hematoma (SDH), subarachnoid bleeding (SAB), diffuse axonal injury (DAI), intra-parenchymal hemorrhage, intraventricular hemorrhage (IVH), and brain contusion), TBI severity at hospital admission (moderate [GCS score, 9-12] or severe [GCS score, ≤8], intracranial hypertension (ICH) (defined as intracranial pressure [ICP] >20 mm Hg), total number and location of ribs fractured, Injury Severity Score (ISS), presence of a flail chest, pneumothorax, hemothorax, pulmonary contusion, facial fracture, and skull fracture, and presence of at least 3 fractured ribs with bicortical displacement). In addition, the following treatment- and outcome-related variables were collected; treatment (operative or nonoperative), chest tube placement, if operated: surgical delay, rib fixation system used, total number of ribs fixated, ICP reducing therapy performed (including details on the provided therapy), type of additional surgeries required.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 25 or higher (SPSS, Chicago, Ill., USA). Normality of continuous variables was tested with the Shapiro-Wilk test, and homogeneity of variances was tested using the Levene's test. A p-value lower than 0.05 was considered statistically significant and all tests were two-sided. Missing data were not imputed since the rate of missing data per variable

was less than 4%, except for "BMI" (13%), "smoking at age of trauma" (28%), and "fracture in every rib region" (11%).

Descriptive analysis was performed in order to report the data for the entire study population and for the treatment groups. Subgroup analysis was performed for the treatment groups, stratified by TBI severity (moderate or severe). For continuous data, the mean and SD (parametric data) or the median and percentiles (non-parametric data) are reported. Statistical significance of differences between SSRF and nonoperative treatment was assessed using Mann-Whitney U-test (non-parametric data). For categorical data, numbers and frequencies are reported per treatment group and compared using Chi-squared or Fisher's Exact test, as applicable.

After univariate analysis, multivariable analysis through logistic regression and linear regression (for binary and continuous outcomes, respectively) was applied in order to control for potential confounding. Potential confounders were selected from literature and from the data of the current study. First a Spearman's rank correlation with outcome measures was determined for the patient demographics and injury characteristics with a known confounding effect (based on literature) or that displayed a p-value of 0.2 or lower in the univariate analysis. Next, the effect of these covariates on the odds ratio (OR) or beta value (for logistic regression and linear regression, respectively) was determined. The covariates with a statistically significant correlation with outcome and/or that had a statistically significant OR or beta value in the regression model were BMI, presence of SDH, SAH, IVH, TBI severity, ICH, number of rib fractures, presence of flail chest, pneumothorax, and pulmonary contusion. Since SDH, SAH, and IVH were likely to reflect TBI severity, only the latter was included in the final regression models. Given the multicenter design of the study, participating center was also considered as a confounder. Study center was however not included in the final model as it did not statistically correlate with outcome. The final regression model consisted of BMI, TBI severity, presence of ICH, number of rib fractures, presence of flail chest, pneumothorax, and pulmonary contusion. The final crude regression model included the outcome measure as the dependent variable, and SSRF as covariate. In the adjusted analysis, the covariates mentioned above were added as covariates. For binary regression analysis, the OR for SSRF over nonoperative treatment is reported with 95% confidence interval (CI) and p-values. For linear regression analysis, the beta value with 95% CI and p-value is reported.

RESULTS

In total, 456 patients (56.1%) of 813 patients with multiple rib fractures and traumatic TBI were included for analysis (Figure 1). The most common exclusion criterion was
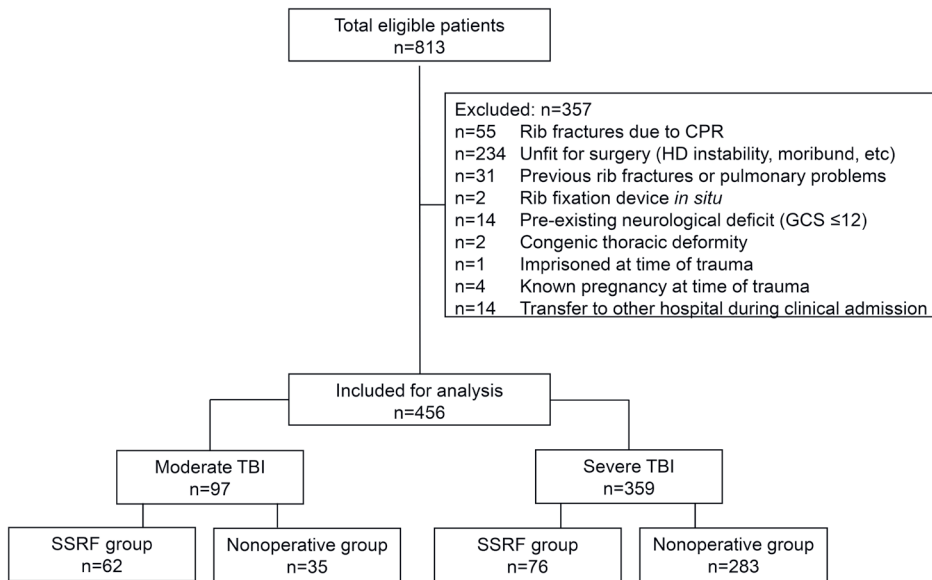
FIGURE 1
Flowchart of the study

unfit (*e.g.*, hemodynamic instability) or moribund patient at hospital admission (n=234).

A total of 111 (24.3%) patients were treated with SSRF. The SSRF group had a significantly higher median BMI (28 (P$_{25}$-P$_{75,}$ 25-31) versus 26 (P$_{25}$-P$_{75,}$ 23-29) kg/m^2; p=0.008) than the nonoperative group. Other patient demographics were similar in both treatment groups (Table 1). With regards to the brain injury characteristics, the SSRF group suffered subdural hematoma (n=41, 36.9% versus n=202, 58.6%; p<0.001), subarachnoid hemorrhage (n=60, 54.1% versus n=240, 69.6%; p=0.004), ICH (n=12, 10.8% versus n=89, 26.5%; p<0.001), and severe TBI (n=76, 68.5% versus n=283, 82.0%; p=0.003) significantly less often than the nonoperative group. Brain contusion was more frequently present in the SSRF group (n=26, 23.4% versus n=43, 12.5%; p=0.009; Table 1). The SSRF group required ICP reducing therapy significantly less frequently than the nonoperative group (n=26, 23.4% versus n=146, 42.3%; p<0.001).

The SSRF group sustained a median of 9 (P$_{25}$-P$_{75,}$ 8-12) rib fractures versus 8 (P$_{25}$-P$_{75,}$ 5-11) in the nonoperative group (p<0.001) and had a flail chest or pneumothorax more often (n=86, 77.5% versus n=135, 39.9%; p<0.001 and n=94, 84.7% versus n=252, 73.0%; p=0.015, respectively). The ISS and rate of performed additional surgeries were similar in both groups. Patients in the subgroups stratified by TBI severity who underwent SSRF had a significantly higher number of rib fractures, more often a flail chest and required a chest tube more often than the nonoperative group (Supplemental Table

S1). The nonoperative group with severe TBI had a higher BMI and more often SDH and SAH than the SSRF group (Supplemental Table S1). SSRF was performed at a median of 3 days (P_{25}-P_{75}, 2-5 days) after admission, and did not differ between the moderate TBI (median, 3 days; P_{25}-P_{75}, 1-5 days) and severe TBI group (median, 3 days; P_{25}-P_{75}, 2-5 days; p=0.160).

During SSRF, a median of 4 (P_{25}-P_{75}, 3-5) ribs were fixated, resulting in a ratio of ribs repaired to fractured (rib fixation ratio) of 0.5 (P_{25}-P_{75}, 0.4-0.6). In 39 (36.0%) patients, additional thoracic procedures were performed during SSRF, such as bronchoscopy in 14 (12.6%) patients, VATS in nine (8.1%) patients, diaphragm repair in four (3.6%) patients, pulmonary repair or resection in nine (8.1%) patients and cryoablation in three (2.7%) patients. Complications related to SSRF were seen in four (3.6%) patients and included an intra-operative intracranial pressure increase which required medicinal intervention after which the SSRF was continued in one (0.9%) patient, a post-operative wound infection in two (1.8%) patients and hardware failure in one (0.9%) patient.

Univariate analysis

In the total cohort, 96.7% patients required mechanical ventilation (n=441) of which 85 had moderate TBI (87.6% of the moderate TBI group) and 356 had severe TBI (99.2% of the severe TBI group). For patients with severe TBI, the number of ventilator-free days was significantly higher after SSRF (median 11; P_{25}-P_{75}, 7-20 days) than after nonoperative treatment (median 10; P_{25}-P_{75}, 1-21 days; p=0.034). The ICU-LOS and HLOS were similar between the two treatment groups in both the total cohort as well as in the subgroups of patients with moderate or severe TBI (Table 2). The rate of pneumonia was significantly lower in both the total cohort as well as in patients with moderate TBI when comparing the SSRF group with the nonoperative group (n=38, 34.2% versus n=164, 47.5%; p=0.016, and n=6, 17.1% versus n=28, 45.2%; p=0.007, respectively). Recovery of mGCS score to 6, in patients in which this had been less than 6, was significantly more frequent in the total cohort and in patients with severe TBI when comparing the SSRF group with the nonoperative group (n=96.2, 93.2% versus n=243, 75.0%; p=0.000 and n=68, 93.2% versus n=272, 72.8%; p<0.001). In the total cohort, this mGCS score recovery to 6 was achieved after a median of 3 days (P_{25}-P_{75}, 1-8) in the SSRF group versus 4 days (P_{25}-P_{75}, 2-14) in the nonoperative group (p=0.020). Both the in-hospital and 30-day mortality rates were significantly lower in the SSRF group in both the total cohort and in patients with severe TBI than in the nonoperative group.

Multivariable analysis
Overall cohort

In the adjusted analysis, the number of ventilator-free days did not differ between the two treatment groups (beta, -1.61; 95% CI, -6.12 to 2.89 days; p=0.483; Table 2 and

Figure 2). The odds of developing pneumonia (OR, 0.59; 95% CI, 0.35-0.98; p=0.043) and odds of 30-day mortality (OR, 0.32; 95% CI 0.11-0.91; p=0.032) were significantly lower and rate of mGCS recovery to 6 (beta, 4.54; 95% CI, 1.77-11.69 days; p=0.002) significantly higher in the SSRF group. The ICU-LOS, HLOS, and the other outcome measures were similar in the SSRF and nonoperative group (Tables 2 and 3 and Figure 2).

TABLE 1
Demographics and injury characteristics of patients with moderate or severe TBI and rib fractures treated operatively (SSRF) or nonoperatively.

	N*	Overall (n=456)	N*	SSRF (n=111)	N*	Non-operative (n=345)	p
Patient characteristics							
Age (y)	456	50 (37-63)	111	50 (37-61)	345	50 (37-63)	0.786
Sex (male)	455	349 (76.7%)	110	80 (72.7%)	345	269 (78.0%)	0.300
BMI (kg/m^2)	398	26 (24-30)	100	28 (25-31)	298	26 (23-29)	**0.008**
Smoking at age of trauma	328	131 (39.9%)	83	38 (45.8%)	245	93 (38.0%)	0.243
COPD	456	27 (5.9%)	111	11 (9.9%)	345	16 (4.6%)	0.061
Diabetes Mellitus	456	49 (10.7%)	111	14 (12.6%)	345	35 (10.1%)	0.482
Injury characteristics							
High-energy trauma (HET)	450	408 (90.7%)	110	100 (90.9%)	340	308 (90.6%)	1.000
Epidural hematoma	456	38 (8.3%)	111	6 (5.4%)	345	32 (9.3%)	0.239
Subdural hematoma	456	243 (53.3%	111	41 (36.9%)	345	202 (58.6%)	**<0.001**
Subarachnoid hemorrhage	456	300 (65.8%)	111	60 (54.1%)	345	240 (69.6%)	**0.004**
DAI	456	90 (19.7%)	111	21 (18.9%)	345	69 (20.0%)	0.891
Intraparenchymal hemorrhage	456	132 (28.9%)	111	34 (30.6)	345	98 (28.4%)	0.718
IVH	456	40 (8.8%)	111	5 (4.5%)	345	35 (10.1%)	0.082
Brain contusion	456	69 (15.1%)	111	26 (23.4%)	345	43 (12.5%)	**0.009**
TBI severity at admission	456		111		345		
Moderate (GCS score, 9-12)		97 (21.3%)		35 (31.5%)		62 (18.0%)	**0.003**
Severe (GCS score, ≤ 8))		359 (78.7%)		76 (68.5%)		283 (82.0%)	
ICH	447	101 (22.6%)	111	12 (10.8%)	336	89 (26.5%)	**<0.001**
No. of ribs fractured	456	8 (6-11)	111	9 (8-12)	345	8 (5-11)	**<0.001**
ISS	456	34 (27-41)	111	33 (27-41)	345	34 (27-41)	0.938
Additional injury							
Flail chest	449	221 (49.2%)	111	86 (77.5%)	338	135 (39.9%)	**<0.001**
Pneumothorax	456	346 (75.9%	111	94 (84.7%)	345	252 (73.0%)	**0.015**
Hemothorax	454	246 (54.2%)	110	67 (60.9%)	344	179 (52.0%)	0.124
Pulmonary contusion	452	337 (74.6%)	111	85 (76.6%)	341	252 (73.9%)	0.617
Facial fracture	456	169 (37.1%)	111	41 (36.9%)	345	128 (37.1%)	1.000
Skull fracture	455	186 (40.9%)	111	42 (37.8%)	344	144 (41.9%)	0.506
Fracture in every rib region	405	141 (34.8%)	100	48 (48.0%)	305	93 (30.5%)	**0.002**

TABLE 1 continues on page 208

TABLE 1 continued from page 207

	N*	Overall (n=456)	N*	SSRF (n=111)	N*	Non-operative (n=345)	p
≥100% displacement of ≥3 ribs	441	301 (68.3%)	109	81 (74.3%)	332	220 (66.3%)	0.125
Treatment characteristics							
Chest tube required	456	330 (72.4%)	111	99 (89.2%)	345	231 (67.0%)	**<0.001**
ICP reducing therapy required	456	172 (37.7%)	111	26 (23.4%)	345	146 (42.3%)	**<0.001**
Additional surgeries performed							
Facial surgery	456	34 (7.5%)	111	13 (11.7%)	345	21 (6.1%)	0.061
Clavicle surgery	456	16 (3.5%)	111	8 (7.2%)	345	8 (2.3%)	**0.032**
Thoracotomy	456	19 (4.2%)	111	8 (7.2%)	345	11 (3.2%)	0.096
Laparotomy	456	54 (11.8%)	111	11 (9.9%)	345	43 (12.5%)	0.612
Pelvic surgery	456	46 (10.1%)	111	11 (9.9%)	345	35 (10.1%)	1.000
Long bone surgery	456	109 (23.9%)	111	33 (29.7%)	345	76 (22.0%)	0.124
Spine surgery	456	45 (10.1%)	111	6 (5.4%)	345	40 (11.6%)	0.070

CI, confidence interval; HLOS, hospital length of stay; ICU-LOS, Intensive Care Unit length of stay; mGCS, motor Glasgow Coma Scale; N.D., not determined; OR, odds ratio; SSRF, surgical stabilization of rib fractures; TBI, traumatic brain injury.

*: provides the exact number of patients for which the outcome measure was known. The multivariable analysis shows the effect of SSRF over nonoperative treatment. In the corrected analysis, body mass index (BMI), TBI severity, intracranial hypertension (ICH), number of rib fractures, flail chest, pneumothorax, and pulmonary contusion were entered as covariate.

ORs and beta values are shown with 95% confidence interval; bold p-values are considered statistically significant.

Moderate TBI

In patients with moderate TBI, the number of ventilator-free days did not differ between the two treatment groups (beta, -0.47; 95% CI, -9.60 to 8.65 days; p=0.918; Table 2 and Figure 2). The odds of developing pneumonia and of mortality were similar in both treatment groups. No difference in ICU-LOS, HLOS, and the other outcome measures was demonstrated.

Severe TBI

In patients with severe TBI, the number of ventilator-free days was similar in both groups (beta, -1.77; 95% CI, -7.03 to 3.49 days; p=0.508; Table 2 and Figure 2). The odds of 30-day mortality (OR, 0.19; 95% CI, 0.04-0.88; p=0.034) was significantly lower and the rate of mGCS score recovery to 6 (beta, 5.95; 95% CI 1.91 to 18.53 days; p=0.002) significantly higher in the SSRF group. The odds of developing pneumonia, the HLOS, ICU-LOS, and the other outcome measures were similar in both treatment groups.

TABLE 2
Univariate and multivariable in-hospital outcome of SSRF versus nonoperative treatment in patients with rib fractures and moderate or severe TBI.

Outcome	Univariate analysis					Multivariable analysis					
	SSRF		Nonoperative			Crude analysis			Adjusted analysis		
	N*		N*		p	N*	Beta or OR (95% CI)	p	N*	Beta or OR (95% CI)	p
Ventilator-free days											
All	111	11 (7-20)	345	10 (1-21)	0.069	456	-0.53 (-4.27 to 3.21)	0.781	381	-1.61 (-6.12 to 2.89)	0.483
Moderate TBI	35	12 (7-18)	62	10 (5-23)	0.523	97	-1.95 (-8.67 to 4.77)	0.566	79	-0.47 (-9.60 to 8.65)	0.918
Severe TBI	76	11 (7-20)	283	10 (1-21)	**0.034**	359	0.14 (-4.39 to 4.67)	0.952	302	-1.77 (-7.03 to 3.49)	0.508
ICU-LOS											
All	111	12 (7-19)	345	14 (7-22)	0.209	456	-2.23 (-4.67 to 0.01)	0.051	381	-2.03 (-4.56 to 0.49)	0.114
Moderate TBI	35	8 (5-15)	62	12 (5-15)	0.209	97	-2.96 (-6.79 to 0.87)	0.128	79	-1.83 (-5.72 to 2.07)	0.353
Severe TBI	76	14 (8-20)	283	14 (7-22)	0.824	359	-1.23 (-3.93 to 1.47)	0.373	302	-1.86 (-4.92 to 1.21)	0.234
HLOS											
All	111	21 (14-32)	345	22 (13-38)	0.990	456	-2.82 (-7.29 to 1.65)	0.215	381	-3.82 (-9.15 to 1.51)	0.159
Moderate TBI	35	19 (13-24)	62	19 (13-30)	0.784	97	-5.43 (-13.11 to 2.24)	0.163	79	-4.84 (-14.73 to 5.06)	0.333
Severe TBI	76	23 (16-34)	283	23 (13-39)	0.536	359	-0.99 (-6.43 to 4.45)	0.721	302	-3.11 (-9.43 to 3.22)	0.334
Pneumonia											
All	111	38 (34.2%)	345	164 (47.5%)	**0.016**	456	0.58 (0.37 to 0.90)	**0.015**	381	0.59 (0.35 to 0.98)	**0.043**
Moderate TBI	35	6 (17.1%)	62	28 (45.2%)	**0.007**	97	0.25 (0.09 to 0.69)	**0.007**	79	0.35 (0.11 to 1.14)	0.082
Severe TBI	76	32 (42.1%)	283	136 (48.1%)	0.368	359	0.79 (0.47 to 1.31)	0.357	302	0.69 (0.39 to 1.25)	0.221
mGCS score recovery to 6											
All	103	96 (93.2%)	324	243 (75.0%)	**<0.001**	427	4.57 (2.04 to 10.25)	**<0.001**	356	4.54 (1.77 to 11.69)	**0.002**
Moderate TBI	30	28 (93.3%)	52	45 (86.5%)	0.475	82	2.18 (0.42 to 11.24)	0.353	65	N.D.	N.D.
Severe TBI	73	68 (93.2%)	272	198 (72.8%)	**<0.001**	345	5.08 (1.97 to 13.10)	**0.001**	291	5.95 (1.91 to 18.53)	**0.002**
In-hospital mortality											
All	111	8 (7.2%)	345	68 (19.7%)	**0.002**	456	0.32 (0.15 to 0.68)	**0.003**	381	0.40 (0.15 to 1.04)	0.061
Moderate TBI	35	4 (11.4%)	62	9 (14.5%)	0.765	97	0.76 (0.22 to 2.68)	0.669	79	N.D.	N.D.
Severe TBI	76	4 (5.3%)	283	59 (20.8%)	**0.001**	359	0.21 (0.07 to 0.60)	**0.004**	302	0.30 (0.08 to 1.06)	0.061
30-d mortality											
All	111	7 (6.3%)	345	64 (18.6%)	**0.001**	456	0.30 (0.13 to 0.67)	**0.003**	381	0.32 (0.11 to 0.91)	**0.032**
Moderate TBI	35	4 (11.4%)	62	9 (14.5%)	0.765	97	0.76 (0.22 to 2.68)	0.669	79	N.D.	N.D.
Severe TBI	76	3 (3.9%)	283	55 (19.4%)	**0.001**	359	0.17 (0.05 to 0.56)	**0.004**	302	0.19 (0.04 to 0.88)	**0.034**

N.D., not determined.
*: provides the exact number of patients for which the outcome measure was known. The multivariable analysis shows the effect of SSRF over nonoperative treatment. In the corrected analysis, BMI, TBI severity, ICH, number of rib fractures, flail chest, pneumothorax, and pulmonary contusion were entered as covariate.
ORs and beta values are shown with 95% confidence interval; bold p-values are considered statistically significant.

CHAPTER 10
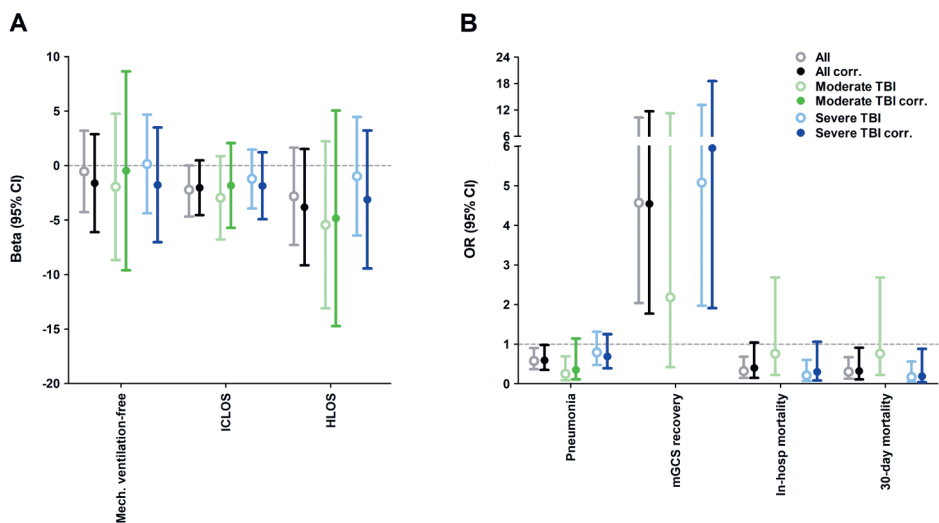
FIGURE 2

Forrest plots for the effect of SSRF over nonoperative treatment for (A) continuous and (B) binary outcomes in all patients as well as in patients with moderate or severe TBI, based on (un)adjusted regression models. Unadjusted and adjusted beta values and ORs (for continuous and binary outcomes, respectively) are shown. For binary outcomes, nonoperative treatment served as reference group. In the adjusted analysis, BMI, TBI severity, ICH, number of rib fractures, flail chest, pneumothorax, and pulmonary contusion were entered as covariate.

DISCUSSION

This multicenter retrospective cohort study is the first to examine SSRF versus non-operative treatment on in-hospital outcome in patients with multiple rib fractures and TBI (GCS score, ≤12). Although there was no difference in the primary outcome of ventilator-free days, this study demonstrated that the SSRF group had, after multivariable analysis, a significantly lower odds of developing pneumonia and of 30-day mortality than the nonoperative group. In patients with severe TBI, SSRF was associated with a significantly lower odds of 30-day mortality. The HLOS, and ICU-LOS were similar in both treatment groups. Furthermore, SSRF in patients with TBI is a safe procedure which can be performed relatively early after admission, without perioperative neuro-logical impairment and a low complication rate.

TBI is considered a traditional contraindication for SSRF as TBI increases the risk of pneumonia regardless of other injuries, as well as the duration of mechanical ventilation, ICU-LOS, and HLOS based on slow neurological recovery. Also, patients with TBI might deteriorate neurologically perioperatively and the neurologic outcome is difficult to predict [12, 13, 18]. Accordingly, the main impediment to ventilator

TABLE 3
In-hospital outcome in patients with moderate or severe TBI and rib fractures treated operatively (SSRF) or nonoperatively.

	N*	All			Moderate TBI			Severe TBI		
		SSRF (n = 111)	Nonop. (n = 345)	p	SSRF (n = 35)	Nonop. (n = 62)	p	SSRF (n = 76)	Nonop. (n = 62)	p
Tracheostomy performed	456	35 (31.5%)	135 (39.1%)	0.176	6 (17.1%)	16 (25.8%)	0.450	29 (38.2%)	119 (42.0%)	0.600
Time to tracheostomy (days)	456	9 (5-12)	10 (7-15)	0.125	5.8 (SD 4.2)	10.0 (SD 5.2)	0.120	10 (6-13)	11 (7-15)	0.363
Pleural empyema	456	1 (0.9%)	5 (1.4%)	1.000	1 (2.9%)	1 (1.6%)	1.000	0 (0.0%)	4 (1.4%)	0.583
Time until mGCS score =6 (days)	456	3 (1-8)	4 (2-14)	**0.020**	2 (1-4)	3 (1-8)	0.092	4 (2-9)	5 (2-15)	0.178

FU, follow-up; Nonop, nonoperative treatment; SEPS; subdural evacuation port system.
*: provides the exact number of patients for which the outcome measure was known.
Data are shown as N (%), mean (SD), or as median (P_{25}-P_{75}); bold p-values are considered statistically significant

liberation has been traditionally considered to be the TBI as opposed to the chest wall injury, rendering SSRF theoretically of little benefit. Furthermore, no published data are available on the effect of SSRF compared with nonoperative treatment in the patient with TBI. Due to this non-evidence-based consensus, participating centers, while forerunners in the field of SSRF, might have been discrete in performing SSRF at an early stage. However, early (within 48 hours) fixation of rib fractures is associated with shorter duration of mechanical ventilation, HLOS, and ICU-LOS in various patient groups without TBI [14, 19-21].

The mortality rate in patients who sustain TBI is high and known to be approximately 25% in polytraumatized patients [1, 22]. The in-hospital and 30-day mortality rate in the current study cohort for all nonoperatively treated patients with rib fractures and TBI was 19.7% and 18.6%, respectively. In the entire SSRF group, the mortality rates decreased with 12.5% for in-hospital mortality and 12.3% for 30-day mortality. Patients with severe thoracic injury on CT may have a three times higher odds of 30-day mortality [23]. In this study, after correcting for the TBI severity and presence of ICH, an odds ratio of 0.32 for 30-day mortality for the entire SSRF group and an odds ratio of 0.19 for the SSRF group with severe TBI was found. This indicates a possible beneficial effect of stabilizing the severely injured chest wall by SSRF on the mortality rate of patients with concomitant multiple rib fractures and TBI. Thus, TBI should no longer be seen as a contraindication to SSRF.

Both the presence of TBI and multiple rib fractures are known risk factors for the development of pneumonia [1, 8, 24, 25]. SSRF is known to decrease the rate of pneumonia and has been studied extensively in patients with multiple rib fractures and a flail chest [26, 27]. The SSRF group in this cohort had a median of one additional fractured rib and 37.6% more often a flail chest than the nonoperative group. Although having more severe thoracic injury than the nonoperative group, the rate of pneumonia was 13.3% lower in the SSRF group than in the nonoperative group in the total cohort and 28.1% lower in patients with moderate TBI. After logistic regression, the odds of developing pneumonia in the SSRF group was 0.59 for the total cohort. No effect of SSRF on the pneumonia rate was found in the group with severe TBI. A possible explanation for the lack of this beneficial effect in the SSRF group with severe TBI might be the lengthy mechanical ventilation which these patients often require. This consequently increases the risk of ventilator-associated pneumonia of which rates of 45 to 60% have been found in these patients [28, 29]. Due to the similar number of ventilator-free days in the SSRF group and nonoperative group of the patients with severe TBI, a comparable rate of ventilator-associated pneumonia could be expected.

While SSRF was associated with significantly lower odds of developing pneumonia and 30-day mortality, the number of ventilator-free days was similar in both groups in the total cohort. As no distinction was made in mechanical ventilation mode, SSRF

could have improved respiratory mechanics, allowing for a quicker wean to a less invasive ventilation mode such as pressure support. This might have decreased the odds of developing pneumonia in the SSRF group in this acute phase or decreased pain and consequently added to the prevention of pneumonia after extubation. In addition, the apparent beneficial effect of SSRF on the odds of developing pneumonia and 30-day mortality in the total study cohort, did not significantly decrease HLOS and ICU-LOS. After correction for the potential confounders, these outcome measures were found to be statistically similar but suggest a modest positive effect of an almost 4 days decrease for HLOS and 2 days decrease for ICU-LOS in favor of the SSRF group in the total cohort. A possible explanation for the similar HLOS and ICU-LOS might be the extensive other injuries of these patients. With a similar rate of additional surgeries performed and a high median ISS greater than 30 in the SSRF and nonoperative group of the total cohort, the exact effect of these extra-cranial and extra-thoracic injuries on the HLOS and ICU-LOS is unclear.

The current study demonstrated that SSRF in patients with TBI is a safe procedure and does not introduce additional neurological damage perioperatively. Four of the 111 patients developed a SSRF-related complication of which only one occurred perioperatively. In this patient, ICP increased during positioning in the operating room, but SSRF could successfully be continued after administration of mannitol and reverse-Trendelenburg positioning. In a patient with TBI, factors related to surgery such as fluid resuscitation overload cause an elevating central venous pressure or prone positioning can result in an increasing ICP requiring prompt intervention [30]. While the effect of SSRF has not been specifically studied in patients with TBI, studies have evaluated the effect of timing of orthopedic fracture fixation in patients with TBI. Some of these studies demonstrated deleterious effects of early fracture fixation due to high rates of perioperative hypotension, increased intracranial pressure and poor neurological outcome possibly due to secondary brain injury [31]. On the other hand it is suggested that orthopedic injuries should be managed aggressively while maintaining sufficient cerebral perfusion pressure through adequate monitoring and fluid resuscitation, but supporting literature is not clear and low in quality [32]. In the postoperative setting of this study, no iatrogenic neurological damage was found with similar times to mGCS score recovery to 6 in the SSRF group and nonoperative group and a higher rate of mGCS score recovery to 6 in the SSRF group of the total cohort and in patients with severe TBI. This outcome measure does not imply that SSRF improves neurological outcome after TBI compared with nonoperative treatment. It does however suggest that SSRF and the appurtenant perioperative setting is safe and does not deteriorate or slow down neurological recovery after TBI, even when SSRF is performed as early as three days after trauma.

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The parameter GCS score at admission was chosen to define TBI severity as there currently is no gold standard [33]. The GCS is the most widely used measure of TBI severity [34]. However, while this variable has known limitations (e.g., in intoxicated patients), other parameters such as the AIS Head also have limitations and a weak correlation with long and short term outcome [35, 36]. Due to the retrospective nature of this study, GCS score at the time of SSRF or sudden GCS score improvements after admission were not known. However, while AIS Head might be a superior indicator for defining TBI severity, which should be evaluated in future research, the GCS score is one of the best severity measurements for immediate clinical care [37]. To correct for non-traumatic reasons leading to a lowered GCS score, the combination of GCS score and presence of intracranial abnormalities on head CT was chosen as an inclusion criterion. This was readily available for all participating centers and of clinical importance during the early post-traumatic phase as SSRF performed within 48 hours is associated with improved outcome [19]. In addition, the logistic regression analysis abstracted and controlled for parameters beyond GCS score that captured severity of TBI, such as the presence of ICH.

While this cohort study is the first, to date, to evaluate the effect of SSRF on in-hospital outcome in patients with multiple rib fractures and TBI, several limitations should be considered when interpreting the outcome. First, due to the retrospective nature of this study, missing data and underreporting might have affected outcome through information bias. Through data collection in which all variables were obligatory and low-threshold communication as the providing co-authors were CWIS members, there were hardly any missing data concerning the included patients.

Second, while the multicenter design resulted in a large number of patients, the sample size of subgroups might have been too low to detect small but clinically meaningful differences in outcome between treatment groups. As lower sample size result in larger confidence intervals, this may explain why the lower odds of developing pneumonia found for the total SSRF group was not seen for the moderate and severe TBI subgroups. The size of the total cohort was unclear beforehand. Therefore the use of an adjusted regression model was chosen instead of propensity score matching. The multicenter design might also have affected outcome due to heterogeneity in clinical practice resulting in effect modification or potential confounding of within-center covariates [38]. On the other hand, the multicenter design has made the results more generalizable.

Third, the study was non-randomized. The mortality difference between the SSRF and nonoperative group might therefore be suggestive of the fact that patients with a better neurological status and consequently prognosis, are more likely to be selected for SSRF, confounding this outcome. With no standardized treatment protocol and the more severe TBI characteristics in the nonoperative group, the treating clinician might

have chosen to perform SSRF on the patient in which a better outcome and prognosis was expected. This might have introduced some bias in the outcome, but mimics daily clinic. A possible consequent survival bias was however mitigated by using the number of ventilator-free days instead of the duration of mechanical ventilation as the primary outcome and by performing a linear regression analysis.

Fourth, the presented logistic and linear regression model only included possible confounders which were identified from available literature and the current data. The confounding effect of non-included parameters, such as AIS Head, is therefore not known. A prospective design with set variables and a standardized treatment protocol might overcome these shortcomings. In addition, due to the retrospective data on in-hospital outcome, future research should focus on the outcome after discharge and cost effectiveness in order to provide a complete overview on outcome after SSRF in this type of patient. Prior to conducting expensive and potentially risky prospective studies, such as randomized controlled trials (RCTs), on this issue, it is important to establish through retrospective research that there is, as this study showed, at least equipoise and, specifically, that SSRF does not harm patients with TBI.

In summary, in patients with moderate to severe TBI a difference in the primary outcome of number of ventilator-free days between the SSRF and nonoperative groups was not demonstrated. However, this exploratory study suggests a reduced odds of both pneumonia and 30-day mortality in patients who underwent SSRF as compared to nonoperative treatment. Moreover, SSRF is shown to be a safe procedure with a low complication rate, and TBI should no longer be seen as an absolute contra-indication to surgery. Prospective studies should strengthen this conclusion in future research.

CHAPTER 10

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CHAPTER 10

SUPPLEMENTAL DATA

SUPPLEMENTAL TABLE S1
Demographics and injury characteristics of patients with moderate (GCS score, 9-12) or severe (GCS score, ≤8) traumatic brain injury (TBI) and rib fractures treated operatively (SSRF) or nonoperatively.

	Moderate TBI					Severe TBI				
	N*	SSRF (n=35)	N*	Nonoperative (n=62)	p	N*	SSRF (n=76)	N*	Nonoperative (n=283)	p
Patient characteristics										
Age (years)	35	56 (SD 16.2)	62	53 (SD 17.1)	0.468	76	46 (SD 14.2)	283	49 (SD 16.8)	0.208
Sex (male)	35	24 (68.6%)	62	52 (83.9%)	0.122	75	56 (74.7%)	283	217 (76.7%)	0.761
BMI (kg/m²)	29	27 (24-33)	53	26 (24-31)	0.380	71	28 (25-31)	245	26 (23-29)	**0.014**
Smoking at age of trauma	24	7 (29.2%)	45	17 (37.8%)	0.598	59	31 (52.5%)	200	76 (38.0%)	0.051
COPD	35	5 (14.3%)	62	2 (3.2%)	0.094	76	6 (7.9%)	283	14 (4.9%)	0.395
Diabetes Mellitus	35	2 (5.7%)	62	5 (8.1%)	1.000	76	12 (15.8%)	283	30 (10.6%)	0.229
Injury characteristics										
High-energy trauma (HET)	35	30 (85.7%)	61	55 (90.2%)	0.522	75	70 (93.3%)	279	253 (90.7%)	0.646
Epidural hematoma	35	3 (8.6%)	62	4 (6.5%)	0.700	76	3 (3.9%)	283	28 (9.9%)	0.112
Subdural hematoma	35	15 (42.9%)	62	36 (58.1%)	0.204	76	26 (34.2%)	283	166 (58.7%)	**<0.001**
Subarachnoid hemorrhage	35	17 (48.6%)	62	39 (62.9%)	0.202	76	43 (56.6%)	283	201 (71.0%)	**0.019**
Diffuse axonal injury (DAI)	35	4 (11.4%)	62	4 (6.5%)	0.454	76	17 (22.4%)	283	65 (23.0%)	1.000
Intra-parenchymal hemorrhage	35	10 (28.6%)	62	18 (29.0%)	1.000	76	24 (31.6%)	283	80 (28.3%)	0.572
Intraventricular hemorrhage	35	0 (0.0%)	62	0 (0.0%)	N.D.	76	5 (6.6%)	283	35 (12.4%)	0.217
Brain contusion	35	8 (22.9%)	62	5 (8.1%)	0.061	76	18 (23.7%)	283	38 (13.4%)	**0.034**
Intracranial hypertension (ICH)	35	0 (0.0%)	61	5 (17.2%)	0.141	76	11 (22.0%)	275	65 (35.7%)	0.088
Number of ribs fractured	35	9 (8-12)	62	8 (6-10)	**0.023**	76	9 (8-12)	283	8 (5-11)	**<0.001**
Injury Severity Score (ISS)	35	29 (24-36)	62	29 (24-36)	0.961	76	34 (29-43)	283	34 (27-41)	0.596
Additional injury										
Flail chest	35	24 (68.6%)	59	19 (32.2%)	**0.001**	76	62 (81.6%)	279	116 (41.6%)	**<0.001**
Pneumothorax	35	28 (80.0%)	62	42 (67.6%)	0.242	76	66 (86.8%)	283	210 (74.2%)	**0.021**
Hemothorax	35	22 (62.9%)	62	33 (53.2%)	0.399	75	45 (60.0%)	282	146 (51.8%)	0.241

	Moderate TBI					Severe TBI				
	N*	SSRF (n=35)	N*	Nonoperative (n=62)	p	N*	SSRF (n=76)	N*	Nonoperative (n=283)	p
Pulmonary contusion	35	25 (71.4%)	62	44 (71.0%)	1.000	76	60 (78.9%)	279	208 (74.6%)	0.457
Facial fracture	35	10 (28.6%)	62	22 (35.5%)	0.511	76	31 (40.8%)	283	106 (37.5%)	0.597
Skull fracture	35	9 (25.7%)	61	21 (34.4%)	0.493	76	33 (43.4%)	283	123 (43.5%)	1.000
Fracture in every rib region	33	13 (39.4%)	54	18 (33.3%)	0.647	67	35 (52.2%)	251	75 (29.9%)	**0.001**
≥100% displacement of ≥3 ribs	34	27 (79.4%)	61	43 (70.5%)	0.467	75	54 (72%)	271	177 (65.3%)	0.333
Treatment characteristics										
Chest tube required	35	32 (91.4%)	62	38 (61.3%)	**0.002**	76	67 (88.2%)	283	193 (68.2%)	**<0.001**
ICP reducing therapy required	35	2 (5.7%)	62	18 (29.0%)	**0.008**	76	24 (31.6%)	283	128 (45.2%)	**0.037**
Mannitol	35	1 (2.9%)	62	9 (14.5%)	0.089	76	11 (14.5%)	283	50 (17.7%)	0.607
Hypertonic saline	35	1 (2.9%)	62	11 (17.7%)	0.051	76	9 (11.8%)	283	56 (19.8%)	0.132
Ventriculostomy	35	0 (0.0%)	62	4 (6.5%)	0.293	76	10 (13.2%)	283	52 (18.4%)	0.311
SEPS drain	35	0 (0.0%)	62	0 (0.0%)	N.D.	76	0 (0.0%)	283	3 (1.1%)	1.000
Pentobarbital/Nembutal	35	0 (0.0%)	62	3 (4.8%)	0.551	76	5 (6.6%)	283	24 (8.5%)	0.813
Craniotomy	35	0 (0.0%)	62	6 (9.7%)	0.084	76	4 (5.3%)	283	46 (16.3%)	**0.014**
Anti-epileptics	35	1 (2.9%)	62	1 (1.6%)	1.000	76	0 (0.0%)	283	7 (2.5%)	0.353
Additional surgeries performed										
Facial surgery	35	4 (11.4%)	62	4 (6.5%)	0.454	76	9 (11.8%)	283	17 (6.0%)	0.131
Clavicle surgery	35	1 (2.9%)	62	0 (0.0%)	0.361	76	7 (9.2%)	283	8 (2.8%)	**0.022**
Thoracotomy	35	2 (5.7%)	62	2 (3.2%)	0.618	76	6 (7.9%)	283	9 (3.2%)	0.099
Laparotomy	35	4 (11.4%)	62	6 (9.7%)	1.000	76	7 (9.2%)	283	37 (13.1%)	0.435
Pelvic surgery	35	1 (2.9%)	62	8 (12.9%)	0.150	76	10 (13.2%)	283	27 (9.5%)	0.395
Long bone surgery	35	11 (31.4%)	62	10 (16.1%)	0.122	76	22 (28.9%)	283	66 (23.3%)	0.367
Spine surgery	35	2 (5.7%)	62	8 (12.9%)	0.321	76	4 (5.3%)	283	32 (11.3%)	0.136

BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; GCS, Glasgow Coma Scale; ICP, intracranial pressure; N.D., not determined; SEPS, subdural evacuation port system; SSRF, surgical stabilization of rib fractures; TBI, traumatic brain injury. *: provides the exact number of patients for which the parameter was known. Data are shown as mean (SD), N (%), or as median (P25-P75); bold p-values are considered statistically significan

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CHAPTER 11

Surgical stabilization versus nonoperative treatment for flail and non-flail rib fracture patterns in patients with traumatic brain injury

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ABSTRACT

Purpose
Literature on outcomes after SSRF, stratified for rib fracture pattern is scarce in patients with moderate to severe traumatic brain injury (TBI; Glasgow Coma Scale ≤ 12). We hypothesized that SSRF is associated with improved outcomes as compared to nonoperative management without hampering neurological recovery in these patients.

Methods
A post-hoc subgroup analysis of the multi-center, retrospective CWIS-TBI study was performed in patients with TBI and stratified by having sustained a non-flail fracture pattern or flail chest between January 1, 2012 and July 31, 2019. The primary outcome was mechanical ventilation-free days and secondary outcomes were in-hospital outcomes. In multivariable analysis, outcomes were assessed, stratified for rib fracture pattern.

Results
In total, 449 patients were analyzed. In patients with a non-flail fracture pattern, 25 of 228 (11.0%) underwent SSRF and in patients with a flail chest, 86 of 221 (38.9%). In multivariable analysis, ventilator-free days were similar in both treatment groups. For patients with a non-flail fracture pattern, the odds of pneumonia were significantly lower after SSRF (odds ratio, 0.29; 95% CI 0.11-0.77; p=0.013). In patients with a flail chest, the ICU LOS was significantly shorter in the SSRF group (beta, -2.96 days; 95% CI -5.70 to -0.23; p=0.034).

Conclusion
In patients with TBI and a non-flail fracture pattern, SSRF was associated with a reduced pneumonia risk. In patients with TBI and a flail chest, a shorter ICU LOS was observed in the SSRF group. In both groups, SSRF was safe and did not hamper neurological recovery.

INTRODUCTION

Traumatic brain injury (TBI) and thoracic trauma are the number one and two leading causes of trauma-related mortality annually, respectively [1, 2]. In the Intensive Care Unit (ICU), rib fractures and TBI are the most prevalent injuries and up to 25% of patients with multiple rib fractures have concomitant TBI [3, 4]. Both injuries are associated with prolonged mechanical ventilation requirement and ICU days, and combined they have been shown to increase the risk of pneumonia, which is a strong independent predictor of mortality after trauma [1, 3, 5].

Utilization of surgical stabilization of rib fractures (SSRF) has increased significantly over the last two decades [6-8]. In patients with a flail chest, SSRF has been associated with a reduced pneumonia rate, and shorter duration of mechanical ventilation and hospital and ICU length of stay (HLOS and ICU LOS) as compared to nonoperative management [9-13]. Studies specifically evaluating outcomes after SSRF in patients with a non-flail fracture pattern are scarce [14]. A recent randomized controlled trial indicated less pain at two weeks follow-up and fewer pleural space complications after SSRF in these patients [15]. Other injury characteristics for which SSRF has been recommended include ≥3 bi-cortically displaced rib fractures or a hemithorax volume loss of ≥30% [16]. The exact effect of SSRF in these populations remains uncertain however as these are often collectively evaluated with patients with a flail and non-flail fracture pattern [17].

The presence of TBI has been considered a relative contraindication for surgery, including SSRF and was often used as an exclusion criterion for rib fracture-related research [15, 18-20]. Recently however, the multi-center, retrospective Chest Wall Injury Society (CWIS)-TBI study reported SSRF to be safe in the presence of moderate to severe TBI (Glasgow Coma Scale [GCS] score ≤12) and associated with a reduced odds ratio of pneumonia and 30-day mortality [21]. This study was the first to specifically assess SSRF in the TBI population with rib fractures, but did not stratify by rib fracture pattern. As the established grounds for SSRF have expanded, a small number of studies have assessed the flail chest and non-flail fracture pattern separately due to their injury-related dissimilarities [14, 22].

Therefore, the aim of this study was to evaluate the effect of SSRF versus nonoperative management in patients with TBI and either a flail chest or non-flail fracture pattern on ventilator-free days. Secondary aims were to assess in-hospital outcomes such as pneumonia rate, motor neurological status, HLOS, ICU LOS, and mortality. We hypo-thesized that SSRF is associated with improved outcomes including more ventilator-free days, shorter ICU LOS, and a lower pneumonia rate, as compared to nonoperative management without hampering neurological recovery in patients with both flail and non-flail rib fracture patterns.

METHODS

Design and participants

This CWIS-TBI study was a multi-center, retrospective cohort study involving 19 trauma centers conducted through the Chest Wall Injury Society (www.cwisociety.org) [21]. The study was approved by each center's local medical research ethics committee or institutional review board and informed consent was exempted. Eligible patients were identified through the hospitals' electronic medical record and by searching their trauma registry for admitted patients with a registered Abbreviated Injury Scale (AIS) for rib or sternal fractures in combination with an AIS ≥3 of the head. Figure 1 lists the inclusion and exclusion criteria. Patients were stratified by having sustained a flail chest or non-flail fracture pattern. A flail chest was defined as having sustained ≥3 bi-cortical consecutive ribs fractured in two or more locations on chest computed tomography (CT; radiographic flail segment) or ≥3 ribs fractured with a paradoxical chest wall respiratory motion (physiologic flail chest). A non-flail fracture pattern was defined as the absence of a radiographic on chest CT or physiologic flail chest.

Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1. Age ≥18 years	1. Rib fractures due to CPR
2. ≥3 fractures of ribs 3-10 with a flail chest or bicortical displacement of ≥3 fractured ribs (diagnosed on chest CT)	2. Unfit for surgery (HD instability, moribund, etc)
	3. Previous rib fractures or pulmonary problems
3. Moderate or severe TBI (GCS score ≤12 at admission with posttraumatic intracranial changes (diagnosed on CT)	4. Rib fixation device *in situ*
	5. Pre-existing neurological deficit (GCS score, ≤12)
4. Trauma sustained between January 1, 2012 and July 1,2019	6. Congenital thoracic deformity
5. Blunt thoracic trauma	7. Imprisoned at time of trauma
6. Admission to participating hospital ≤7 days with documented GCS at presentation	8. Known pregnancy at time of trauma
	9. Transfer to other hospital during clinical admission

FIGURE 1
Study inclusion and exclusion criteria.
CPR, cardiopulmonary resuscitation; CT, computed tomography; GCS, Glasgow Coma Scale; HD, hemodynamic; TBI, traumatic brain injury.

Data collection and outcome measures

The primary outcome measure was the number of ventilator-free days during primary hospital admission, defined as the number of days the patient breathed without assisted (non)-invasive ventilation. Secondary outcome measures were ICU LOS, HLOS, the occurrence of thoracic complications (i.e., pneumonia within 30 days as defined according to the Centers for Disease Control and Prevention (CDC) guidelines [23], pleural empyema

within 30 days as diagnosed on CT-scan and/or pus evacuation [24]), and SSRF-related complications (i.e., superficial and deep wound infection, post-operative bleeding, implant failure requiring removal, and perioperative intracranial pressure increase requiring [non]invasive intervention), neurological outcome (rate of and time to motor GCS [mGCS] score = 6 achieved), and <30 days and in-hospital mortality.

In addition to the outcome measures, patient characteristics and injury-related variables were collected. The TBI severity at hospital admission was defined as moderate (GCS score, 9-12) or severe (GCS score, ≤8). Intracranial hypertension was defined as an intracranial pressure (ICP) of >20 mm Hg. Also, treatment- and outcome-related variables were collected. Therapy for reducing ICP consisted of having received or undergone ≥1 of the following: mannitol, hypertonic saline, pentobarbital, ventriculostomy, craniotomy, or placement of a subdural evacuation port system.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 25 or higher (SPSS, Chicago, Ill., USA). Normality of continuous variables was tested with the Shapiro-Wilk test, and homogeneity of variances was tested using the Levene's test. A p value lower than 0.05 was considered statistically significant and all tests were two-sided. Descriptive analysis was performed to report the data for the entire flail chest and non-flail fracture pattern population and for the treatment groups. For continuous data, the median and percentiles (non-parametric data) were reported. Statistical significance of differences between treatment groups was assessed using Mann-Whitney U test (non-parametric data). For categorical data, numbers and frequencies are reported per treatment group and compared using Chi-squared or Fisher's Exact test, as applicable.

In multivariable analysis, a regression model was developed to control for potential confounders, as described in the main study manuscript [21]. The final regression model for the non-flail fracture pattern group consisted of the covariates number of fractured ribs, chest tube requirement, and intracranial hypertension presence. The model for the flail chest group consisted of BMI, COPD, number of fractured ribs, chest tube requirement, and intracranial hypertension presence. Given the multi-center design of the study, participating center was also considered as a confounder. Study center was however not included in the final model as it did not statistically correlate with outcomes. The final crude regression model included the outcome measure as the dependent variable, and SSRF as covariate. In the adjusted analysis, the covariates mentioned above were added as covariates. For binary regression analysis, the OR for SSRF over nonoperative treatment is reported with 95% confidence interval (CI) and p values. For linear regression analysis, the beta value with 95% CI and p value is reported.

RESULTS

In total, 449 (55.2%) patients with multiple rib fractures and TBI were included (Figure 2). For each study center, the number of included patients with multiple rib fractures and TBI ranged from 2 to 65. The percentage of these patients who underwent SSRF ranged from 0 to 67%.
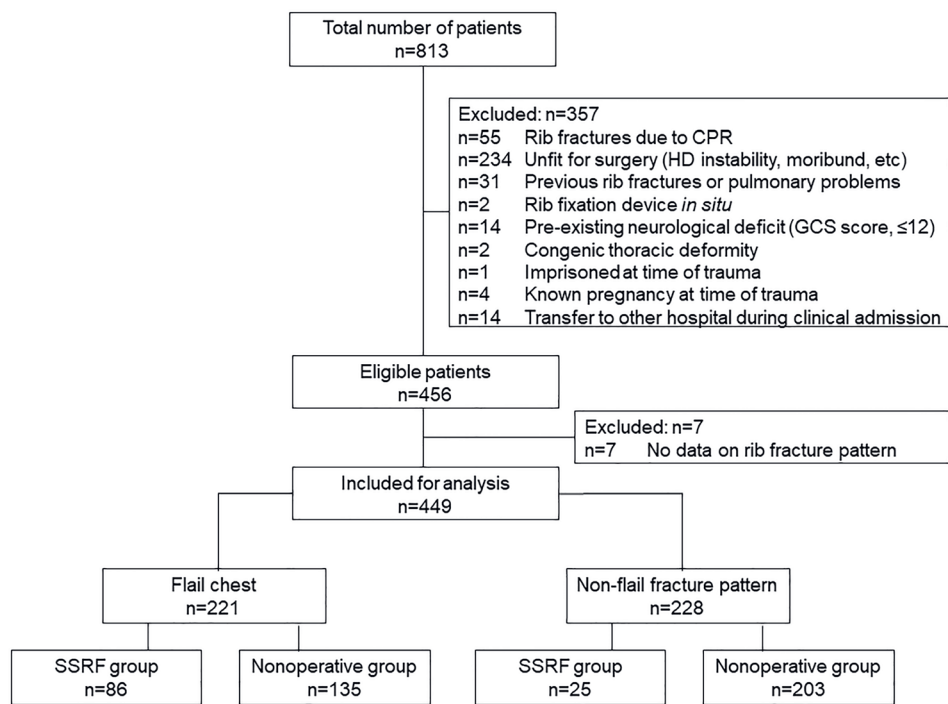
FIGURE 2
Study flow chart.
CPR, cardiopulmonary resuscitation; GCS, Glasgow Coma Scale; HD, hemodynamic; SSRF, surgical stabilization of rib fractures.

Patients with a non-flail fracture pattern

In total, 228 patients had a non-flail fracture pattern, of whom 25 (11.0%) underwent SSRF (Table 1). Operatively treated patients had a higher number of fractured ribs (8, P_{25}-P_{75} 7-12, vs. 6, P_{25}-P_{75} 5-9; p=0.009). In addition, these patients had severe TBI less frequently (n=14, 56% vs. n=163, 80.3%; p=0.010) than nonoperatively treated patients. Other patient and injury characteristics, such as the presence of intracranial hypertension after trauma, were similar. Regarding treatment characteristics, patients who underwent

SSRF more often required a chest tube at admission (n=22, 88% vs. n=121, 59.6%; p=0.004) and less often ICP reducing therapy (n=4, 16% vs. n=81, 39.9%; p=0.027; Table 1). SSRF was performed at a median of 2 days (P_{25}-P_{75} 1-6) after trauma during which a median of 5 ribs (P_{25}-P_{75} 4-6) were repaired, resulting in a ratio of ribs repaired to fractured of 0.5 (P_{25}-P_{75} 0.4-0.8). Two patients developed a wound infection (8%) following SSRF, of which one required implant removal. There were no perioperative neurological complications, post-operative bleeding, or implant failure during hospitalization in the SSRF group.

In univariate analysis, ventilator-free days were similar in both the operative and nonoperative group (Table 1). The SSRF group had a lower rate of pneumonia (n=6, 24% vs. n=96, 47.3%;p=0.033) and 30-day mortality (n=0, 0% vs. n=36, 17.7%; p=0.018). The SSRF group also had a higher rate of mGCS recovery to 6 (n=23, 100% vs. n=149, 78.0%; p=0.010) which was achieved in fewer days (2 days, P_{25}-P_{75} 1-6 vs. 4 days, P_{25}-P_{75} 1-14; p=0.045).

In multivariable adjusted analysis, ventilator-free days did not differ between the treatment groups (Table 2). Odds of developing pneumonia were significantly lower in patients who underwent SSRF (OR, 0.29; 95% CI 0.11-0.77; p=0.013). Other outcomes, including mortality, were similar across the treatment groups.

CHAPTER 11

TABLE 1
Patient, injury, and treatment characteristics and in-hospital outcomes in patients with a non-flail rib fracture pattern and moderate to severe traumatic brain injury who underwent surgical stabilization of rib fractures (SSRF) or nonoperative management.

	All (n=228)		SSRF (n=25)		Nonoperative (n=203)		p
	Nª		Nª		Nª		
Patient characteristics							
Age (years)	228	49 (35-63	25	50 (32-62)	203	49 (35-64)	0.797
BMI (kg/m²)	194	25.8 (23.5-29.4)	22	27.2 (24.3-29.7)	172	25.9 (23.1-29.4)	0.371
Sex (male)	228	174 (76.3%)	25	17 (68%)	203	157 (77.3%)	0.321
Smoking	160	71 (44.4%)	21	10 (48%)	139	61 (43.9%)	0.816
COPD	228	10 (4.4%)	25	0 (0%)	203	10 (4.9%)	0.607
Diabetes Mellitus	228	25 (11.0%)	25	3 (12%)	203	22 (10.8%)	0.743
Injury characteristics							
Fractured ribs (N)	228	7 (5-9)	25	8 (7-12)	203	6 (5-9)	**0.009**
Bilateral rib fractures	228	83 (36.4%)	25	9 (36%)	203	74 (36.5%)	1.000
Fracture in every rib region	194	34 (17.5%)	20	5 (25%)	174	29 (16.7%)	0.356
≥100% displacement of ≥3 ribs	223	159 (71.3%)	24	21 (88%)	199	138 (69.3%)	0.092
Pneumothorax	228	153 (67.1%)	25	20 (80%)	203	133 (65.5%)	0.179
Hemo-thorax	228	101 (44.5%)	25	13 (52%)	203	88 (43.6%)	0.523
Pulmonary contusion	228	165 (73.0%)	25	21 (84%)	203	144 (71.6%)	0.237
ISS	228	29 (25-38)	25	29 (25-36)	203	33 (26-41)	0.502
Epidural hematoma	228	23 (10.1%)	25	3 (12%)	203	20 (9.9%)	0.725
Subdural hematoma	228	127 (55.7%)	25	9 (36%)	203	118 (58.1%)	0.053
Subarachnoid hemorrhage	228	154 (67.5%)	25	15 (60%)	203	139 (68.5%)	0.497
Diffuse axonal injury	228	44 (19.3%)	25	5 (20%)	203	39 (19.2%)	1.000
Intraparenchymal hemorrhage	228	76 (33.3%)	25	12 (48%)	203	64 (31.5%)	0.117
Intraventricular hemorrhage	228	16 (7.0%)	25	1 (4%)	203	15 (7.4%)	1.000
Brain contusion	228	18 (7.9%)	25	4 (16%)	203	14 (6.9%)	0.119
Intracranial hypertension	228	50 (22.4%)	25	2 (8%)	203	48 (24.2%)	0.077
Severe TBI (GCS ≤8)	228	177 (77.6%)	25	14 (56%)	203	163 (80.3%)	**0.010**
Treatment characteristics							
Chest tube required	228	134 (62.7%)	25	22 (88%)	203	121 (59.6%)	**0.004**
ICP reducing therapy required	228	87 (38.2%)	25	4 (16%)	203	83 (40.9%)	**0.016**
Tracheostomy required	228	88 (38.6%)	25	10 (40%)	203	78 (38.4%)	1.000
Additional surgeries required							
Emergency thoracotomy	228	6 (2.6%)	25	1 (4%)	203	5 (2.5%)	0.506
Emergency laparotomy	228	25 (11.0%)	25	2 (8%)	203	23 (11.3%)	1.000
Pelvic surgery	228	24 (10.5%)	25	1 (4%)	203	23 (11.3%)	0.487

TABLE 1 continues on page 229

	All (n=228)		SSRF (n=25)		Nonoperative (n=203)		p
	Nᵃ		Nᵃ		Nᵃ		
Long bone surgery	228	48 (21.1%)	25	4 (16%)	203	44 (21.7%)	0.612
Spine surgery	228	29 (12.7%)	25	2 (8%)	203	27 (13.3%)	0.750
Outcome characteristics							
Mechanical ventilation (days)	228	10 (4-18)	25	8 (4-19)	203	10 (4-18)	0.802
Ventilator-free days (days)	228	10 (2-21)	25	9 (7-17)	203	11 (1-23)	0.815
Motor GCS score recovery to 6	214	172 (80.4%)	23	23 (100%)	191	149 (78.0%)	**0.010**
Time to motor GCS 6 (days)	162	3 (1-11)	22	2 (1-6)	140	4 (1-14)	**0.045**
Pneumonia	228	102 (44.7%)	25	6 (24%)	203	96 (47.3%)	**0.033**
Pleural empyema	228	4 (1.8%)	25	0 (0%)	203	4 (2%)	1.000
ICU LOS	228	13 (6-21)	25	12 (7-20)	203	13 (6-21)	0.921
HLOS	228	21 (13-39)	25	21 (14-28)	203	21 (13-40)	0.681
30-day mortality	228	36 (15.8%)	25	0 (0%)	203	36 (17.7%)	**0.018**
In-hospital mortality	228	40 (17.5%)	25	1 (4%)	203	39 (19.2%)	0.090
Mortality cause							
Traumatic brain injury	31	13 (42%)	1	0 (0%)	30	13 (43%)	0.366
Pulmonary origin	31	5 (16%)	1	0 (0%)	30	5 (17%)	
Septic shock	31	6 (19%)	1	0 (0%)	30	6 (20%)	
Hemorrhagic shock	31	0 (0%)	1	0 (0%)	30	0 (0%)	
Cardiac origin	31	1 (3%)	1	0 (0%)	30	1 (3%)	
Withdrawal of care	31	6 (19%)	1	1 (17%)	30	5 (17%)	

Data are shown as median (P_{25}-P_{75}) or as N (%).
BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; GCS, Glasgow Coma Scale; HLOS, hospital length of stay; ICP, intracranial pressure; ICU LOS, intensive care unit length of stay; ISS, injury severity score; SSRF, surgical stabilization of rib fractures; TBI, traumatic brain injury.
Bold and underlined p values are considered statistically significant.
ᵃ: provides the exact number of patients for whom data were available.

Patients with a flail chest

In total, 221 patients had a flail chest of whom 86 (38.9%) underwent SSRF (Table 3). These patients more often had COPD than the nonoperative group (n=11, 13% vs. n=12, 8.9%; p=0.016). Other patient and thoracic injury characteristics were similar across groups. Following injury, the SSRF group had lower rates of intracranial hypertension (n=10, 12% vs. n=38, 29.0%; p=0.003), severe TBI (n=62, 72% vs. n=116, 85.9%; p=0.015) and less often required ICP reducing therapy (n=21, 24% vs. n=59, 43.7%; p=0.004). Also, patients who underwent SSRF more often required a chest tube at admission

(n=77, 90% vs. n=103, 76.3%; p=0.014). Patients underwent SSRF at a median of 3 days (P_{25}-P_{75} 2-5) during which a median of 4 ribs (P_{25}-P_{75} 3-5) were repaired, resulting in a ratio of ribs repaired to fractured of 0.5 (P_{25}-P_{75} 0.4-0.6). Two SSRF-related complications occurred (2.3%); one patient developed increased intraoperative intracranial pressure requiring mannitol and reverse Trendelenburg positioning after which the SSRF was completed, and one mechanical implant failure requiring implant removal during the hospitalization.

In univariate analysis, SSRF patients had more ventilator-free days than nonoperatively treated patients (13 days, P_{25}-P_{75} 8-20 vs. 9 days, P_{25}-P_{75} 1-21; p=0.034; Table 3). The SSRF had lower 30-day (n=7, 8% vs. n=26, 19.3%; p=0.032) and in-hospital mortality than the nonoperative group (n=7, 8% vs. n=27, 20.0%; p=0.021). Patients who underwent SSRF had a higher rate of mGCS recovery to 6 (n=73, 91% vs. n=88, 69.8%; p<0.001). In multivariable adjusted analysis, ventilator-free days did not differ between treatment groups (Table 4). The SSRF group showed a significantly shorter ICU LOS (beta, -2.96 days; 95% CI -5.70 to -0.23; p=0.034) and higher odds of mGCS recovery to 6 (OR, 3.98; 95% CI 1.40 to 11.33; p=0.010). Other outcomes, including mortality, were similar in both groups.

TABLE 2

Multivariable in-hospital outcomes of surgical stabilization of rib fractures versus nonoperative treatment in patients with a non-flail rib fracture pattern and moderate to severe traumatic brain injury.

Outcome	Multivariable analysis					
	Crude analysis			Adjusted analysis		
	N[a]	Beta or OR (95% CI)	p	N[a]	Beta or OR (95% CI)	p
Ventilator-free days	228	-4.09 (-12.27 to 4.10)	0.326	228	-5.91 (-14.39 to 2.58)	0.171
ICU LOS	228	-1.24 (-6.13 to 3.65)	0.618	228	-2.85 (-7.82 to 2.12)	0.260
HLOS	228	-5.32 (-14.96 to 4.31)	0.278	228	-8.62 (-18.55 to 1.31)	0.089
Pneumonia	228	0.35 (0.14 to 0.92)	**0.033**	228	0.29 (0.11 to 0.77)	**0.013**
Motor GCS score recovery to 6	214	ND	ND	214	ND	ND
In-hospital mortality	228	0.18 (0.02 to 1.34)	0.093	228	0.24 (0.03 to 1.90)	0.176
30-day mortality	228	ND	ND	228	ND	ND

The multivariable analysis shows the effect of SSRF over nonoperative treatment. In the adjusted analysis, the number of fractured ribs, chest tube requirement, and presence of intracranial hypertension were entered as covariate.

CI, confidence interval; HLOS, hospital length of stay; ICU LOS, intensive care unit length of stay; mGCS, motor Glasgow Coma Scale; ND, not determined; OR, odds ratio.

ORs and beta values are shown with 95% confidence interval; bold and underlined p values are considered statistically significant.

[a]: provides the exact number of patients for whom data were available.

TABLE 3
Patient, injury, and treatment characteristics and in-hospital outcomes in patients with a flail chest and moderate to severe traumatic brain injury who underwent surgical stabilization of rib fractures (SSRF) or nonoperative management.

	All (n=221)		SSRF (n=86)		Nonoperative (n=135)		p
	N[a]		N[a]		N[a]		
Patient characteristics							
Age (years)	221	51 (40-62)	86	49 (38-60)	135	51 (42-62)	0.508
BMI (kg/m²)	189	27.1 (23.9-31.3)	78	27.8 (24.6-32.6)	120	26.3 (23.5-30.0)	0.057
Sex (male)	220	168 (76.4%)	85	63 (74%)	135	105 (77.8%)	0.625
Smoking	163	59 (36.2%)	101	28 (45%)	62	31 (30.7%)	0.067
COPD	221	16 (7.2%)	86	11 (13%)	135	5 (3.7%)	**0.016**
Diabetes Mellitus	221	23 (10.4%)	86	11 (13%)	135	12 (8.9%)	0.373
Injury characteristics							
Fractured ribs (N)	221	9 (8-12)	86	9 (8-12)	135	9 (7-12)	0.855
Bilateral rib fractures	221	100 (45.2%)	86	35 (41%)	135	65 (48.1%)	0.332
Fracture in every rib region	207	104 (50.2%)	80	43 (54%)	127	61 (48.0%)	0.476
≥100% displacement of ≥3 ribs	214	138 (64.5%)	85	60 (71%)	129	78 (60.5%)	0.146
Pneumothorax	221	186 (84.2%)	86	74 (86%)	135	112 (83.0%)	0.577
Hemo-thorax	220	140 (63.6%)	85	54 (64%)	135	86 (63.7%)	1.000
Pulmonary contusion	219	165 (75.3%)	86	64 (74%)	133	101 (75.9%)	0.873
ISS	221	34 (29-44)	86	34 (29-43)	135	36 (29-45)	0.235
Epidural hematoma	221	15 (6.8%)	86	3 (3%)	135	12 (8.9%)	0.171
Subdural hematoma	221	110 (49.8%)	86	32 (37%)	135	78 (57.8%)	**0.004**
Subarachnoid hemorrhage	221	141 (63.8%)	86	45 (52%)	135	96 (71.1%)	**0.006**
Diffuse axonal injury	221	43 (19.5%)	86	16 (19%)	135	27 (20.0%)	0.863
Intraparenchymal hemorrhage	221	55 (24.9%)	86	22 (26%)	135	33 (24.4%)	0.874
Intraventricular hemorrhage	221	24 (10.9%)	86	4 (5%)	135	20 (14.8%)	**0.025**
Brain contusion	221	50 (22.6%)	86	22 (26%)	135	28 (20.7%)	0.414
Intracranial hypertension	221	48 (22.1%)	86	10 (12%)	135	38 (29.0%)	**0.003**
Severe TBI (GCS ≤8)	221	178 (80.5%)	86	62 (72%)	135	116 (85.9%)	**0.015**
Treatment characteristics							
Chest tube required	221	180 (81.4%)	86	77 (90%)	135	103 (76.3%)	**0.014**
ICP reducing therapy required	221	81 (36.7%)	86	22 (26%)	135	59 (43.7%)	**0.007**
Tracheostomy required	221	81 (36.7%)	86	25 (29%)	135	56 (41.5%)	0.065

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TABLE 3 continued from page 231

	All (n=221)		SSRF (n=86)		Nonoperative (n=135)		p
	Nᵃ		Nᵃ		Nᵃ		
Additional surgeries required							
Emergency thoracotomy	221	12 (5.4%)	86	7 (8%)	135	5 (3.7%)	0.223
Emergency laparotomy	221	29 (13.1%)	86	9 (11%)	135	20 (14.8%)	0.417
Pelvic surgery	221	22 (10.0%)	86	10 (12%)	135	12 (8.9%)	0.501
Long bone surgery	221	58 (26.2%)	86	29 (34%)	135	29 (21.5%)	0.059
Spine surgery	221	17 (7.7%)	86	4 (5%)	135	13 (9.6%)	0.205
Outcome characteristics							
Mechanical ventilation (days)	221	10 (5-18)	86	9 (5-14)	135	11 (5-21)	**0.040**
Ventilator-free days (days)	221	11 (4-21)	86	13 (8-20)	135	9 (1-21)	**0.034**
Motor GCS score recovery to 6	206	161 (78.2%)	80	73 (91%)	126	88 (69.8%)	**<0.001**
Time to motor GCS 6 (days)	144	4 (2-11)	69	4 (1-9)	75	5 (2-14)	0.075
Pneumonia	221	98 (44.3%)	86	32 (37%)	135	66 (48.9%)	0.097
Pleural empyema	221	2 (0.9%)	86	1 (1%)	135	1 (0.7%)	1.000
ICU LOS	221	14 (7-21)	86	12 (7-17)	135	15 (7-23)	0.066
HLOS	221	22 (14-34)	86	22 (16-33)	135	23 (11-35)	0.914
30-day mortality	221	33 (14.9%)	86	7 (8%)	135	26 (19.3%)	**0.032**
In-hospital mortality	221	34 (15.4%)	86	7 (8%)	135	27 (20.0%)	**0.021**
Mortality cause							
Traumatic brain injury	28	13 (46%)	7	2 (29%)	21	11 (52%)	0.191
Pulmonary origin	28	6 (21%)	7	1 (14%)	21	5 (24%)	
Septic shock	28	3 (11%)	7	2 (29%)	21	1 (5%)	
Hemorrhagic shock	28	1 (4%)	7	1 (14%)	21	0 (0%)	
Cardiac origin	28	3 (11%)	7	1 (14%)	21	2 (10%)	
Withdrawal of care	28	1 (4%)	7	0 (0%)	21	2 (10%)	

Data are shown as median (P_{25}-P_{75}) or as N (%).
BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; HLOS, hospital length of stay; GCS, Glasgow Coma Scale; ICP, intracranial pressure; ICU LOS, intensive care unit length of stay; ISS, injury severity score; SSRF, surgical stabilization of rib fractures; TBI, traumatic brain injury.
Bold and underlined p values are considered statistically significant.
*: provides the exact number of patients for whom data were available.

TABLE 4
Multivariable in-hospital outcomes of surgical stabilization of rib fractures versus nonoperative treatment in patients with a flail chest and moderate to severe traumatic brain injury

Outcome	Multivariable analysis					
	Crude analysis			Adjusted analysis		
	Nᵃ	Beta or OR (95% CI)	p	Nᵃ	Beta or OR (95% CI)	p
Ventilator-free days	221	1.25 (-2.85 to 5.35)	0.547	221	-0.28 (-4.91 to 4.35)	0.905
ICU LOS	221	-2.72 (-5.21 to -0.23)	**0.033**	221	-2.96 (-5.70 to -0.23)	**0.034**
HLOS	221	-1.76 (-6.82 to 3.30)	0.494	221	-3.36 (-8.97 to 2.26)	0.240
Pneumonia	221	0.62 (0.36 to 1.08)	0.089	221	0.75 (0.39 to 1.43)	0.382
Motor GCS score recovery to 6	206	4.50 (1.90 to 10.68)	**0.001**	206	3.98 (1.40 to 11.33)	**0.010**
In-hospital mortality	221	0.35 (0.15 to 0.86)	**0.021**	221	0.39 (0.12 to 1.26)	0.114
30-day mortality	221	0.37 (0.15 to 0.90)	**0.028**	221	0.40 (0.12 to 1.29)	0.126

The multivariable analysis shows the effect of SSRF over nonoperative treatment. In the adjusted analysis, BMI, COPD, the number of fractured ribs, chest tube requirement, and presence of intracranial hypertension were entered as covariate.
BMI, body mass index; CI, confidence interval; COPD, Chronic Obstructive Pulmonary Disease; HLOS, hospital length of stay; ICU LOS, intensive care unit length of stay; mGCS, motor Glasgow Coma Scale; OR, odds ratio. Data are shown as odds ratio (OR; categorical outcome) or beta (continuous outcome) with 95% confidence interval. Bold and underlined p values are considered statistically significant.
ᵃ: provides the exact number of patients for whom data were available.

DISCUSSION

This study investigated the effect of SSRF versus nonoperative management on in-hospital outcomes in patients with a flail or non-flail fracture pattern and concomitant TBI. For both types of rib fracture patterns, no beneficial effect of SSRF on the primary outcome of ventilator-free days was demonstrated. In patients with a flail chest, a 3-day decrease in ICU LOS was observed in patients who underwent SSRF. In patients with a non-flail fracture pattern, SSRF was associated with three times lower odds of pneumonia. In both rib fracture groups, SSRF was safe with a low complication rate and no pre- or postoperative neurological deterioration.

Patients with multiple rib fractures and TBI are often not considered candidates for SSRF, regardless of pulmonary abnormalities [12, 13]. This reason is likely multi-factorial: the perioperative setting might cause increased intracranial pressure and patients with TBI are often expected to have lengthy mechanical ventilation requirement and ICU LOS, making it difficult to distill an effect of the severe rib fractures and SSRF on in-hospital outcomes. This dogma was challenged by the CWIS-TBI study, which showed that SSRF did not impair neurological recovery, had a low perioperative risk, and was associated with a lower risk of pneumonia and mortality [21]. As follow-up to this study, CWIS-TBI data was used to evaluate whether more specific rib fracture

patterns benefit from SSRF. Patients with a non-flail fracture pattern who underwent SSRF had relatively similar thoracic injuries as compared to the nonoperative group. Patients with a flail chest had more severe thoracic injuries in the SSRF group and more severe brain injuries in the nonoperative group. This finding might provide reflection of the surgeon's decision-making who considers TBI a contraindication for SSRF, and subsequently is more likely to offer SSRF to patients with the more severe rib fracture patterns and less severe TBI characteristics or improved neurologic prognosis. For both rib fracture pattern groups, the current study indicates that SSRF is safe and might be of benefit in these patients.

In patients with a flail chest, SSRF has previously been associated with decreased ICU LOS, as compared to nonoperative treatment [18, 20, 25, 26]. Several of these studies however, including two randomized controlled trials, specifically excluded patients with TBI [5, 18, 20]. In the current study a shorter ICU LOS was observed in the SSRF group of patients with a flail chest, and SSRF was safe without signs of periprocedural neurologic deterioration in the patient with TBI. This ICU LOS decrease did not result in shorter HLOS or increased ventilator-free days on multivariable analysis. This might be due to for example the effect of TBI extent or another unaccounted confounder which impacted ventilator-free days more strongly than chest wall injury severity or SSRF. This is supported by the increased ventilator-free days on univariate analysis for the SSRF group which was similar on multivariable analysis after correcting for intracranial hypertension presence. Also, with no data on mechanical ventilation mode, SSRF might have improved respiratory mechanics, assisted in stabilizing the patient, and allowed for a quicker wean and more rapid discharge from the ICU after complete ventilation liberation. A shorter ICU stay is also beneficial for the cost-effectiveness as SSRF has been shown to be economically more beneficial regarding hospital charges [26, 27].

Literature on the effect of SSRF versus nonoperative treatment in patients with a non-flail fracture pattern is scarce [14]. Only three studies have assessed the outcome pneumonia and either excluded patients with TBI or did not provide insight in patient selection [15, 28, 29]. This study is the first to specifically assess pneumonia rates following SSRF or nonoperative treatment in patients with a non-flail fracture pattern and TBI. On multivariable analysis, SSRF was associated with three times lower odds for developing pneumonia. Interestingly, this lower risk did not appear to have clinical consequences in terms of shorter hospital or ICU stay or increased ventilator-free days. It does highlight that besides TBI, chest wall injury plays a role in developing pneumonia and SSRF might be beneficial in reducing this risk.

Furthermore, as has been corroborated by the previous CWIS-TBI study, SSRF is a safe procedure in patients with TBI, also when specifically evaluated in chest wall injury subgroups. With high rates of mGCS score recovery to 6 and a low complication rate,

SSRF and the consequent perioperative setting is safe and does not hamper neurological recovery. This is of importance as early SSRF (≤48-72h after trauma) is associated with shorter HLOS, ICU LOS, mechanical ventilation duration, and lower rates of pneumonia [30-32]. With a median time from trauma to SSRF of two and three days in patients with a non-flail fracture pattern and a flail chest, respectively, this benefit of early SSRF might already be present. The optimal timing of SSRF in this population requires further evaluation. The benefit of early SSRF and the demonstrated safe perioperative SSRF setting might assist surgeons in decision-making in the acute setting when neurological prognosis is often unsure.

The results of this study should be interpreted acknowledging several limitations. First, the inclusion criterion of TBI through using a single GCS score at admission has known limitations (e.g., in intoxicated patients) and might be of less clinical significance than ongoing GCS score assessment or the GCS score at the day of SSRF. In order to minimize the impact of this limitation, the presence of intracranial injuries on brain CT was required. In addition, patients were identified for having a head AIS of ≥3 besides rib fractures, thus excluding patients with minor TBI with a lowered GCS. Also, the GCS score is the most commonly used parameter to assess TBI severity and is readily available in the acute setting in contrast to the AIS [33, 34]. Furthermore, the regression model corrected for TBI severity through the variable intracranial hypertension which was more strongly associated with outcomes than individual intracranial injuries. Future research should prospectively evaluate (acute and long-term) outcomes in the patient with TBI and use standardized treatment protocols across centers, consider ongoing GCS scores or on the day of SSRF instead of at admission, whether intracranial hypertension might be a SSRF contraindication instead of the general umbrella title TBI, and TBI improvement post-SSRF through CT scan instead of mGCS.

Second, the observational non-randomized study design might have introduced selection bias. Patients who are selected for SSRF often have more severe thoracic injuries but are also younger with less comorbidities than those treated nonoperatively, requiring adjusting for when assessing outcomes [35, 36]. In the current study, the treatment groups were relatively similar regarding thoracic injury severity but had significant dissimilarities in the severity of TBI and rate of associated intracranial injuries, being higher in the nonoperative group. Previously, recommendation of SSRF has been shown to be significantly impacted by TBI presence and degree; the more severe TBI, the less likely SSRF was recommended [37]. The prognosis assessment in patients with TBI remains difficult and a standardized treatment protocol regarding SSRF in this population is lacking [12, 38]. This might have resulted in SSRF being performed in patients with a better neurological status or those who were expected to have improved outcomes in terms of (neurological) recovery and during hospitalization, confounding observed outcomes which might subsequently be more strongly affected by the effect

of the associated injuries than the treatment effect. To mitigate this effect, multivariable analyses was performed adjusting for intracranial hypertension. However, the extent to which the individual intracranial injuries or other uncaptured confounders might have affected outcomes or (not) being selected for SSRF remains unknown.

Third, the multi-center design might have impacted outcomes as both the numbers of included patients and rates of SSRF performed varied significantly between centers. Also, since there was no standardized (non)operative treatment protocol, heterogeneity of managing rib fractures across centers or potential confounding of within-center covariates might be present [39, 40]. However, the variable "study center" did not correlate significantly with outcomes and this design made the results more generalizable to daily practice. The large variability in the rate of patients with TBI who underwent SSRF shows that there currently is no consensus on this patient group's optimal treatment. The retrospective nature of this study might have resulted in missing data or underreporting, but the rate of missing data was <4% for all variables except BMI and smoking status.

In conclusion, SSRF did not impact the number of ventilator-free days in patients with a flail or a non-flail rib fracture pattern and TBI. In patients with TBI and a non-flail fracture pattern, SSRF was associated with a reduced pneumonia risk. In patients with TBI and a flail chest, a shorter ICU LOS was observed in the SSRF group. In addition, SSRF was a safe procedure in both rib fracture groups and did not hamper neurological recovery. The presence of TBI in patients with a specific severe rib fracture pattern that possibly necessitates SSRF, should not be considered a contraindication for this treatment. In the setting of TBI, the decision to perform SSRF should be made by carefully weighing the risks of surgery against the benefits of both pulmonary and overall recovery.

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CHAPTER 12

Surgical stabilization of rib fractures versus nonoperative treatment in patients with multiple rib fractures following cardiopulmonary resuscitation: an international, retrospective Chest Wall Injury Society matched case-control study (CWIS-CPR)

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ABSTRACT

Background
The presence of six or more rib fractures or a displaced rib fracture due to cardio-pulmonary resuscitation (CPR) has been associated with longer hospital and intensive care unit (ICU) length of stay. Evidence on the effect of surgical stabilization of rib fractures (SSRF) for rib fractures following CPR is limited. This study aimed to evaluate the effect of SSRF versus nonoperative management on in-hospital outcomes in patients with multiple rib fractures after CPR.

Methods
An international, retrospective study was performed in patients who underwent SSRF or nonoperative management for multiple rib fractures following CPR between January 1, 2012 and July 31, 2020. Patients who underwent SSRF were matched to one or two nonoperative controls by cardiac arrest location, cause of arrest, rib fracture pattern (i.e., unilateral or bilateral, flail chest, or flail sternum), and age. The primary outcome was mechanical ventilator-free days, defined as the number of days without mechanical breathing.

Results
Thirty-nine patients underwent SSRF and were matched to 69 nonoperative controls. The treatment groups had comparable matching criteria and CPR-related characteristics. Patients who underwent SSRF more often had one or more displaced rib fractures (n=28, 72% vs. n=31, 47%; p=0.015) and a higher median number of displaced ribs (2, P25-P75 0-3 vs. 0, P25-P75 0-3; p=0.014). SSRF was performed at a median of 5 days (P25-P75 3-8) after CPR. In the nonoperative group, a rib fixation specialist was consulted in 14 patients (21%). No difference was demonstrated for the number of mechanical ventilator-free days between treatment groups. The ICU LOS was significantly longer in the operative group (13 days, P25-P75 9-23 vs. 9 days, P25-P75 5-15; p=0.004). Other outcomes were similar across the treatment groups.

Conclusion
Despite more consequential chest wall injury in the SSRF group, both treatment groups had relatively similar outcomes. Other variables than the included injury and radiographic characteristics might result in rib fixation consultation in this population, highlighted by the low consultation in the nonoperative group. Careful patient selection and prospective studies are required before embedding or abandoning this procedure in these patients.

INTRODUCTION

Chest compressions as part of cardiopulmonary resuscitation (CPR) for sudden cardiac arrest are vital in providing oxygenated blood to the heart and brain, but are also traumatic [1-3]. Rib fractures are the most common chest wall injury following CPR and seen in 66% to 88% of patients who survived sudden cardiac arrest [4-8]. Various studies have associated sustaining post-traumatic rib fractures, an increasing number of rib fractures, and fracture displacement over half the ribs' width as risk factors for mortality and pulmonary complications including pneumonia [9-14]. In post-CPR patients with good neurologic recovery, the presence of ≥6 rib fractures and ≥1 bicortically displaced rib fractures have been associated with prolonged hospital length of stay (HLOS) and intensive care unit length of stay (ICU LOS) [8]. In addition, iatrogenic rib fractures (e.g., CPR-related) as compared to post-traumatic rib fractures are associated with longer HLOS and a higher mortality rate [15].

Traumatic flail chest is currently an indication for surgical stabilization of rib fractures (SSRF) as this has been shown to reduce pneumonia risk, ICU LOS, and mechanical ventilation duration as compared to nonoperatively managed patients [16-18]. To date, evidence on SSRF in the post-CPR population is limited to case reports and series without control group [19-22]. It is hypothesized that restoring chest wall integrity and improving respiratory capacity through SSRF aids ventilator liberation and improves outcomes.

Whether post-traumatic SSRF indications also account for the post-CPR population remains unknown. This international, retrospective, matched case-control study aimed to evaluate the effect of SSRF over nonoperative management on mechanical ventilator-free days in patients with multiple rib fractures following CPR as well as in subgroups based on temperature management requirement (TTM) and time to SSRF. Secondary outcomes were ICU LOS, HLOS, thoracic complication rate, and mortality.

METHODS

Design and participants

This was an international, retrospective, matched case-control study involving 12 level I and II trauma centers. Centers were asked to participate through email by the Chest Wall Injury Society (www.cwisociety.org). Centers had to have performed at least one SSRF case for multiple rib fractures following CPR. The study was approved by each center's medical research ethics committee or institutional review board. Eligible patients were identified through the hospitals' electronic medical record based on intervention, diagnosis, or injury codes for sudden cardiac arrest, or, if available, a local

cardiac arrest database. Figure 1 displays the inclusion, exclusion, and matching criteria. SSRF patients were matched against nonoperative patients in a 1:2 ratio, or 1:1 ratio if this was not possible. SSRF patients were excluded if no eligible control was available. A flail chest was defined as having sustained ≥3 consecutive fractured ribs in ≥2 locations (radiographic flail segment) on chest computed tomography (CT) or paradoxical chest wall respiratory motion (physiologic flail chest). A flail sternum was defined as two adjacent fractured ribs on both sides of the sternum.

Data collection and outcome measures

Data were extracted from the patient's medical files. The primary outcome measure was the number of mechanical ventilator-free days during primary hospital admission, defined as the number of days the patient breathed without assisted invasive mechanical ventilation. Secondary outcome measures were ICU LOS, HLOS, the occurrence of complications (i.e., pneumonia, pleural empyema, thoracic bleeding [requiring radiological or surgical intervention, or blood transfusion], superficial or deep wound infection after SSRF [requiring pharmacological or surgical intervention], SSRF implant failure requiring removal, additional CPR-setting, and tracheostomy requirement), time to mortality, and mortality rate.

Additional patient-related, CPR-related, injury-related, treatment-related, and outcome-related characteristics were also collected. Patient characteristics included risk factors for sudden cardiac arrest (i.e., myocardial infarction <30 days prior to initial CPR, major cardiothoracic or abdominal surgery, chemotherapy, sepsis, and organ failure) and previous cardiac interventions (i.e., percutaneous coronary intervention [PCI], coronary artery bypass grafting [CABG], implantable cardioverter defibrillator [ICD], or pacemaker). Rib fracture characteristics were classified according to the CWIS taxonomy paper [23]. In case of a total Glasgow Coma Scale (GCS) <8 according to international guidelines or if a patient had a motor GCS <5, TTM was initiated [24].

CPR, cardiopulmonary resuscitation; CT, computed tomography; ECMO, extracorporeal membranous oxygenation; HD, hemodynamic; SSRF, surgical stabilization of rib fractures; VAD, ventricular assist device; ROSC, return of spontaneous circulation.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 25 or higher (SPSS, Chicago, IL, USA). Normality of continuous variables was confirmed by the Shapiro-Wilk test. A p-value lower than 0.05 was considered statistically significant and all tests were two-sided. Descriptive analysis was performed to report the data for the entire cohort and for the treatment groups. For continuous data, the median and percentiles (non-parametric data) were reported. Statistical significance of differences between treatment groups was assessed using Mann-Whitney U-test (non-parametric

Inclusion, exclusion, and matching criteria

Inclusion criteria
1) Age ≥18 years
2) Sudden cardiac arrest without traumatic cause between January 1, 2012 and July 31, 2020
3) Rib fractures sustained after manual and/or mechanical CPR with ROSC
4) If out-of-hospital cardiac arrest, admission ≤24 hours after CPR
5) For ribs 3-10, ≥3 fractured ribs (diagnosed on chest CT) with either a) flail chest, b) flail sternum, or c) bicortical displacement of ≥3 ribs

Exclusion criteria
1) ECMO, VAD, or intra-aortic balloon pump used due to risk of iatrogenic thoracic injuries
2) Unfit for surgery (*e.g.*, HD instability, moribund, infaust cerebral prognosis)
3) Previous rib fractures or pulmonary problems requiring continuous oxygen use at home
4) Congenital thoracic deformity
5) Transfer to other hospital during admission
6) Imprisoned at time of CPR
7) Known pregnancy at time of CPR

Eligible patients

Matching criteria (2 controls:1 SSRF or 1:1)
1) Same place of arrest: out-of-hospital or in-hospital
2) Same cause of arrest: cardiac or non-cardiac
3) Same rib fracture pattern: unilateral or bilateral
4) Same flail chest status: with or without flail chest
5) Same flail sternum status: with or without flail sternum
6) Similar age: within 10 years; if two controls, then one older and one younger control; if multiple controls, two controls with age nearest to that of the case

FIGURE 1
Overview of inclusion, exclusion and matching criteria.

data). For categorical data, numbers and frequencies are reported per treatment group and compared using Chi-squared or Fisher's Exact test, as applicable.

Subgroup analysis was performed to determine the effect of SSRF in patients in whom TTM was or was not initiated and in those who underwent SSRF within or after 3 days from admission, as compared to their individually matched nonoperative patients.

RESULTS

In total, 105 patients were included. Thirty-nine patients (37.1%) underwent SSRF and these were matched with 66 nonoperatively treated patients (62.9%). There were no significant differences between the treatment groups for the matching criteria (Table 1).

Operatively treated patients had a lower median BMI than nonoperatively treated patients (25.1, P_{25}-P_{75} 21.7-28.0 vs. 27.7, P_{25}-P_{75} 24.8-31.8; p=0.012; Table 1). Other patient characteristics such as rate of patients using anticoagulants and comorbidities were similar across treatment groups (Table 1; Supplemental Table 1). There were no differences between the groups in terms of CPR-related characteristics including GCS score on admission and time from CPR to ROSC.

TABLE 1
Patient, sudden cardiac, injury, and outcome characteristics in patients following cardiopulmonary resuscitation for sudden cardiac arrest who underwent operative or nonoperative management of rib fractures.

	N*	Overall (n=105)	N*	SSRF (n=39)	N*	Nonoperative (n=66)	p
Patient characteristics							
Age (years)	105	68 (61-73)	39	68 (60-73)	66	68 (61-72)	0.745
Sex (male)	105	85 (81.0%)	39	34 (87%)	66	51 (77%)	0.304
BMI (kg/m²)	99	26.7 (24.0-29.8)	37	25.1 (21.7-28.0)	62	27.7 (24.8-31.8)	**0.012**
Smoking at age of CPR	78	26 (33.3%)	33	10 (30%)	45	16 (36%)	0.808
Anticoagulation use at age of CPR	105	42 (40.0%)	39	15 (39%)	66	27 (41%)	0.839
Comorbidities							
Hypertension	105	61 (58.1%)	39	20 (51%)	66	41 (62%)	0.311
Diabetes Mellitus	105	18 (17.1%)	39	5 (13%)	66	13 (20%)	0.431
COPD	105	24 (22.9%)	39	7 (18%)	66	17 (26%)	0.472
Cardiomyopathy	105	8 (7.6%)	39	3 (8%)	66	5 (8%)	1.000
Cardiac arrhythmia	105	25 (23.8%)	39	8 (21%)	66	17 (26%)	0.639
Myocardial infarction	105	18 (17.1%)	39	6 (15%)	66	12 (18%)	0.794
Chronic heart failure	105	8 (7.6%)	39	4 (10%)	66	4 (6%)	0.466
Cerebrovascular accident	105	6 (5.7%)	39	2 (5%)	66	4 (6%)	1.000
Risk factor for sudden cardiac arrest	104	10 (9.6%)	39	5 (13%)	65	5 (8%)	0.496
Previous cardiac interventions	105	14 (13.3%)	39	8 (21%)	66	6 (9%)	0.137
Cardiac arrest and CPR characteristics							
Cardiac cause of arrest	105	77 (73.3%)	39	28 (72%)	66	49 (74%)	0.822
GCS score on admission	96	3 (3-10)	37	3 (3-12)	59	3 (3-10)	0.517
Time from arrest to start CPR							
0-5 minutes	92	83 (90.2%)	35	31 (89%)	57	52 (91%)	0.312
6-10 minutes	92	7 (7.6%)	35	4 (11%)	57	3 (5%)	
11-15 minutes	92	2 (2.2%)	35	0 (0%)	57	2 (4%)	
Time from start CPR to ROSC							
0-5 minutes	102	16 (15.7%)	37	8 (22%)	65	8 (12%)	0.074
6-10 minutes	102	35 (34.3%)	37	8 (22%)	65	27 (42%)	
11-15 minutes	102	17 (16.7%)	37	4 (11%)	65	13 (20%)	
16-20 minutes	102	20 (19.6%)	37	11 (30%)	65	9 (14%)	
>20 minutes	102	14 (13.7%)	37	6 (16%)	65	8 (12%)	
Mechanical CPR	105	7 (6.7%)	39	5 (13%)	66	2 (3%)	0.099
Thoracic injury characteristics							
No. of fractured ribs	105	10 (9-12)	39	10 (10-13)	66	10 (9-12)	0.172
No. of rib fractures	105	11 (9-13)	39	13 (10-16)	66	10 (9-12)	0.055

	N*	Overall (n=105)	N*	SSRF (n=39)	N*	Nonoperative (n=66)	p
Flail chest	105	22 (21.0%)	39	10 (26%)	66	12 (18%)	0.458
Flail sternum	105	101 (96.2%)	39	37 (95%)	66	64 (97%)	0.627
≥3 displaced fractured ribs	105	33 (31.4%)	39	15 (39%)	66	18 (27%)	0.279
≥1 displaced fractured ribs	105	59 (56.2%)	39	28 (72%)	66	31 (47%)	**0.015**
No. of displaced fractured ribs	105	1 (0-3)	39	2 (0-3)	66	0 (0-3)	**0.014**
Sternum fracture	105	44 (41.9%)	39	20 (51%)	66	24 (36%)	0.155
Pneumothorax	105	17 (16.2%)	39	8 (21%)	66	9 (14%)	0.415
Hemothorax	105	50 (48.5%)	39	22 (56%)	66	28 (44%)	0.230
Pulmonary contusion	105	55 (52.4%)	39	23 (59%)	66	32 (49%)	0.319
Treatment characteristics							
TTM requirement	105	65 (61.9%)	39	21 (54%)	66	44 (67%)	0.216
TTM duration (days)	61	1 (1-2)	19	2 (1-2)	42	1 (1-2)	0.242
mGCS score <24h after TTM stop	55	6 (5-6)	15	5 (5-6)	40	6 (5-6)	0.312
Consultation for rib fixation	105	53 (50.5%)	39	39 (100%)	66	14 (21%)	**<0.001**
Time to rib fixation consultation (days)	53	3 (2-5)	39	3 (2-5)	14	3 (1-8)	0.870
Chest tube on admission	105	14 (13.3%)	39	7 (18%)	66	7 (11%)	0.374
PCI after CPR	105	39 (37.1%)	39	16 (41%)	66	23 (35%)	0.538
CABG after CPR	105	10 (9.5%)	39	2 (5%)	66	8 (12%)	0.316
ICD or pacemaker after CPR	105	31 (29.5%)	39	10 (26%)	66	21 (32%)	0.658
Outcome characteristics							
Mechanical ventilator-free days	105	17 (10-23)	39	17 (10-23)	66	18 (11-24)	0.559
ICU LOS (days)	105	12 (6-19)	39	13 (9-23)	66	9 (5-15)	**0.004**
HLOS (days)	105	24 (17-35)	39	26 (20-39)	66	24 (16-32)	0.205
Tracheostomy	105	22 (21.0%)	39	11 (28%)	66	11 (17%)	0.215
Pneumonia	105	49 (46.7%)	39	16 (41%)	66	33 (50%)	0.422
Pleural empyema	105	1 (1.0%)	39	1 (3%)	66	0 (0%)	0.371
Thoracic bleeding	105	10 (9.5%)	39	6 (15%)	66	4 (6%)	0.168
Additional CPR-setting	105	9 (8.6%)	39	3 (8%)	66	6 (9%)	1.000
Discharged home	87	53 (60.9%)	32	18 (56%)	55	35 (64%)	0.505
In-hospital or 30-day mortality	105	18 (17.1%)	39	7 (18%)	66	11 (17%)	1.000
Time to mortality (days)	17	15 (11-24)	7	13 (9-27)	10	17 (12-23)	0.696

Data are shown as median (P_{25}-P_{75}) or as n (%); bold p-values are considered statistically significant.
*: provides the exact number of patients for whom the parameter was known.
BMI, body mass index; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; CPR, cardiopulmonary resuscitation; HLOS, hospital length of stay; ICD, implantable cardioverter defibrillator; ICU LOS, intensive care unit length of stay;
mGCS, motor Glasgow Coma Scale; PCI, percutaneous coronary intervention; ROSC, return of spontaneous circulation; SSRF, surgical stabilization of rib fractures; TTM, targeted temperature management.

The SSRF group sustained 250 rib fractures with a median of 10 ribs (P_{25}-P_{75} 10-13) and 13 fractures (P_{25}-P_{75} 10-16) per patient which was similar to the median of 10 ribs (P_{25}-P_{75} 9-12; p=0.172) and 10 fractures (P_{25}-P_{75} 9-12; p=0.055) of the nonoperative group (totaling 1023 fractures). The operative group more frequently had at least 1 displaced fractured rib (n=28, 72% vs. n=31, 47%; p=0.015) and a higher median number of displaced ribs (2, P_{25}-P_{75} 0-3 vs. 0, P_{25}-P_{75} 0-3; p=0.014). Intra-thoracic injury rates of pneumothorax, hemothorax, and pulmonary contusion were similar between groups. There were no abdominal injuries in the nonoperative group and one spleen rupture requiring surgery in the SSRF group.

In the entire cohort, 65 patients (61.9%) required TTM for a median of 1 day (P_{25}-P_{75} 1-2 days) after which the motor GCS score recovered to 6 (P_{25}-P_{75} 5-6) within 24 hours after cessation. The treatment groups had similar TTM requirement, duration, and motor GCS recovery. In the nonoperative group, a rib fixation specialist was consulted for possible rib fixation in 14 patients (21%) at a median of 3 days (P_{25}-P_{75} 1-8 days). In the operative group, a rib fixation specialist was consulted at a median of 3 days (P_{25}-P_{75} 2-5 days) and SSRF was performed at a median of 5 days (P_{25}-P_{75} 3-8) after CPR. Pre-SSRF, anticoagulants were stopped in 6 patients (17%; all anticoagulants stopped in three patients and partial anticoagulants stopped in three patients). During SSRF, a median of 6 ribs (P_{25}-P_{75} 4-7) and 6 fractures (P_{25}-P_{75} 4-8) were repaired, resulting in a ribs fractured to ribs repaired ratio of 0.5 (P_{25}-P_{75} 0.4-0.7). Nine patients had concomitant sternal repair. Two patients (5%) developed a surgical site infection requiring pharmacological or surgical intervention.

Mechanical ventilator-free days were similar after SSRF or nonoperative treatment (Table 1). The ICU LOS was significantly longer in the operative group (13 days, P_{25}-P_{75} 9-23 days vs. 9 days, P_{25}-P_{75} 5-15 days; p=0.004). Other outcomes such as the HLOS and pneumonia, thoracic bleeding, and mortality rate were similar across the treatment groups.

Figure 2 shows that ribs 3-6 in the SSRF group and ribs 2-7 in the nonoperative group were most often fractured anteriorly (SSRF: n=209, 83.6%; nonoperative: n=768, 75.2%), simple (SSRF: n=217, n=86.8%; nonoperative: n=937, 91.6%), and undisplaced (SSRF: n=103, 41.2%; nonoperative: n=621, 60.7%).

Targeted temperature management

In the subgroup of patients in whom TTM was initiated (SSRF: n=21 and nonoperative: n=44), the SSRF group more often had had previous cardiac interventions (n=7, 33% vs. n=5, 11%; p=0.045), a higher frequency of mechanical CPR performed (n=5, 24% vs. n=1, 2%; p=0.011), ≥1 displaced fractured ribs (n=15, 71% vs. n=18, 41%; p=0.033), and number of rib fractures (6, P_{25}-P_{75} 5-7 vs. 5, P_{25}-P_{75} 5-6; p=0.019) than the nonoperative group (Supplemental Table 2). SSRF was performed at a median of 5 days after admission

SSRF

A — Location

Σ	PV	P	L	A	CC	Rib	CC	A	L	P	PV	Σ
0	0	0	0	0	0	1	0	0	0	0	0	0
3	0	0	0	3	0	2	0	1	0	0	0	1
24	0	0	1	20	3	3	2	12	0	0	0	14
32	0	0	2	28	2	4	3	27	1	0	0	31
35	0	0	2	31	2	5	1	29	2	0	0	32
21	0	0	2	16	3	6	2	19	2	0	0	23
10	0	0	0	8	2	7	3	9	1	0	0	13
3	0	0	0	2	1	8	1	4	1	0	0	6
1	0	0	0	0	1	9	0	0	1	0	0	1
0	0	0	0	0		10		0	0	0	0	0
0	0	0	0			11		0	0	0	0	0
0	0	0				12			0	0	0	0
Σ 129	0	0	7	108	14		12	101	8	0	0	121

B — Type

Σ	C	W	S	Rib	S	W	C	Σ
0	0	0	0	1	0	0	0	0
3	1	0	2	2	1	0	0	1
24	4	1	19	3	9	2	3	14
32	2	2	28	4	27	2	2	31
35	4	2	29	5	30	1	1	32
21	2	0	19	6	21	2	0	23
10	0	0	10	7	13	0	0	13
3	0	1	2	8	6	0	0	6
1	1	0	0	9	1	0	0	1
0	0	0	0	10	0	0	0	0
0	0	0	0	11	0	0	0	0
0	0	0	0	12	0	0	0	0
Σ 129	14	6	109		108	7	6	121

C — Dislocation

Σ	D	O	U	Rib	U	O	D	Σ
0	0	0	0	1	0	0	0	0
3	1	0	2	2	0	1	0	1
24	8	9	7	3	6	4	4	14
32	10	11	11	4	12	11	8	31
35	7	14	14	5	13	14	5	32
21	7	6	8	6	12	5	6	23
10	2	1	7	7	5	4	4	13
3	0	1	2	8	4	2	0	6
1	1	0	0	9	0	0	1	1
0	0	0	0	10	0	0	0	0
0	0	0	0	11	0	0	0	0
0	0	0	0	12	0	0	0	0
Σ 129	36	42	51		52	41	28	121

Nonoperative management

A — Location

Σ	PV	P	L	A	CC	Rib	CC	A	L	P	PV	Σ
10	0	4	0	6	0	1	2	9	0	2	0	13
70	0	0	4	62	4	2	6	57	6	2	0	71
86	0	2	14	67	3	3	4	75	11	2	1	93
93	0	3	14	69	7	4	9	67	12	0	1	89
87	0	2	10	64	11	5	6	67	11	1	1	86
88	0	3	11	68	6	6	7	67	12	1	1	88
58	0	2	8	39	9	7	8	36	8	1	1	54
18	0	1	3	9	5	8	1	5	4	1	1	11
2	0	0	0	1	1	9	1	1	1	0	1	4
0	0	0	0			10		0	0	0	1	1
0	0	0	0			11		0	0	0	1	1
0	0	0				12			0	0	0	0
Σ 512	0	17	64	385	46		44	384	65	9	9	511

B — Type

Σ	C	W	S	Rib	S	W	C	Σ
10	1	1	8	1	12	1	0	13
70	1	9	60	2	63	7	1	71
86	4	7	75	3	83	7	3	93
93	5	5	83	4	81	5	3	89
87	3	7	77	5	83	2	1	86
88	3	2	83	6	85	3	0	88
58	1	2	55	7	53	1	0	54
18	1	0	17	8	11	0	0	11
2	0	0	2	9	4	0	0	4
0	0	0	0	10	1	0	0	1
0	0	0	0	11	1	0	0	1
0	0	0	0	12	0	0	0	0
Σ 512	19	33	460		477	26	8	511

C — Dislocation

Σ	D	O	U	Rib	U	O	D	Σ
10	0	1	9	1	10	1	2	13
70	13	21	36	2	39	27	5	71
86	13	25	48	3	59	29	5	93
93	15	25	53	4	59	22	8	89
87	11	30	46	5	51	23	12	86
88	14	18	56	6	60	22	6	88
58	6	18	34	7	37	15	2	54
18	4	5	9	8	7	4	0	11
2	0	0	2	9	4	0	0	4
0	0	0	0	10	1	0	0	1
0	0	0	0	11	1	0	0	1
0	0	0	0	12	0	0	0	0
Σ 512	76	143	293		328	143	40	511

FIGURE 2

Heat maps displaying the fracture location (A), fracture type (B), and degree of dislocation (C) per rib, per treatment group. Thick borders around specific ribs represent hotspots which comprise ≥50% of the total number of rib fractures.

A, anterior; C, complex; CC, costochondral; D, displaced; L, lateral; O, offset; P, posterior; PV, paravertebral; S, simple; U, undisplaced; W, wedge.

(P_{25}-P_{75} 3-7 days). The primary outcome of mechanical ventilator-free days was similar between the treatment groups, but the SSRF group had longer ICU LOS (12 days, P_{25}-P_{75} 7-25 vs. 8 days, P_{25}-P_{75} 5-16; p=0.027). Other outcomes were similar in the treatment groups.

In patients who had not undergone TTM (SSRF: n=18, nonoperative: n=22), the SSRF group had a lower BMI (25 kg/m^2, P_{25}-P_{75} 21-28 vs. 28 kg/m^2, P_{25}-P_{75} 26-32; p=0.016). SSRF was performed at 7 days after admission (P_{25}-P_{75} 4-10). Mechanical ventilator-free days as well as the other outcomes did not differ for patients who underwent SSRF or nonoperative treatment.

CHAPTER 12

Surgical stabilization of rib fractures ≤3 or >3 days

In the subgroups of patients who underwent SSRF within 3 days after admission (SSRF: n=10, nonoperative: n=19) , the SSRF and nonoperative group had similar patient-, CPR-, and injury characteristics (Supplemental Table 3). The time to consultation of a rib fixation specialist was shorter in the SSRF group as compared to their matched nonoperative controls (2 days, P_{25}-P_{75} 1-2 vs. 4 days, P_{25}-P_{75} 2-10; p=0.032) and SSRF was performed at 2 days after admission (P_{25}-P_{75} 2-3). The number of ventilator-free days were similar for the treatment groups. Other outcomes were similar, but the SSRF group more often had a thoracic bleeding (n=3, 30% vs. n=0, 0%; p=0.033).

In patients who underwent SSRF after 3 days (SSRF: n=29, nonoperative: n=47), the SSRF group had a higher BMI (25, P_{25}-P_{75} 21-28 vs. 28, P_{25}-P_{75} 25-33; p=0.031) and higher number of displaced fractured ribs as compared to their matched nonoperative controls (2, P_{25}-P_{75} 0-4 vs. 0, P_{25}-P_{75} 0-3; p=0.043). SSRF was performed at a median of 7 days after admission (P_{25}-P_{75} 5-10). While mechanical ventilator-free days and other outcomes were similar, the SSRF group had a longer ICU LOS (16 days, P_{25}-P_{75} 12-25 vs. 10 days, P_{25}-P_{75} 6-15; p=0.004).

DISCUSSION

This international, retrospective matched case-control study is, to our knowledge, the first to compare in-hospital outcomes after SSRF and nonoperative management in the patient with multiple rib fractures following CPR for sudden cardiac arrest. Despite no difference in the number of mechanical ventilator-free days and secondary outcomes, patients who underwent SSRF had a significantly longer ICU LOS than nonoperatively treated patients. Also, SSRF, as compared to nonoperative management, was not associated with improved outcomes in subgroups based on TTM initiation and early (≤72 hours) or late SSRF.

Previous studies on SSRF often excluded patients with rib fractures after CPR and focused solely on post-traumatic rib fractures [25, 26]. This exclusion could be due to similar reasons as the patient with traumatic brain injury, such as the unclear (neuro-logical) prognosis, assumed increased perioperative risk and confounding of outcomes because of an increased risk of prolonged mechanical ventilation and mortality [27]. In studies describing the post-CPR population, SSRF is mostly used as a late salvage intervention to aid mechanical ventilation liberation with time to SSRF ranging from seven to 38 days after CPR [19-22]. Early SSRF, is advocated by contemporary guidelines in the case of severe post-traumatic rib fractures as late SSRF has no benefit on in-hospital outcomes over nonoperative management [17, 28, 29]. In our study, time to SSRF was 5 days after admission, which is considered late. Early SSRF in this population

is however difficult, due to time consuming interventions such as TTM needed to treat underlying cardiac pathology and subsequent complications. This makes early cardiac and neurologic prognosis uncertain. Furthermore, anticoagulant therapy for the unstable cardiac pathology increases perioperative risks, resulting in additional reasons to delay surgery. Nevertheless, no benefit of SSRF over nonoperative management on outcomes was seen in subgroups based on TTM status or SSRF timing.

The two treatment groups were well matched and had similar cardiac treatment characteristics such as rate of TTM requirement, TTM duration, and motor GCS score <24 hours after TTM stop. Mechanical ventilator-free days and other outcomes were similar, but the ICU LOS was four days longer for the SSRF group. Noteworthy, the SSRF group had a more severe rib fracture pattern with a higher rate of at least one displaced fractured rib as well as a higher median of displaced fractured ribs. In patients with post-traumatic rib fractures, the presence of displaced rib fractures has been associated with longer mechanical ventilation and HLOS [30]. Also, a displaced rib fracture increases the risk of pulmonary complications such as pneumonia [13]. In patients following CPR for out-of-hospital cardiac arrest, the presence of one or more displaced rib fractures is associated with a longer ICU LOS [8]. Thus, the presence and higher number of displaced ribs might be a surrogate marker of more severe chest wall trauma, in concordance with post-traumatic rib fracture characteristics. Possibly, SSRF aided mechanical ventilation liberation through diminishing the negative effects of the displaced ribs on mechanical ventilation requirement, but patients remained dependent of non-invasive ventilation options. This might have subsequently increased ICU LOS. Contrarily, the restoration of chest wall integrity through SSRF which has shown to be of benefit in patients with post-traumatic rib fractures might be less ostensive in patients with iatrogenic rib fractures due to CPR.

Complications related to SSRF were relatively low, with a surgical site infection in 5% of patients and similar rates of thoracic bleeding and additional CPR settings after admission. The surgical site infection rate is higher than the approximately 2% after SSRF for post-traumatic rib fractures [31, 32]. The relatively low sample size as compared to previous post-traumatic literature could explain this discrepancy or since the stratification for superficial or deep infection was not made in the current study. In the early SSRF subgroup as compared to their matched controls, thoracic bleeding more often occurred, indicating that when early SSRF is considered, anticoagulant use or temporary stop should be weighed carefully.

When interpreting the outcomes of this study, several limitations should be taken into account. First, the retrospective study design has its inherent limitations, such as potential information bias due to missing data. To minimize this effect, all collected variables were made obligatory in the database and low-threshold communication was possible as most were members of CWIS or collaborated on other research. More

importantly, the retrospective design might have introduced attrition and selection bias. The treatment had similar rates of thoracic injuries such as a flail chest, flail sternum, and three or more displaced rib fractures which are (relative) indications for SSRF in the patient with post-traumatic rib fractures [17, 28, 33, 34]. However, only in 21% of nonoperatively treated patients, a rib fixation specialist was consulted. Thus, patients who improve clinically during the first days after admission receive nonoperative management, whereas patients who do not improve ultimately undergo SSRF at the median of five days after admission. Since collected characteristics were similar between treatment groups, uncaptured variables might have urged consultation of a rib fixation specialist. Instead of specific radiographic fracture patterns, clinical variables such as high ventilator setting requirements, need for inotropes, or presence of paradoxical breathing movements might have impacted the decision for consultation and salvage SSRF more strongly. Second, patient matching was largely based on rib fracture characteristics commonly used in rib fracture literature. These matching criteria or indications for SSRF in post-traumatic rib fractures can possibly not be extrapolated to assess the effect of SSRF in patients with iatrogenic rib fractures such as the post-CPR group, resulting in unknown dissimilar treatment groups. Third, rib fractures were delineated following the accepted taxonomy for multiple rib fractures [23]. A fracture type not included in this taxonomy but often seen in patients after CPR, is an incomplete buckle fracture. These fractures were scored as simple fractures, but future studies are required to assess whether this is an individual fracture type of interest in this population and for example to what extent its presence affects outcomes as compared to the other fracture types. Last, the multicenter, international design might have confounded outcomes due to heterogeneity in patient management and within-center covariates [35]. Different treatment pathways such as prophylactic antibiotic administration following CPR and (suspicion of) aspiration might have resulted in lower pneumonia rates. Also, time to chest CT performance was not known and might have affected thoracic injury rates such as hemothorax or pulmonary contusion which might not be detected on chest CT at admission, but can negatively impact outcomes. However, the multicenter, international design also made results more generalizable and resulted in the first comparative study on the effect of SSRF over nonoperative management in the post-CPR patient.

In summary, in patients with multiple rib fractures following CPR for sudden cardiac arrest, the use of SSRF over nonoperative management was not associated with a higher number of mechanical ventilator-free days. Despite more consequential chest wall injury in the SSRF group, both treatment groups had relatively similar outcomes. Other variables than the included injury and radiographic characteristics might result in rib fixation consultation in this population, highlighted by the low consultation in the nonoperative group. Careful patient selection and prospective studies are required before embedding or abandoning this procedure in these patients.

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SUPPLEMENTAL DATA

SUPPLEMENTAL TABLE 1
Additional patient and cardiac arrest characteristics in patients following cardiopulmonary resuscitation for sudden cardiac arrest who underwent operative or nonoperative management of rib fractures.

	N*	Overall (n=105)	N*	SSRF (n=39)	N*	Non-operative (n=66)	p
Anticoagulation use at age of CPR							
Aspirin	105	18 (17.1%)	39	7 (18%)	66	11 (17%)	1.000
Vitamin K antagonist (VKA)	105	13 (12.4%)	39	3 (8%)	66	10 (15%)	0.363
Non-VKA	105	8 (7.6%)	39	3 (8%)	66	5 (8%)	1.000
Thrombocyte aggregation inhibitor	105	6 (5.7%)	39	3 (8%)	66	3 (5%)	0.668
Risk factor for sudden cardiac arrest							
Myocardial infarction <30 days	104	2 (1.0%)	39	0 (0%)	65	2 (3%)	0.527
Major cardiothoracic surgery	104	1 (1.0%)	39	1 (3%)	65	0 (0%)	0.375
Major abdominal surgery	104	1 (1.0%)	39	0 (0%)	65	1 (2%)	1.000
Chemotherapy	104	0 (0%)	39	0 (0%)	65	0 (0%)	NA
Sepsis	104	2 (1.9%)	39	1 (3%)	65	1 (2%)	1.000
Organ failure	104	1 (1.0%)	39	1 (3%)	65	0 (0%)	0.375
Previous cardiac interventions							
PCI	105	10 (9.5%)	39	6 (15%)	66	4 (6%)	0.168
CABG	105	4 (3.8%)	39	0 (0%)	66	4 (6%)	0.294
ICD or pacemaker	105	2 (1.9%)	39	2 (5%)	66	0 (0%)	0.136
Cardiac cause of arrest							
Acute MI	77	33 (43%)	28	14 (50%)	49	19 (39%)	0.146
Scar tissue/old MI	77	21 (27%)	28	8 (29%)	49	13 (27%)	
Cardiomyopathy	77	10 (13%)	28	0 (0%)	49	10 (20%)	
Primary rhythm disturbance	77	11 (14%)	28	5 (18%)	49	6 (12%)	
Cardiac, unknown origin	77	2 (3%)	28	1 (4%)	49	1 (2%)	
Non-cardiac cause of arrest							
Exacerbation COPD	28	4 (14%)	11	2 (18%)	17	2 (12%)	0.597
Submersion, hypoxia, asphyxia	28	6 (21%)	11	3 (27%)	17	3 (18%)	
Intoxication	28	4 (14%)	11	2 (18%)	17	2 (12%)	
Hypovolemic shock	28	4 (14%)	11	3 (27%)	17	1 (6%)	
Septic shock	28	3 (11%)	11	1 (9%)	17	2 (12%)	
Anaphylactic shock	28	1 (4%)	11	0 (0%)	17	1 (6%)	
Pulmonary embolism	28	2 (7%)	11	0 (0%)	17	2 (12%)	

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SUPPLEMENTAL TABLE 1 continued from page 255

	N*	Overall (n=105)	N*	SSRF (n=39)	N*	Non-operative (n=66)	p
Intracranial bleeding	28	1 (4%)	11	0 (0%)	17	1 (6%)	
Hypoglycemia	28	1 (4%)	11	0 (0%)	17	1 (6%)	
Non-cardiac, unknown origin	28	2 (7%)	11	0 (0%)	17	2 (12%)	
Mortality cause							
Cardiogenic cause	15	4 (27%)	6	2 (33%)	9	2 (22%)	0.645
Respiratory cause	15	6 (40%)	6	2 (33%)	9	4 (44%)	
Multi-organ failure	15	3 (20%)	6	2 (33%)	9	1 (11%)	
Neurogenic cause	15	1 (7%)	6	0 (0%)	9	1 (11%)	
Withdrawal of care	15	1 (7%)	6	0 (0%)	9	1 (11%)	

Data are shown as median (P_{25}-P_{75}) or as n (%); bold p-values are considered statistically significant.
*: provides the exact number of patients for whom the parameter was known.
COPD, chronic obstructive pulmonary disease; CABG, coronary artery bypass graft; ICD, implantable cardioverter defibrillator; NA, not applicable; NOM, nonoperative management; PCI, percutaneous coronary intervention; SSRF, surgical stabilization of rib fractures.

SUPPLEMENTAL TABLE 2
Patient, cardiac arrest, injury, and outcome characteristics in patients following cardiopulmonary resuscitation who underwent operative or nonoperative management of rib fractures, stratified for initiation of targeted temperature management.

	Targeted Temperature Management					No Targeted Temperature Management				
	N*	SSRF (n=21)	N*	NOM (n=44)	p	N*	SSRF (n=18)	N*	NOM (n=22)	p
Patient characteristics										
Age (years)	21	69 (62-73)	44	68 (61-71)	0.844	18	68 (59-74)	22	70 (61-75)	0.396
Sex (male)	21	20 (95%)	44	34 (77%)	0.088	18	14 (78%)	22	17 (77%)	1.000
BMI (kg/m²)	20	25.5 (22.4-28.9)	41	27.7 (24.5-32.1)	0.216	17	24.8 (21.1-27.5)	21	28.0 (26.2-32.2)	**0.016**
Smoking at age of CPR	16	3 (19%)	31	9 (29%)	0.505	17	7 (41%)	14	7 (50%)	0.725
Anticoagulation use at age of CPR	21	9 (43%)	44	19 (43%)	1.000	18	6 (33%)	22	8 (36%)	1.000
Comorbidities										
Hypertension	21	9 (43%)	44	25 (57%)	0.426	18	11 (61%)	22	16 (73%)	0.509
Diabetes Mellitus	21	3 (14%)	44	7 (16%)	1.000	18	2 (11%)	22	6 (27%)	0.258
COPD	21	2 (10%)	44	10 (23%)	0.309	18	5 (28%)	22	7 (32%)	1.000
Cardiomyopathy	21	1 (5%)	44	5 (11%)	0.655	18	2 (11%)	22	0 (0%)	0.196
Cardiac arrhythmia	21	4 (19%)	44	10 (23%)	1.000	18	4 (22%)	22	7 (32%)	0.723
Myocardial infarction	21	5 (24%)	44	10 (23%)	1.000	18	1 (6%)	22	2 (9%)	1.000
Chronic heart failure	21	1 (5%)	44	2 (5%)	1.000	18	3 (17%)	22	2 (9%)	0.642
Cerebrovascular accident	21	1 (5%)	44	3 (7%)	1.000	18	1 (6%)	22	1 (5%)	1.000
Risk factor for sudden cardiac arrest	21	2 (10%)	44	1 (2%)	0.242	18	3 (17%)	21	4 (19%)	1.000
Previous cardiac interventions	21	7 (33%)	44	5 (11%)	**0.045**	18	1 (6%)	22	1 (5%)	1.000
Cardiac arrest and CPR characteristics										
Cardiac cause of arrest	21	18 (86%)	44	39 (89%)	0.706	18	10 (56%)	22	10 (46%)	0.751
GCS score on admission	19	3 (3-3)	38	3 (3-3)	0.504	18	11 (3-15)	21	11 (5-14)	0.646

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SUPPLEMENTAL TABLE 2 continued from page 257

	Targeted Temperature Management					No Targeted Temperature Management				
	N*	SSRF (n=21)	N*	NOM (n=44)	p	N*	SSRF (n=18)	N*	NOM (n=22)	p
Time from arrest to start CPR										
0-5 minutes	19	16 (84%)	37	32 (87%)	0.422	16	15 (94%)	20	20 (100%)	0.444
6-10 minutes	19	3 (16%)	37	3 (8%)		16	1 (6%)	20	0 (0%)	
11-15 minutes	19	0 (0%)	37	2 (5%)		16	0 (0%)	20	0 (0%)	
Time from start CPR to ROSC										
0-5 minutes	20	0 (0%)	44	3 (7%)	0.064	17	8 (47%)	21	5 (24%)	0.175
6-10 minutes	20	4 (20%)	44	19 (43%)		17	4 (24%)	21	8 (38%)	
11-15 minutes	20	3 (15%)	44	10 (23%)		17	1 (6%)	21	3 (14%)	
16-20 minutes	20	7 (35%)	44	7 (16%)		17	4 (24%)	21	2 (10%)	
>20 minutes	20	6 (30%)	44	5 (11%)		17	0 (0%)	21	3 (14%)	
Mechanical CPR	21	5 (24%)	44	1 (2%)	**0.011**	18	0 (0%)	22	1 (5%)	1.000
Injury characteristics										
No. of fractured ribs	21	10 (10-13)	44	10 (9-11)	0.089	18	11 (9-12)	22	10 (9-14)	0.946
No. of rib fractures	21	6 (5-7)	44	5 (5-6)	**0.019**	18	13 (10-17)	22	13 (9-20)	0.925
Flail chest	21	3 (14%)	44	1 (2%)	0.095	18	7 (39%)	22	11 (50%)	0.537
Flail sternum	21	21 (100%)	44	44 (100%)	1.000	18	16 (89%)	22	20 (91%)	1.000
≥3 displaced fractured ribs	21	7 (33%)	44	11 (25%)	0.558	18	8 (44%)	22	7 (32%)	0.517
≥1 displaced fractured ribs	21	15 (71%)	44	18 (41%)	**0.033**	18	13 (72%)	22	13 (59%)	0.510
No. of displaced fractured ribs	21	1 (0-3)	44	0 (0-3)	0.073	18	2 (0-5)	22	1 (0-3)	0.163
Sternum fracture	21	9 (43%)	44	13 (30%)	0.401	18	11 (61%)	22	11 (50%)	0.537
Pneumothorax	21	3 (14%)	44	2 (5%)	0.318	18	5 (28%)	22	7 (32%)	1.000

SUPPLEMENTAL TABLE 2 continued from page 258

	Targeted Temperature Management					No Targeted Temperature Management				
	N*	SSRF (n=21)	N*	NOM (n=44)	p	N*	SSRF (n=18)	N*	NOM (n=22)	p
Hemothorax	21	13 (62%)	44	17 (39%)	0.111	18	9 (50%)	22	11 (55%)	1.000
Pulmonary contusion	21	16 (76%)	44	25 (57%)	0.173	18	7 (39%)	22	7 (32%)	0.7444
Treatment characteristics										
TTM duration (days)	19	2 (1-2)	42	1 (1-2)	0.242	18	NA	22	NA	NA
mGCS score <24h after TTM stop	15	5 (5-6)	40	6 (5-6)	0.312	18	NA	22	NA	NA
Time to rib fixation consultation (days)	21	4 (2-5)	6	5 (3-13)	0.263	8	3 (1-5)	8	3 (1-4)	0.683
Chest tube on admission	21	1 (5%)	44	2 (5%)	1.000	18	6 (33%)	22	5 (23%)	0.498
Outcome characteristics										
Mechanical ventilator-free days	21	19 (12-30)	44	19 (15-24)	0.833	18	15 (10-19)	22	16 (2-22)	0.925
ICU LOS (days)	21	12 (7-25)	44	8 (5-16)	**0.027**	18	16 (12-21)	22	13 (7-16)	0.147
HLOS (days)	21	26 (19-46)	44	27 (18-31)	0.365	18	25 (19-35)	22	20 (14-34)	0.219
Tracheostomy	21	7 (33%)	44	7 (16%)	0.195	18	4 (22%)	22	4 (18%)	1.000
Pneumonia	21	7 (33%)	44	20 (46%)	0.426	18	9 (50%)	22	13 (59%)	0.750
Pleural empyema	21	0 (0%)	44	0 (0%)	1.000	18	1 (6%)	22	0 (0%)	0.450
Thoracic bleeding	21	3 (14%)	44	4 (9%)	0.672	18	3 (17%)	22	0 (0%)	0.083
Additional CPR-setting	21	3 (14%)	44	3 (7%)	0.379	18	0 (0%)	22	3 (14%)	0.238
Discharged home	17	11 (65%)	39	28 (72%)	0.753	15	7 (47%)	16	7 (44%)	1.000
In-hospital or 30-day mortality	21	4 (19%)	44	5 (11%)	0.455	18	3 (17%)	22	6 (27%)	0.476
Time to mortality (days)	4	11 (8-17)	5	18 (11-26)	0.190	3	27 (12-NA)	5	15 (9-29)	0.571

Data are shown as median (P_{25}-P_{75}) or as n (%); bold p-values are considered statistically significant.

*: provides the exact number of patients for whom the parameter was known.

BMI, body mass index; COPD, chronic obstructive pulmonary disease; CPR, cardiopulmonary resuscitation; HLOS, hospital length of stay; ICU LOS, intensive care unit length of stay; mGCS, motor Glasgow Coma Scale; NA, not applicable; NOM, nonoperative management; ROSC, return of spontaneous circulation; SSRF, surgical stabilization of rib fractures; TTM, targeted temperature management.

CHAPTER 12

SUPPLEMENTAL TABLE 3
Patient, cardiac arrest, injury, and outcome characteristics in patients following cardiopulmonary resuscitation who underwent operative or nonoperative management of rib fractures, stratified for SSRF performed within or after 3 days after admission.

	SSRF ≤3 days					SSRF >3 days				
	N*	SSRF (n=10)	N*	NOM (n=19)	p	N*	SSRF (n=29)	N*	NOM (n=47)	p
Patient characteristics										
Age (year)	10	69 (60-73)	19	68 (58-70)	0.701	29	67 (60-74)	47	68 (61-74)	0.528
Sex (male)	10	10 (100%)	19	16 (84%)	0.532	29	24 (83%)	47	35 (75%)	0.572
BMI (kg/m²)	10	25.8 (21.4-28.2)	18	27.2 (24.6-31.8)	0.226	27	25.1 (21.4-28.1)	44	28.0 (24.9-32.7)	**0.031**
Smoking at age of CPR	7	1 (14%)	14	7 (50%)	0.174	26	9 (35%)	31	9 (29%)	0.777
Anticoagulation use at age of CPR	10	4 (40%)	19	9 (47%)	1.000	29	11 (38%)	47	18 (38%)	1.000
Comorbidities										
Hypertension	10	4 (40%)	19	9 (47%)	1.000	29	16 (55%)	47	32 (68%)	0.329
Diabetes Mellitus	10	1 (10%)	19	3 (16%)	1.000	29	4 (14%)	47	10 (21%)	0.547
COPD	10	1 (10%)	19	4 (21%)	0.633	29	6 (21%)	47	13 (28%)	0.591
Cardiomyopathy	10	0 (0%)	19	1 (5%)	1.000	29	3 (10%)	47	4 (9%)	1.000
Cardiac arrhythmia	10	1 (10%)	19	3 (16%)	1.000	29	7 (24%)	47	14 (30%)	0.792
Myocardial infarction	10	3 (30%)	19	3 (16%)	0.633	29	3 (10%)	47	9 (19%)	0.354
Chronic heart failure	10	0 (0%)	19	0 (0%)	NA	29	4 (14%)	47	4 (9%)	0.472
Cerebrovascular accident	10	1 (10%)	19	1 (5%)	1.000	29	1 (3%)	47	3 (6%)	1.000
Risk factor for sudden cardiac arrest	10	0 (0%)	19	1 (5%)	1.000	29	5 (17%)	47	3 (7%)	0.248
Previous cardiac interventions	10	3 (30%)	19	1 (5%)	0.105	29	5 (17%)	47	5 (11%)	0.492
Cardiac arrest and CPR characteristics										
Cardiac cause of arrest	10	9 (90%)	19	17 (90%)	1.000	29	19 (66%)	47	32 (68%)	1.000
GCS score on admission	9	3 (3-12)	17	3 (3-3)	0.181	28	3 (3-12)	42	3 (3-11)	0.823

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SUPPLEMENTAL TABLE 3 continued from page 260

					p					p
Time from arrest to start CPR										
0-5 minutes	9	8 (89%)	16	14 (88%)	0.693	26	23 (89%)	41	38 (93%)	0.447
6-10 minutes	9	1 (11%)	16	1 (6%)		26	3 (12%)	41	2 (5%)	
11-15 minutes	9	0 (0%)	16	1 (4%)		26	0 (0%)	41	1 (2%)	
Time from start CPR to ROSC										
0-5 minutes	9	1 (11%)	19	1 (5%)	0.289	28	7 (25%)	46	7 (15%)	0.296
6-10 minutes	9	2 (22%)	19	9 (47%)		28	6 (21%)	46	18 (39%)	
11-15 minutes	9	1 (11%)	19	4 (21%)		28	3 (11%)	46	9 (20%)	
16-20 minutes	9	4 (44%)	19	2 (11%)		28	7 (25%)	46	7 (15%)	
>20 minutes	9	1 (11%)	19	3 (16%)		28	5 (18%)	46	5 (11%)	
Mechanical CPR	10	3 (30%)	19	1 (5%)	0.105	29	2 (7%)	47	1 (2%)	0.554
Injury characteristics										
No. of fractured ribs	10	10 (10-13)	19	10 (9-11)	0.456	29	11 (10-13)	47	10 (9-12)	0.324
No. of rib fractures	10	12 (10-14)	19	10 (9-11)	0.151	29	13 (10-17)	47	10 (9-13)	0.171
Flail chest	10	0 (0%)	19	0 (0%)	NA	29	10 (35%)	47	12 (26%)	0.443
Flail sternum	10	10 (100%)	19	19 (100%)	1.000	29	27 (93%)	47	45 (96%)	0.633
≥3 displaced fractured ribs	10	3 (30%)	19	4 (21%)	0.665	29	12 (41%)	47	14 (30%)	0.329
≥1 displaced fractured ribs	10	7 (70%)	19	8 (42%)	0.245	29	21 (72%)	47	23 (49%)	0.057
No. of displaced fractured ribs	10	2 (0-3)	19	0 (0-2)	0.228	29	2 (0-4)	47	0 (0-3)	**0.043**
Sternum fracture	10	4 (40%)	19	8 (42%)	1.000	29	16 (55%)	47	16 (34%)	0.095
Pneumothorax	10	0 (0%)	19	2 (11%)	0.532	29	8 (28%)	47	7 (15%)	0.237
Hemothorax	10	3 (30%)	19	10 (53%)	0.433	29	19 (66%)	47	18 (40%)	0.056
Pulmonary contusion	10	6 (60%)	19	10 (53%)	1.000	29	17 (59%)	47	22 (47%)	0.353

SUPPLEMENTAL TABLE 3 continues on page 262

CHAPTER 12

SUPPLEMENTAL TABLE 3 continued from page 261

	n		n		p-value	n		n		p-value
Treatment characteristics										
TTM requirement	10	8 (80%)	19	17 (90%)	0.592	29	13 (45%)	47	27 (57%)	0.347
TTM duration (days)	8	1 (1-2)	17	1 (1-2)	0.669	11	2 (1-2)	25	1 (1-2)	0.060
mGCS score <24h after TTM stop	7	5 (4-5)	16	6 (5-6)	0.121	8	6 (5-6)	24	6 (5-6)	0.980
Time to rib fixation consultation (days)	10	2 (1-2)	5	4 (2-10)	**0.032**	29	5 (3-5)	9	3 (1-9)	0.296
Chest tube on admission	10	0 (0%)	19	2 (11%)	0.532	29	7 (24%)	47	5 (11%)	0.194
Outcome characteristics										
Mechanical ventilator-free days	10	15 (6-35)	19	16 (14-24)	0.323	29	17 (12-22)	47	18 (9-24)	0.810
ICU LOS (days)	10	10 (7-12)	19	7 (4-18)	0.232	29	16 (12-25)	47	10 (6-15)	**0.004**
HLOS (days)	10	16 (12-40)	19	20 (16-31)	0.434	29	28 (22-40)	47	24 (16-33)	0.090
Tracheostomy	10	1 (10%)	19	1 (5%)	1.000	29	10 (35%)	47	10 (21%)	0.284
Pneumonia	10	2 (20%)	19	11 (58%)	0.114	29	14 (48%)	47	22 (47%)	1.000
Pleural empyema	10	0 (0%)	19	0 (0%)	NA	29	1 (3%)	47	0 (0%)	0.382
Thoracic bleeding	10	3 (30%)	19	0 (0%)	**0.033**	29	3 (10%)	47	4 (9%)	1.000
Additional CPR-setting	10	2 (20%)	19	2 (11%)	0.592	29	1 (3%)	47	4 (9%)	0.644
Discharged home	7	5 (71%)	17	13 (77%)	1.000	25	13 (52%)	38	22 (58%)	0.796
In-hospital or 30-day mortality	10	3 (30%)	19	2 (11%)	0.306	29	4 (14%)	47	9 (19%)	0.755
Time to mortality (days)	3	9 (7-NA)	2	17 (15-NA)	0.083	4	23 (14-42)	8	18 (11-28)	0.443

Data are shown as median (P_{25}-P_{75}) or as n (%); bold p-values are considered statistically significant.
*: provides the exact number of patients for whom the parameter was known

BMI, body mass index; COPD, chronic obstructive pulmonary disease; CPR, cardiopulmonary resuscitation; HLOS, hospital length of stay; ICU LOS, intensive care unit length of stay; mGCS, motor Glasgow Coma Scale; NA, not applicable; NOM, nonoperative management; ROSC, return of spontaneous circulation; TTM, targeted temperature management.

CHAPTER 13

Biomechanical characteristics and anatomical positioning of rib fracture fixation systems

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ABSTRACT

Introduction
Concurrent to the increase in surgical stabilization of rib fractures, there has been an increase in the number of fixation systems. This study aimed to assess implant positioning in relation to the intercostal groove, determine the biomechanical properties after fixation, and to compare these with a non-fixated intact rib.

Methods
Five systems were fixated on the bilateral 6th to 10th rib of five post-mortem human specimens. Then, the shortest distance of the implant to the intercostal groove was measured. Each rib underwent a four-point bending test to determine the bending structural stiffness (EI; Nm^2), load to failure (F_{max}; N), failure mode, and the difference in EI and F_{max} as compared to an intact rib.

Results
The distance from the implants to the intercostal groove ranged from 1.2 mm (standard deviation [SD] 0.74) to 6.6 mm (SD 1.66). As compared to a non-fixated intact rib, the relative difference in stiffness of a fixated intact rib ranged from -0.14 (SD 0.10) to 0.53 (SD 0.35) and for a fixated fractured rib from -0.88 (SD 0.08) to 0.17 (SD 0.50). The most common failure mode was a new fracture at the most anterior drill hole for the plate and screw systems and a new fracture within the anterior portion of the implant for the clamping systems.

Conclusion
There is variability in the anatomical positioning and biomechanical properties of current rib fixation systems. Insight into the implants' differences might guide implant selection and increase the surgeon's awareness for localizing hardware complaints or failure.

INTRODUCTION

Ribs are intimately associated with respiration and thoracic pain caused by rib fractures can result in splinting and ineffective secretion clearance, precipitating pneumonia development or respiratory insufficiency [1]. Rib fractures are the most common bony injury following blunt thoracic trauma and traditionally have been managed nonoperatively [2, 3]. Surgical stabilization of rib fractures (SSRF) has increased exponentially over the last decades following beneficial results in patients with a flail chest with regard to pneumonia rate, hospital, and intensive care unit length of stay (HLOS and ICU LOS) [4, 5]. Moreover, SSRF appears to be cost-effective [6]. Currently, several consensus guidelines recommend SSRF in patients with a flail chest [7-9]. Outcomes after SSRF have been studied for a variety of techniques, including wire cerclages, struts, clips, or plate and screw fixation [10]. Concurrent to the increase in SSRF, there has been an increase in the number of available fixation systems. The occurrence of hardware failure and revision surgery after SSRF is low (3-4% and 3%, respectively), but subjective implant irritation has been shown to be the main reason in patients undergoing implant removal [11-13]. It is hypothesized that biomechanical properties such as the stiffness of an implant are linked to hardware failure or patient discomfort [14, 15]. Additionally, intercostal nerve irritation or damage by a nearby implant might lead to an altered sensatory perception and even chest wall pain.

To date, no study has yet compared anatomical positioning to the intercostal groove and biomechanical properties of the available fixation systems. The primary aim of this study was to assess the positioning of the implants in relation to the intercostal groove. Furthermore, this study aimed to evaluate the implants' biomechanical properties (i.e., stiffness, load to failure, and mode of failure) after fixation on a fractured or intact rib, and compare these properties with a non-fixated intact rib.

METHODS

Study design

A human anatomical specimen study was conducted using five embalmed post mortem human subjects. All donors were part of the national donor program and had given written consent to tissue donation for educational and scientific purposes before passing away. Under these conditions and Dutch law, no approval of the medical research ethics committee was required. In accordance with European privacy regulations, the medical history of the donors was not available. Specimens were excluded if on visual examination thoracic abnormalities such as scars, congenital deformities or signs of previous thoracic procedures that might compromise rib fixation

were observed. For each thorax, the bilateral 6th to 10th rib was selected for fixation because of their functional and morphological similarities, while the 5th rib was used as a baseline reference of a non-fixated intact rib. The following rib fixation systems were used: MatrixRIB™ (DePuy Synthes, West Chester, PA, USA), RibLoc® U+ (Acute Innovations, Hillsboro, OR, USA), RibFixBlu™ (Zimmer Biomet, Jacksonville, FL, USA), STRACOS™ (MedXpert GmbH, Eschbach, Germany), and NiTi Rib (Cosmos Medical International, Luxembourg City, Luxembourg). The fixation systems were randomly designated to the specimens' 6th to 10th rib, while ensuring that every implant was at least allocated twice to the same specimen.

Fixation of the ribs

The specimens were placed on an operating table in a lateral decubitus position. The lateral aspect of the 5th to 10th rib was exposed through a longitudinal incision at the level of the anterior axillary line [16, 17]. After dissection and retraction of the muscles and subcutaneous tissue, the ribs were exposed. A transverse simple rib fracture was made in half of ribs 6 to 10 (n=25), using an oscillating bone saw with a 1 millimeter (mm) cut thickness. These designated ribs were fractured at approximately 50% of the rib's length, measured anteriorly from the costochrondral junction to posteriorly at the transverse process of the associated thoracic vertebra, using a tape measure (centimeters). All intact and fractured ribs 6 to 10 were fixated (n=50) at the same anterolateral level. The fixated intact ribs were used to mimic a consolidated rib fracture.

The rib fixations were performed by board-certified Trauma and Acute Care Surgeons who had performed at least 10 surgical procedures with the particular fixation system. After fixation of the ribs, the intercostal nerve of each fixated rib was dissected over the length of the implant to evaluate if any macroscopic physical contact of the implant with the intercostal nerve was present. Afterwards, the fixated ribs (n=50) and non-fixated ribs (n=10) were resected with the oscillating bone saw at the costochondral junction and costovertebral joint. All ribs were subsequently cleaned from soft tissue and periosteum after which the shortest distance of the implant (i.e., plate, screw, or clips) to the center of the costal groove (mm) was measured using a 150 mm caliper (Kanon, Tokyo, Japan).

Biomechanical test set-up

All resected ribs underwent a four-point bending test on a Lloyd LR5K universal materials testing machine (AMETEK, Berwyn, IL, USA; Figure 1). All tests were performed at room temperature, except for the thermoreactive NiTi Rib system for which the set-up was complemented with a thermostat and hot air blower at 37°C. Implants were tested after fixation on an intact rib and on a fractured rib.
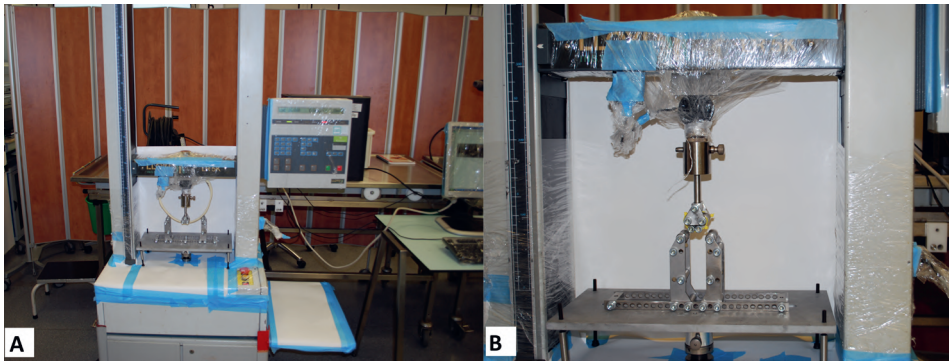
FIGURE 1
Biomechanical four-point bending test set-up (A), close-up (B), and schematic representation (C).

The center (a) and loading (h) span are adjustable. The load cell (i) was connected by a pivot joint (ii) to the load spreader (iii) to allow rotation during bending. The side view shows the loading (iv) and support (v) rollers which provide directional stability. The cross-section of the ribs was described as an ellipse with long (w) and short (b) axis.

Quasi-static testing

First, the ribs were subjected to a single cycle four-point bending test until failure at a crosshead speed of 0.25mm/s and a center span (a) distance of 20 mm and loading span (h) distance of 60 mm (Figure 1C). With the load-displacement curves, the bending stiffness and subsequently the bending structural stiffness (EI; Nm^2) were calculated (Supplemental Digital Content, SDC, 1). The EI is the stiffness of a construct normalized to the dimensional aspects of the rib and test rig which was determined using the standard for reporting in materials testing [18]. In addition, the maximum load to failure (Fmax; N) was determined from the load-displacement curve [18]. Failure was defined as the occurrence of a new rib fracture or hardware failure including dislocation or breaking of the implant associated with a rapid deformation in the load-displacement curve.

For the intact and fractured rib groups, the relative difference in EI was calculated for each fixation system (SDC 1). It represents the effect that an implant has on the stiffness of a fixated rib as compared to that of a non-fixated intact rib. It also allows for comparison of the biomechanical properties between the fixation systems across different specimens. For a fractured rib, for example, a relative difference in EI of "0" indicates that the construct of the implant on the fractured rib has a stiffness similar to that of a non-fixated intact rib. A positive value indicates that the stiffness of the implant and fixated rib exceeds that of a non-fixated intact rib, where a value of "1"

represents an increase of 100% (or twice the stiffness). A negative value means that the fixated rib is less stiff than the non-fixated intact rib, where a value of "-1" represents a decrease of 100%. A similar approach was used to determine the average relative difference in Fmax (SDC 1).

Cyclic testing

Per system, one fixated intact rib was subjected to a cyclic four-point bending test. The center and loading span distance were equal to the quasi-static test. This test was performed at a minimum load of -30 N and maximum load of -3 N to mimic internal and external intercostal forces [19]. The load cycled at a crosshead speed of 1mm/s until failure or until 18 hours when the test was stopped.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 25.0 (SPSS, Chicago, IL). Descriptive analysis was performed to report data for each fixation system. Continuous data are reported as mean and standard deviation, categorical data as numbers and frequencies. For continuous data, statistical significance of differences between fixation systems were assessed using the one-way analysis of variance (ANOVA) and student's t-tests for differences between two systems (with (un) equal variance according to the Levene's test). For categorical data, $\chi 2$ or Fisher's exact test was used as applicable. A p-value lower than 0.05 was considered statistically significant and all tests were two-sided.

RESULTS

Table 1 presents the characteristics of the implanted fixation systems. The post mortem human specimens had a mean age of 76 years (standard deviation [SD] 22) and two (40%) were female. For a non-fixated intact rib five, the mean Fmax was 87.97 N (SD 63.84) and the structural bending stiffness 1.07 Nm^2 (SD 0.87).

Anatomical outcomes

In total, each system was fixated on 10 ribs (n=50). Then, the intercostal nerve was dissected and evaluated for contact with the implant, after which the ribs were resected from the specimens. For each resected rib, depending on the implant type, the shortest distance was measured between the intercostal groove and the clips, screws or plate (Figure 2).

None of the plate and screw systems had direct visible contact with the intercostal nerve, these systems had similar distances to the intercostal groove (Table 2). The screws protruded through the intercostal groove in several ribs. In one of the 10 ribs
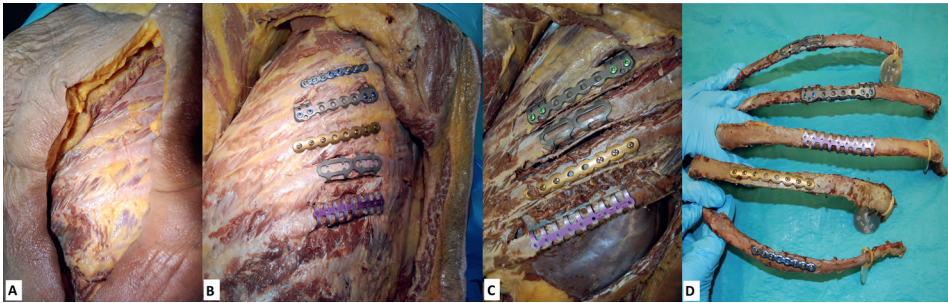
FIGURE 2
Thoraces showing the rib fixation approach (A), implant fixation (B), intercostal nerve dissection (C), and rib resection (D). Figure 2B, from top of the picture to bottom: RibFixBlu™, RibLoc® U+, MatrixRIB™, NiTiRib, and STRACOS™; Figure 2C: RibLoc® U+, NiTiRib, MatrixRIB™, and STRACOS™; Figure 2D: NiTiRib, RibLoc® U+, STRACOS™, MatrixRIB™, and RibFixBlu™.

TABLE 1
Implant-specific characteristics of each fixation system.

Fixation system	Device type	Device length (mm)	Screws required (anterior-posterior)	Type of screw
MatrixRIB™	Plate	80	3-3	Bicortical
RibLoc® U+	Plate	75	2-2	Bicortical
RibFixBlu™	Plate	60	3-3	Bicortical
STRACOS™	Clip	70	None	Not applicable
NiTi Rib	Clip	60	None	Not applicable

fixated by the MatrixRIB™ system, all three posterior screws entered the intercostal groove. In another post mortem human specimen with the MatrixRIB™ system, an iatrogenic fracture occurred around an anterior screw. In one rib with the RibLoc® U+ system, the two anterior screws protruded through the intercostal groove. For the RibFixBlu™ system, the plate was the closest material to the intercostal groove in two ribs of the same specimen, because the screws did not protrude through the rib's inner cortex. The mean distance to the intercostal groove was significantly different between the clips of the STRACOS™ (2.26 mm, SD 0.52) and the NiTi Rib (1.29 mm, SD 0.74) system, and plate of the RibFixBlu™ system (6.60 mm, SD 1.66; $p < 0.001$).

For the clamping systems, the NiTi Rib system had two ribs in which one or several clips were in direct contact with the intercostal groove, without (partial) envelopment of the intercostal nerve. In the STRACOS™ system, contact of the implant with the intercostal nerve was seen in six of the ten ribs (60%) as the implant encircled the intercostal nerve and groove. In two ribs this was over the entire length of the implant and in four ribs there was partial enfolding of the intercostal nerve (Figure 3).
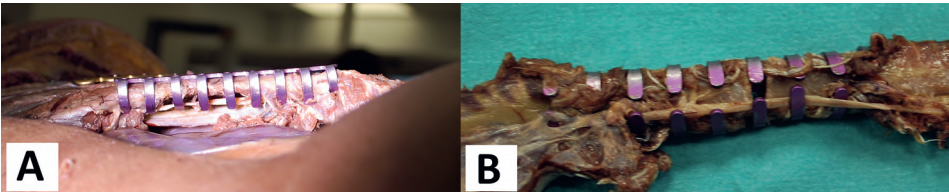
FIGURE 3
Partial intercostal nerve encircling following implant fixation (A) and after rib resection (B).

TABLE 2
Distance to intercostal groove and contact with intercostal nerve for each fixation system

	Fixation system					
	MatrixRIB™ (n=10)	RibLoc® U+ (n=10)	RibFixBlu™ (n=10)	STRACOS™ (n=10)	NiTi Rib (n=10)	p
Distance to intercostal groove (mm)						
Anterior screws	2.42 (0.85)	2.52 (1.29)	2.10 (1.13)	N.A.	N.A.	0.883
Posterior screws	2.37 (1.11)	3.01 (0.86)	2.10 (0.14)	N.A.	N.A.	0.263
Plate or clips	N.A.	N.A.	6.60 (1.66)	2.26 (0.52)	1.29 (0.74)	**<0.001***
ICN contact	0 (0%)	0 (0%)	0 (0%)	6 (60%)	0 (0%)	**<0.001****

Data are shown as mean (standard deviation) or as n (%); bold p-values are considered statistically significant.
*: student's t-test for RibFixBlu™ versus STRACOS™ p<0.001; RibFixBlu™ versus NiTi Rib p<0.001; STRACOS™ versus NiTi Rib p=0.003. **: Fisher's exact test for STRACOS™ versus each of the other systems (MatrixRIB™, RibLoc® U+, RibFixBlu™, and NiTi Rib) p=0.011.
Ant, anterior; ICN, intercostal nerve; mm, millimeters; N.A., not applicable; post, posterior.

Biomechanical outcomes

In total, 44 ribs underwent quasi-static testing, and five ribs cyclic testing, because one rib (RibFixBlu™ system) was excluded from testing due to the occurrence of a new iatrogenic fracture during resection. For the fixated fractured ribs, the average relative difference in EI, Fmax, and the relative difference in Fmax varied significantly between the fixation systems (Figures 4B-D). The average relative difference in EI of a fixated fractured rib ranged from -0.88 (SD 0.08) for the STRACOS™ system to +0.17 (SD 0.50) for the MatrixRIB™ system (p<0.001). The average relative difference in EI of a fractured rib fixated with the MatrixRIB™ system was significantly higher than the other systems and the clamping systems differed significantly from the plate and screw systems (Figure 4B). The average relative difference in Fmax ranged from -0.78 (SD 0.11) for the STRACOS™ system to +0.31 (SD 0.42) for the MatrixRIB™ system (p<0.001). The average relative difference in Fmax of the MatrixRIB™ system was significantly higher than all other systems (Figure 4D).
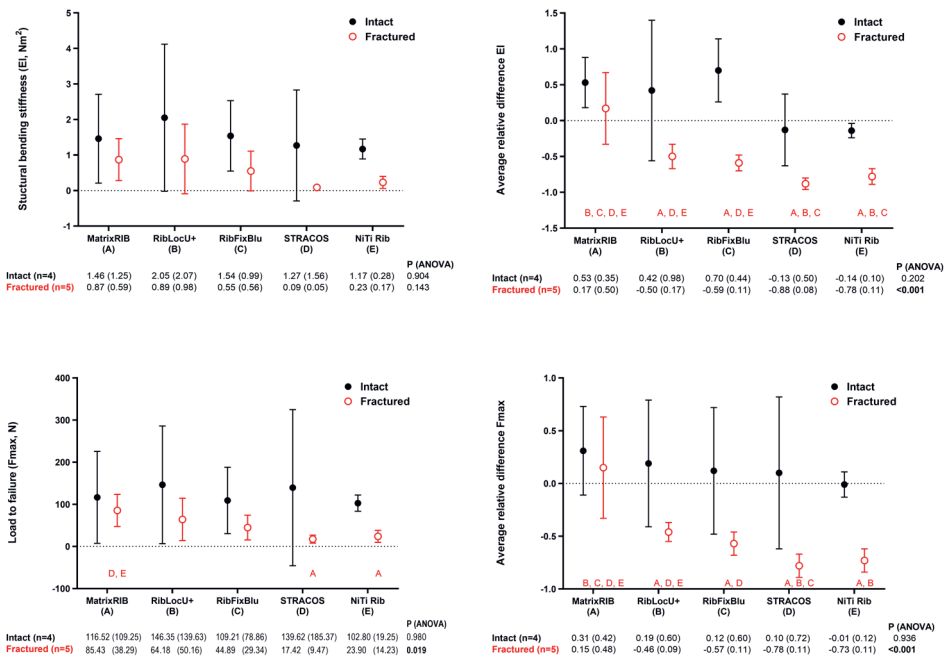
FIGURE 4
The structural bending stiffness (EI; A), average relative difference in EI (B), load to failure (Fmax; C), and average relative difference in Fmax (D) for each fixation system on an intact or fractured rib. Each figure presents a biomechanical outcome for an implant on an intact (black) or fractured rib (red). The colored letters below each dot represent the fixation system (A to E) with which that system has significantly different outcomes. Data are presented as mean ± standard deviation. Bold values represent p-values below 0.05.

For the fixated intact ribs, the biomechanical outcomes were similar between all fixation systems (Figure 4A-D). During cyclic testing, the rib fixated with the RibFixBlu™ system fractured at the drill hole of the most anterior screw. The other systems completed the 18 hours of cyclic testing without failure.

Multiple modes of failure were identified for the different fixation systems. For the MatrixRIB™ system (n=9), the most common failure mode was the occurrence of a new fracture at the most anterior drill hole (n=7, 78%), while the other two fixated ribs failed through plate dislocation at the initial fracture site (Supplemental Figure 1). The occurrence of a new fracture at the most anterior drill hole or end of the plate was also the most common failure mode for the RibFixBlu™ system (n=5, 63%) and RibLoc® U+ system (n=8, 89%). The other fixated ribs failed because of plate deformation for the RibLoc® U+ system in the middle (n=1, 11%) and caused by anterior screw dislodgement for the RibFixBlu™ system (n=3, 37%). For the NiTi Rib (n=9) system, the most common failure modes were a new fracture within the anterior portion of the

implant (n=4, 44%) and plate deformation at the initial fracture site (n=4, 44%; Supplemental Figure 2). In one rib (11%), the initial fracture end dislodged out of the NiTi Rib implant. The failure modes of the STRACOS™ system (n=9) were the occurrence of a new fracture within the anterior portion of the implant (n=3, 33%), a new fracture at the implant's ends (n=3, 33%), and plate deformation at the initial fracture (n=3, 33%).

DISCUSSION

This anatomical and biomechanical study evaluated the anatomical positioning of five currently available rib fixation systems to the intercostal groove and nerve, as well as their biomechanical properties. The available implants differed in their specific characteristics (e.g., plate and screw system or clamping system, and the implant's length), in their relation to the intercostal nerve and groove, and their biomechanical properties. Following fixation, four systems had no contact with the intercostal nerve while one system encircled the intercostal nerve completely or partially in 60% of the cases. For the plate and screw systems, the most common mode of failure was a new fracture at the most anterior drill hole or anterior end of the plate whereas in the clamping systems, a new fracture occurred within the anterior portion of the implant. The average relative difference in stiffness (EI) of the implants on a fractured or intact rib differed strongly between the fixation systems. The constructs' stiffness, as compared to that of a non-fixated intact rib, ranged from -14% to +70% when fixated on an intact rib and from -88% to +17% on a fractured rib.

The negative average relative difference in stiffness of the fixated fractured ribs for all implants except one implies that a non-fixated intact rib is likely stiffer than the construct of an implant on an acutely fractured rib. Previously, studies have confirmed this for both unicortical and bicortical plate fixation, but interestingly these studies used the fixation system which, in the current study, had a higher stiffness than a non-fixated intact rib [14, 20]. This might be explained by the current study's four-point bending test versus their two-point bending test, and use of bending structural stiffness (Nm^2), corrected for the test rig's and rib's dimensional aspects instead of using stiffness (N/mm) alone. A low stiffness can be advantageous because relatively, elastic implants minimize peak stresses which is especially beneficial in fixation of osteoporotic bone [21, 22]. Moreover, implants for SSRF are not designed to withstand high loads such as those in, for example, the lower extremity, necessitating high rigidity, but are required to principally restore chest wall integrity without restricting respiratory kinematics [22]. On the other hand, a high stiffness of the construct might impede with respiratory mechanics in the acute setting, and a too rigid fixation might cause cortical porosity

below the implant, delayed union or nonunion, or new fractures at the end of the implant [13, 22-24].

The main reason for implant removal are subjective complaints of chest tightness and irritation, which might be the consequence of the high stiffness of an implant on a consolidated rib, restricting chest wall movement [12]. Chest tightness has been reported in up to 16% of patients with rib fractures in the long-term, irrespective of treatment modality (SSRF or nonoperative management) [25]. In the current study, intact ribs fixated with a plate had a positive relative difference in stiffness, indicating a higher rigidity than a non-fixated intact rib. The relative difference in stiffness of the intact ribs fixated with a clamping system in the current study was approximately 15% less than that of a non-fixated intact rib. In previous literature, implant removal after SSRF has been performed for subjective complaints of chest tightness, but these patients did not have consequent restricted pulmonary function at the time of removal [15, 26]. This implies that the role of the implant in chest tightness might be less important than the effect of amongst others post-traumatic scar tissue formation. Such aspects require further evaluation. Furthermore, intercostal nerve damage by the implant or operative procedure has been hypothesized to be associated with chronic pain or dysesthesia, but the precise mechanism remains unknown while the available studies are relatively old, only assess plate and screw systems or have low sample sizes [27-29]. In this study, the larger part of ribs fixated with the STRACOS™ system showed encirclement of the intercostal nerve by the implant and several ribs fixated with plates had screws protruding through the inner cortex at the level of the intercostal groove. Whether this finding or intra-procedural iatrogenic nerve damage are surrogate markers associated with neuralgic thoracic pain or other complications such as pleural irritation requires further evaluation in in vivo studies. A previous study has shown similar stability for unicortical and bicortical screw fixation, advocating unicortical screw use to minimize occurrence of these hypothesized complications [20]. Another explanation for the chest tightness complaints could be maladaptive callus formation between fixated ribs, which has been seen in 16-23% of patients following SSRF [19, 30].

This study might aid decision-making on which implant to choose. A lower stiffness (clamping system) might be preferred in the long-term after fracture consolidation or for acute solitary simple rib fractures. In more comminuted or non-united rib fractures, a higher stiffness (plate and screws system) might be beneficial to sufficiently stabilize the fracture ends [22]. While this study provides relevant biomechanical data for the specific configurations of rib fixation systems, many injury and implant related factors were not investigated. For example, segmental rib fractures might require a larger plate instead of two standard plates or clamps because this might increase the fixated rib's stiffness [31]. In addition, the implant's length and the amount and location(s) of surface contact between the implant and bone might affect the biomechanical properties

CHAPTER 13

of a specific construct. Posteriorly located rib fractures have relatively worse outcomes in terms of deformity and secondary displacement, even when a concomitant lateral fracture in a flail segment is reduced and fixated [32]. Due to their proximity to the vertebral column and difficult surgical approach due to osseous, muscular and ligamentous attachments, posterior fractures might be less likely to be fixated with a plate and screw system. Using a smaller implant with clips instead of bilateral screw requirement might be a feasible alternative for these posterior rib fractures. Other implant-specific characteristics such as combining plate and screw and clamping systems, the (minimal) invasiveness of the surgical approach, operation time, and cost-effectiveness should be compared in future clinical studies.

Insight into the fixation system's mode of failure is of clinical relevance. Hardware failure after SSRF is rare (4%) with mechanical failure (60%) as the most common cause [13]. Literature on the prevalence and effect of additional thoracic trauma after SSRF is limited. The average relative difference in load to failure was lower for fixated fractured ribs and similar or up to 30% higher for fixated intact ribs. On chest CT for additional thoracic trauma, one should be suspicious of possible new rib fractures at the most anterior drill hole or anterior end of the implant for plate and screw systems and for fractures within the implant or implant deformation at the initial fracture site in case of the clamping systems. The amount of pressure on each rib from surrounding muscles is thought to be up to 30 N during 80% of maximum respiratory effort [19, 33]. On an intact rib, the Fmax of all systems was >100 N before failure. On a fractured rib, the clamping systems' Fmax (<25 N) might have problems. Nevertheless, these systems did not fail on cyclic testing when undergoing loads up to 30 N.

This study has several limitations. First, due to European privacy regulations, the only available baseline characteristics were gender and age. Other patient characteristics such as a diminished BMD are associated with a higher rate of rib fractures after thoracic trauma [34]. The large SD of the Fmax of the 5th rib indicates this variability in bone quality of the different specimens. This discrepancy was corrected for by evenly designating the systems to each specimen, using the structural bending stiffness and the average relative difference in EI and Fmax in relation to a non-fixated intact 5th rib. One specimen had a nonunion of an old rib fracture which became visible during fixation. The rib was considered a fractured rib during biomechanical testing, but this might have affected the biomechanical properties of the fixated rib. Second, ribs and fixated implants were only tested in a quasi-static loading mode through a four-point bending test whereas in real life, ribs are subjected to forces distributed over the entire rib's length as well in other direction (e.g., rotational). The exact stiffness and force to failure for the implants and ribs is likely different due to secondary stabilization from adjacent ribs and surrounding muscles and ligaments in vivo [22]. In addition, biomechanical testing was limited to fixated lateral simple transverse

fractures and did not assess other fracture types or anatomical locations. Third, due to fixating different systems on one hemi thorax, specific procedural variances such as exposure and approach could not be evaluated. During an actual surgical intervention, it is likely that crucial fixation aspects such as rib thickness measurements would have been performed more accurately to provide optimal adaptation to the anatomical circumstances. With the NiTi Rib system, the required body temperature might not have been reached in the test setting, possibly impacting the biomechanical characteristics. Also, not all screw, plate, and clamp sizes were available for all systems, possibly affecting its biomechanical properties or resulting in screw protrusion through the inner cortex for several systems. This might have been prevented if all available systems were complete. The sample sizes per fixation system were too low to, for example, provide a classification system for the best implant in a patient with specific (fracture) characteristics. Also, for the MatrixRIB™ system, only universal non-pre-contoured implants were available. Despite these limitations, to our knowledge, this is the first study to collectively evaluate current fixation systems and provide a starting point for future preclinical research.

In conclusion, the current fixation systems differ in their design, mode of action, impact on the intercostal groove or nerve, and biomechanical properties. Differences in biomechanical properties such as stiffness and load to failure especially apply to fractured ribs. Furthermore, insight into the failure modes of these implants does not only aid in early discovery of new fractures after SSRF with or without new trauma, but also helps in the development of improved implants in the future. Insight in the differences between the systems might guide more specific implant selection, choosing an implant based on rib fracture type and location, in addition to the preferred aim of fixation; flexible (clamping system) or more rigid (plate and screws system). Future prospective clinical studies are required to assess the effect of these differences on intra-operative characteristics and short- and long-term outcomes in patients who undergo SSRF.

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SUPPLEMENTAL DATA

SUPPLEMENTAL FIGURE 1
The most common failure mode of the plate and screw fixation system: a new fracture at the most anterior drill hole or anterior end of the plate of the MatrixRIBTM (A), RibLoc® U+ (B), and RibFixBluTM system (C).
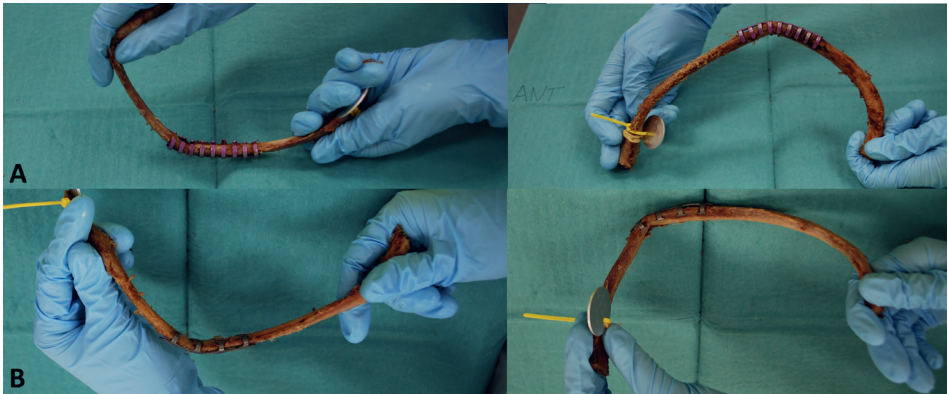
SUPPLEMENTAL FIGURE 2
The most common failure mode of the clamping systems: a new fracture within the anterior portion of the implant of the STRACOSTM (A) and NiTi Rib system (B).

CHAPTER 14

General discussion and future perspectives

GENERAL DISCUSSION

The aim of this thesis was to provide insight into the epidemiology, management, and outcomes of patients with one or more rib fractures. These aspects were evaluated through a multidimensional approach, performing national database studies, meta-analyses, multicenter clinical trials, and biomechanical research.

This thesis indicates that rib fractures are common and a significant health and economic burden in the individual patient and on a nationwide scale. In the acute setting, rib fractures are associated with lengthy hospitalization and high direct costs. In the long-term, rib fractures are associated with extensive work absence and high associated indirect costs as well as a high prevalence of subjective complaints. Initial chest wall injury severity nor treatment modality seem to impact long-term outcomes. This signifies that sustaining even one or two rib fractures significantly impacts the patient's long-term health. In patient subgroups such as those ≥50 years, a diminished bone mineral density (BMD) increases rib fracture rate and consequently costal fractures might be considered an osteoporotic fracture.

In patients who underwent cardiopulmonary resuscitation (CPR), thoracic injuries and especially rib fractures are common and negatively affect in-hospital outcomes. The surgical stabilization of rib fractures (SSRF) appears to be an effective technique for severe rib fractures in the acute setting. Patient groups with severe rib fractures such as multiple displaced rib fractures or a flail chest with traditional relative contra-indications (e.g., traumatic brain injury) require individual assessment and might benefit from SSRF in terms of in-hospital outcomes. Last, the currently available rib fixation systems differ in their fixation mode as well as the biomechanical properties. These differences, in addition to aspects such as invasiveness and costs, might facilitate the surgeon's implant selection for various indications.

Highlighted by this thesis' meta-analysis and the included chapters is the use of a retrospective design in a large part of rib fracture research. The retrospective design has inherent limitations and the specific studies are not able to distill for example conclusions regarding causality between rib fractures or SSRF and outcomes. While prospective studies are needed to answer these questions, these retrospective studies do provide insight into the extent of the impact of rib fractures and establish ground for treatment options such as SSRF, consequently offering a framework for future studies.

There is little research on the epidemiology of rib fractures. Rib fractures are common with an incidence rate of 47 per 100,000 person years which increase sharply with increasing age [1]. Six out of every 10 patients with rib fractures require hospitalization.

Furthermore, work absence averaged 44 days per patient and associated direct and indirect costs were €6,800 ($8,500) and €15,500 ($18,500), respectively. This study adds to the current literature as epidemiologic studies on incidence rate and costs are scarce or address admitted patients only [2]. While the associated (in)direct costs in these patients were high, these appeared to be affected most by admission status and age [1]. The direct costs are lower than the $10,200 from a US study analyzing admitted patients with rib fractures as primary diagnosis [3]. As both concern admitted patients, this could be due to differences in national health care costs.

Another study concluded that rib fractures are a marker of severe injury as almost half of patients are polytraumatized and 25% requires intensive care unit (ICU) admission [4]. The current study supports this conclusion as rib fractures were associated with extensive hospital length of stay (HLOS), lengthy work absence, and high costs. It is, however, difficult to compare outcomes of these studies as the current study only had insight into study year, age, and fracture severity. Improvement of the available Dutch nationwide databases is warranted. For example, the current databases do not allow differentiation between rib fractures as primary or secondary diagnosis, rib fracture treatment, and complications. Also, multiple rib fractures were defined as ≥2 rib fractures contradicting current rib fracture literature (≥3). A high-quality nationwide trauma registry with a more detailed focus on rib fractures or possibility to link individual databases is essential in determining its exact epidemiology and impact.

Previous literature has shown that rib fractures and age, as early as 45 years, are associated with a higher rate of pulmonary complications and mortality [5-8]. In patients aged ≥50 years, a diminished bone mineral density (BMD) is associated with a higher rib fracture rate, while concomitant intrathoracic injuries and rib fracture type characteristics were not associated with diminished BMD [9]. The current study strengthens the results of previous studies concluding that decreased BMD is a risk factor for sustaining rib fractures [10, 11]. Remarkably, only 35% of our registered patients had undergone a DXA scan [9]. This is higher than the 12% in another study, but is still a low rate since half of the patients were diagnosed with a diminished BMD after DXA scan [12]. Hence, rib fractures should possibly be considered an osteoporotic fracture and routine DXA scanning is recommended in patients aged ≥50 years to improve understanding of the effect of a diminished BMD on thoracic injuries and clinical outcomes. However, from a clinical perspective, DXA scanning should only be routinely performed if diminished BMD has therapeutic consequences for the individual patient regarding treatment of the rib fractures (e.g., threshold for SSRF) or osteoporosis.

Most studies on rib fracture outcomes focus on the acute setting and insight in the long-term outcomes is limited. At one year after trauma, several studies report that

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pulmonary function following SSRF or nonoperative treatment has returned to values considered normal [13-16]. Also, while one study indicates a significantly improved pulmonary function after SSRF as compared to nonoperative management, another study finds no difference between these groups [14, 15]. Of note, all of these studies have low sample sizes (<65 patients) and none assessed the effect of initial rib fracture severity. Quality of life has been reported at over one year after rib fractures by multiple studies, but these showed a large methodologic heterogeneity in terms of the used non-rib fracture specific questionnaires [17]. Comparative studies have found no benefit of SSRF over nonoperative management for long-term quality of life [18-23]. Altogether, the effect of initial rib fracture severity or rib fracture treatment modality on long-term outcomes remains unknown with studies on long-term outcomes often focusing on one treatment strategy or outcome.

This thesis combines these mentioned long-term outcomes and assesses the impact of initial rib fracture severity and treatment modality on these outcomes. At three years after trauma, a cohort of 300 patients showed pulmonary function and quality of life recovery to values within normal population ranges [24]. Moreover, SSRF did not impact long-term outcomes and this thesis complements to current literature that initial chest wall injury severity did also not affect these outcomes. While the outcomes recover to values considered normal, subjective complaints including moderate to severe thoracic pain (NRS>3; 21%), dyspnea in rest or during mild effort (23%) and chest tightness (16%) remained frequently present in our cohort. Chronic pain and long-term morbidity have long been associated with rib fractures and consequently in advocating SSRF in acute setting to improve these complaints [20, 25, 26]. The findings of our study do however not associate improved long-term outcomes with SSRF as compared to nonoperative treatment. Furthermore, this thesis provides valuable insights for both patient education regarding long-term outcomes after rib fractures.

Interest in SSRF is increasing and the available literature on this topic is abundant [27]. The larger part of these studies focuses on in-hospital outcomes after SSRF versus nonoperative management. Several consensus guidelines recommend SSRF in patients with a flail segment, radiologically, defined as ≥3 ribs fractured in ≥2 places or physiologically, defined as flail chest which results in paradoxical breathing movements [28, 29]. This recommendation is largely based on three small randomized controlled trials, retrospective and prospective observational series, as well as meta-analyses. These studies indicate a lower pneumonia rate and ventilator days and intensive care unit length of stay (ICU LOS) after SSRF [15, 30-34]. Currently, the use of SSRF is increasing annually and its utilization extends beyond the traditional flail chest [35, 36].

To determine additional indications for which SSRF might be of value, large, high-quality studies are needed. However, the current literature on outcomes after SSRF

and nonoperative management for multiple rib fractures is of low quality with heterogeneous populations and non-standardized outcome measures [37]. The patient with a flail chest differs significantly from the patient with a non-flail fracture pattern in terms of injury severity and this can confound outcomes [38]. Furthermore, patients with multiple rib fractures are often pooled, not taking into account injury and patient characteristics (e.g., number of fractures, degree of dislocation, or age) which are known risk factors for worse in-hospital outcomes in patients with rib fractures [6, 39, 40]. One recent retrospective study on patients with a non-flail fracture pattern found no benefit of SSRF in the acute setting, while in the first randomized controlled trial (RCT) on this patient type, less thoracic pain at two weeks follow-up and fewer pleural space complications were associated with SSRF [41, 42].

Thus, while the vast majority of patients with multiple rib fractures have a non-flail fracture pattern, the extent or absence of benefit of SSRF in this patient remains unknown territory. Since we believe that a prospective observational study would not sufficiently eliminate confounders in this population, a multicenter RCT on the effect of SSRF versus nonoperative management for multiple simple rib fractures with a non-flail fracture pattern was initiated at the Erasmus MC (Rotterdam) and currently involves 13 collaborating hospitals [43]. The outcomes of this study might guide both clinicians and future prospective observational or randomized trials on whether to extend or narrow indications for SSRF. This is the first RCT to study this population during a one-year follow-up after trauma, including in-hospital outcomes, pulmonary function, thoracic pain, quality of life, and cost-effectiveness. We assume that with the calculated 180 patients, this RCT is able to determine most characteristics which influence outcome after SSRF and identify which patient might benefit most from SSRF.

Despite several proven benefits of SSRF, the exact patient that benefits the most remains a topic of debate. Besides the above mentioned indications for SSRF, contra-indications to this procedure have also taken shape. One traditional relative contra-indication to SSRF is traumatic brain injury (TBI) [28, 44, 45]. On the one hand, these patients are often excluded in SSRF studies as they might confound outcomes because of an increased risk of mortality, complications, and prolonged mechanical ventilation duration [27, 29]. On the other hand, it is hypothesized that patients with TBI might deteriorate perioperatively because of an intracranial pressure increase caused by anesthetics or patient positioning. As a result, these patients are the least likely to be recommended for SSRF, regardless of their pulmonary abnormalities or thoracic injury extent [46]. The international, multicenter, retrospective Chest Wall Injury Society TBI (CWIS-TBI) study is, to our knowledge, the first to examine the effect of SSRF in patients with moderate to severe TBI (GCS score ≤12) [47]. This study demonstrated that SSRF was associated with lower odds of developing pneumonia and 30-day mortality. In the

subsequent post-hoc subgroup analysis, patients were stratified for having sustained a non-flail fracture pattern or flail chest. In the patient with moderate to severe TBI, an over three-times lower odds of pneumonia was observed in the patient with a non-flail fracture pattern and a decrease of three days in ICU LOS in the patient with a flail chest. Also, the SSRF-related complication rate was low (4%) with only one related to the peri-operative setting.

Altogether, SSRF is a safe procedure with a low complication rate and TBI should therefore not be seen as a contraindication to SSRF. Also, future studies on rib fractures or rib fracture treatment should not exclude patients with TBI. While this study has its limitations including the retrospective design and using a single GCS score at admission, it provides valuable information and aids in the search for the optimal benefit of SSRF.

Another patient group which is often excluded in studies on SSRF, is the post-CPR population. Survivors of CPR have extensive thoracic injuries and especially rib fractures are common (83%). These patients sustain a median of eight fractured ribs which are most often undisplaced, simple, anterior fractures of the 2nd to 7th ribs [48]. The number of sustained rib fractures is in line with similar studies on chest computed tomography (CT)-detected injuries in survivors of sudden cardiac arrest, but the current study adds detailed rib fracture information such as location, type, and degree of dislocation according to the Chest Wall Injury Society taxonomy of multiple rib fractures [49-53]. Patients with good neurologic recovery (motor Glasgow Coma Scale [GCS] score, 5-6) had longer HLOS and ICU LOS when ≥6 rib fractures or ≥1 displaced ribs were present.

Whether the post-CPR population might benefit from SSRF has only been studied in case reports or series where it is used as a late salvage procedure and without nonoperative control group [54-57]. To our knowledge, this thesis presents the first study to assess the effect of SSRF versus nonoperative management for multiple rib fractures following CPR. In this matched case-control study, patients who underwent SSRF, more frequently had displaced rib fractures and a higher number of displaced rib fractures. In the nonoperative group, a rib fixation specialist was consulted in only one in every five patients. The SSRF group had longer ICU LOS while other outcomes were similar. One matching criterion was rib fracture pattern, based on radiographic characteristics such as a flail sternum or flail chest. The dissimilarities in rib fracture severity and consultation for SSRF might suggest that the indications based on radiology used in the traumatic rib fracture population can not simply be extrapolated to the post-CPR population. The decision to perform SSRF in the post-CPR population might be based on clinical variables such as the inability to wean from mechanical ventilation, need for inotropes, or presence of paradoxical breathing movements. Therefore, to improve understanding of the effect of SSRF in this population, prospective studies

are required to determine which covariates result in rib fixation consultation and the decision to perform SSRF.

While prospective studies are superior in their methodological design, retrospective studies also provide useful information. Before conducting expensive and potentially risky prospective studies in patients with injury and patient characteristics considered contra-indications to SSRF, it is important to establish that there is at least equipoise and that SSRF does not harm these patients. This is where retrospective, multicenter research can be of importance. Through the multicenter design, large sample sizes can be obtained to assess the effect of SSRF in for example patients with an infected surgical field or extensive pulmonary contusion, factors considered traditional contra-indications. Further collaboration between centers on a global level with a central organization can provide answers to questions which cannot be answered in single center or even national studies.

Thus, the current literature is establishing ground for the overall effectiveness of SSRF in a broadening trauma and non-trauma population, but little is known on how a SSRF program and associated clinical outcomes evolve over time. For example, in cardio-thoracic or vascular surgery, outcomes such as operative time and complication rate decrease with increasing case volume or years after implementation [58]. This is referred to as a "learning curve". To our knowledge, this thesis presents the first "learning curve" of SSRF for in-hospital outcomes and operative characteristics. It corroborates previous cardiothoracic and vascular surgery literature as in-hospital outcomes such as the odds of complications decrease significantly with each increasing years of experience with the operative procedure. Unexpectedly, operative time increased over the years while patient selection remained similar. Future research should focus on more specific (intra-)operative characteristics such as onboarding of new surgeons or a lower threshold for residents to partake in surgery, minimally invasive approaches, and variability in rib fixation systems. As in-hospital outcomes improve and operative time increase over the years, it is recommended to correct for study year in future research.

In patients with a hip fracture as well as polytraumatized patients with amongst others pelvic or spine fractures, early fixation (24-48 hours after admission) is advocated over late fixation as it is associated with improved in-hospital outcomes such as hospital length of stay and complication rate [59-61]. For SSRF, no consensus on the optimal timing exists, but in absence of contra-indications is believed to be the earlier the better. This thesis presents the current literature specifically addressing the timing of SSRF, indicating that early SSRF (≤72 hours after trauma) was associated with improved

in-hospital outcomes as compared to both nonoperative management and late salvage SSRF [45]. Interestingly, all studies on timing to SSRF were retrospective without data on why patients did or did not undergo SSRF, introducing selection and attrition biases. Patients with less severe extra-thoracic injuries and a lower perioperative risk, might be more likely selected for early SSRF. Improved outcomes might therefore result from the patient's (lack of) associated injuries. Also, patients who are considered for early SSRF but improve after observation are evaluated in the nonoperative group, introducing possible attrition bias. By contrast, patients who deteriorate after an uncomplicated nonoperative period, might ultimately undergo SSRF and represent the (late) SSRF group. Thus, while it appears that the optimal timing to SSRF is the earlier the better, prospective high-quality studies, such as the FixCon trial are warranted to assess why patients undergo early or late SSRF and distill the exact effect timing on outcomes [43].

The increased interest in the literature and implementation of SSRF is accompanied by a surge in available rib fixation systems. Current biomechanical literature has principally focused on the biomechanical evaluation of a single fixation system, stability before and after rib fracture fixation, or following unicortical and bicortical screw fixation [62-65]. In this thesis, five currently available fixation systems are evaluated and it is shown that there is significant variability amongst them. First, their fixation mode varies from either plate and screw fixation to a clamping system with clips. When fixated on an intact rib, the stiffness of the plate and screw construct is 42-70% higher than a non-fixated intact rib. Subjective complaints such as chest tightness and irritation are the most common reason for implant removal and it has been hypothesized that this is the consequence of the implant's high stiffness which results in (the sensory perception of) chest wall movement restriction [17]. On a fractured rib, the stiffness measured -50% to +17% for a plate and screw construct and -88% to -78% for the clamping system, as compared to a non-fixated intact rib.

This study might aid the surgeon's selection for a specific implant: a lower stiffness (clamping system) might be preferred in the long-term after fracture consolidation or for acute solitary simple rib fractures. In more comminuted or hypertrophic non-united rib fractures, a higher stiffness (plate and screws system) might be beneficial to sufficiently stabilize the fracture ends [62]. Whether encircling of the intercostal nerve by a clamping system, protrusion of the bi-cortical screw through the intercostal groove, or intra-procedural iatrogenic nerve damage have clinical relevance and might be surrogate markers for (neuralgic) thoracic pain or other complications such as pleural irritation requires further evaluation in in vivo studies.

The results of this study should be interpreted in the light of several limitation such as the low sample sizes for each implant and sole assessment of outcomes on a lateral, simple rib fracture. Also, other implant-specific characteristics such as combining plate and screw and clamping systems, the (minimal) invasiveness of the surgical approach,

operation time, and cost-effectiveness should be evaluated in future clinical studies. As the first study to collectively evaluate available fixation systems, it is designed to provide insights which might facilitate implant choice, while also examining differences and characteristics that are associated with clinically relevant outcomes and of interest for future clinical trials.

FUTURE PERSPECTIVES

This thesis addresses research questions related to the epidemiology, management, and outcomes of rib fractures. While aiming to answer these, many new debates have emerged. With ongoing innovations and increasing research interest, the upcoming years will be crucial to answer these questions. This chapter presents recommendations for current patient care and future studies.

This thesis, in addition to previous literature, indicates that rib fractures are both a marker of severe injury and a severe injury itself. Concerning rib fracture epidemiology, a first direction for future studies is the prevention of this injury. This could mean research on the effect of measures to reduce household falls in the elderly and sports-related or work-related injuries in the middle aged population. Furthermore, rib fractures in the elderly are an osteoporotic fracture. Thus, future work should determine whether these patients benefit from vitamin D and calcium supplementation or prescription of bisphosphonates.

While the conclusion that rib fractures are a severe injury has established ground through numerous publications, there is a large variety in the methodological quality of the current research. For example, rib fractures are often diagnosed on chest radiography. Although recent studies commonly use chest CT to evaluate rib fracture characteristics, studies using nationwide data or meta-analyses often do not discern between rib fractures diagnosed on chest radiography or CT. Corroborated by this thesis, non-traumatic patients who sustain rib fractures such as the post-CPR population often solely undergo conventional radiography. Chest radiography should remain reserved for diagnosing possibly lethal acute injuries at first screening. Chest CT on the other hand, should be mandatory in diagnosing the number and severity of the rib fractures and thoracic wall injuries and associated research. A possible revised or novel consensus guideline, for example through the Chest Wall Injury Society, might be required to establish this. Subsequently, studies could assess whether this liberal chest CT use warrants adjustment of implemented admission algorithms based on characteristics such as the number of rib fractures since a chest CT diagnoses a higher number of rib fractures in the same patient.

Rib fractures are known to have extensive long-lasting impact on the patient's well-being. However, the current literature is limited to a retrospective design and quality of life questionnaires which do not fully capture the origin of the reported problems. First, prospective studies should assess outcomes including quality of life and thoracic pain on standardized follow-up moments in the first year but also for example on an annual basis after the first year. This results in more detailed data on the effect of treatment and chest wall injury severity on outcomes over time. Second, the development of a rib fracture-specific quality of life questionnaire might distill the exact effect of sustaining rib fractures on quality of life. A substantial part of this thesis discusses the management of rib fractures.

Nonoperative management will remain the treatment cornerstone as the larger part of patients with one or more rib fractures undergoes nonoperative management. Topics of interest which could be investigated further are for example the effect of locoregional anesthetic blocks over systemic analgesics, the effect of bronchodilators and chest physical therapy on thoracic pain and pulmonary complication rates in the patient with rib fractures. Most comparative studies on SSRF and nonoperative management are retrospective studies of low quality, combining patients with a flail chest and non-flail fracture pattern. Future studies, when aiming to provide statements on the optimal treatment modality, should assess patients with a non-flail fracture pattern and flail chest separately due to differences in physiology and the associated injuries.

On a different note, the terminology of a flail chest might require re-evaluation. Originally, a flail chest is defined either clinically (paradoxical breathing movements) or radiologically (≥3 ribs fractured in ≥2 locations). More recently, it has been recommended to use flail chest as the physiological definition of paradoxical movement of (part of) the chest wall while a flail segment is the radiological finding of ≥2 ribs fractured in ≥2 locations. Potentially, future studies should assess the effect of sustaining a clinical flail chest or radiological flail segment on outcomes. If significantly different, it could be hypothesized that these two injuries should be stratified when determining the effect of treatment. In addition, the proposed CWIS taxonomy for multiple rib fractures should be further evaluated for the effect of rib fracture type, location, or degree of dislocation on clinically relevant in-hospital or patient-related outcomes.

With the current innovations in rib fracture treatment, there are plenty of novel hypotheses for numerous future studies. Nonoperative management is considered as one treatment modality in this thesis, but future research should focus on specific nonoperative aspects. such as the effect of nebulizers in patients with rib fractures or the optimal pain adjunct based on patient and rib fracture characteristics. Also, insight

into the effect of pulmonary physical therapy, early mobilization out-of-bed or daily spirometry on outcomes could improve patient care.

Future research and high quality studies are also a necessity for numerous SSRF-related interventions for which the evidence is currently limited or paper thin. For instance, the optimal ratio of fractured ribs repaired to fractured regarding outcomes such as thoracic complications, pulmonary function recovery, and subjective complaints including chest tightness. Also, the use of intra-operative cryoablation or single dose intercostal nerve block for pain control over the placement of an indwelling continuous peripheral or systemic analgesic catheter should be investigated. Other niches include the effect of completely thoracoscopic SSRF and the development of an intrathoracic rib fixation set.

Extra-thoracic SSRF is the current standard, but the currently available rib fixation systems have substantial differences in terms of their biomechanical properties. This thesis might aid in choosing a specific system or initiate the development of a system that has plate and screw implants as well as clamping implants. Future studies should also focus on the clinical impact of these differences and possibly aim to develop an algorithm to define what rib fracture characteristics (e.g., segmental versus simple fracture, acute fracture versus nonunion) require which type of fixation. Furthermore, it could be valuable to prospectively investigate the differences in the invasiveness of the operative approaches of the different fixation systems and effect on thoracic pain or chest tightness.

Regarding contra-indications of SSRF, forthcoming studies should address these patients on an individual basis, starting in a retrospective, preferably multicenter design. Just like the relative contra-indication TBI and age, retrospective studies are a way to establish ground for SSRF as a safe procedure before conducting expensive and potentially risky prospective studies [47, 66]. Upcoming research could focus on patients with severe rib fractures (e.g., a flail chest or ≥3 displaced rib fractures) and present contra-indications such as other high priority injuries (e.g., spine or pelvic fractures), pleural empyema, pulmonary contusion, or pneumonia.

With these opportunities and challenges in consideration, improving care in the patient with multiple rib fractures requires collaboration and persistence. While the amount of available literature is abundant, this thesis has set out to provide generalizable results of good quality, focusing on numerous aspects, aiming to mutually improve existing knowledge and investigate new subgroups of patients and outcomes. The primary aim of this thesis has been to provide valuable scientific insights into the epidemiology, management, and outcomes of multiple rib fractures. Likewise, this thesis might provide a framework for health care professionals to educate patients with substantiated information on the impact of rib fractures and possible (dis)advantages of available treatment options.

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CHAPTER 15

Summary / Summary in Dutch

SUMMARY AND CONCLUSIONS

Chapter 1 is the general introduction which highlights several main facets within the topic of rib fractures and current gaps in scientific literature. It provides a framework, stressing the pertinence of the included studies.

Chapter 2 investigated the population-based trends in the incidence rate of rib fractures in the Netherlands (2015-2018) and presents an overview of associated health care consumption and (in)direct costs. During the study period, 32,124 patients were registered with ≥1 rib fractures of whom 19,885 (62%) required hospitalization and 19,997 (59%) sustained multiple (≥2) rib fractures. The incidence rate of rib fractures was 47 per 100,000 person years which increased strongly with age. The mean hospital length of stay was 7.7 days for the total cohort and increased with rib fracture severity The mean direct costs for a rib fracture patient were €6,800 ($8,500) and admitted patients accounted for 91% of these costs. The mean indirect costs were €15,500 ($18,500) and admitted patients accounted for 90% of these costs. The duration of work absence averaged 44 days per patient (65 days for admitted patients and 8 days for non-admitted patients).

In conclusion, rib fractures are common and associated with lengthy hospitalization and work absence as well as high (in)direct costs. These outcomes appear to be affected by admission status and age rather than by sustaining one or multiple rib fractures.

Chapter 3 assessed rib fracture rate, type, and associated (intra)thoracic injuries after blunt thoracic trauma in patients ≥50 years with normal or diminished bone mineral density (BMD [*i.e.,* osteopenia or osteoporosis], T-score < -1.0). In total, 119 patients were included. Patients with diminished BMD more often had rib fractures than patients with a normal BMD (n=43, 74% vs. n=31, 51%; p=0.014), but had a similar number of ribs fractured, presence of a flail chest, and associated intrathoracic injuries. Furthermore, the sustained rib fracture type (*i.e.,* simple, wedge, or complex) was evenly distributed across the two groups.
When assessing patients aged ≥50 years after blunt thoracic trauma, the presence of diminished BMD and subsequent rib fracture risk should be evaluated. Performing a DXA scan is recommended to improve understanding of the true prevalence and effect of BMD in these patients.

The prevalence of chest wall injuries and the effect on in-hospital outcomes in patients who underwent cardiopulmonary resuscitation (CPR) for out-of-hospital cardiac arrest (OHCA) was determined in **Chapter 4**. A total of 344 patients was included of whom

291 (85%) had CPR-related chest wall injury. Rib fractures were the most common injury (n=285, 83%). Rib fracture patients had a median of 8 fractured ribs (P_{25}-P_{75} 4-10) which were most often undisplaced, simple, anterior fractures of ribs 2 to 7. In patients with good neurologic recovery (motor GCS score 5-6), sustaining ≥6 rib fractures or ≥1 displaced rib fractures was associated with a longer hospital and ICU stay, respectively. Also, pneumonia rate was 31% in patients with good neurologic recovery and rib fractures versus 9% in patients without rib fractures (p=0.077).

Altogether, chest wall injury and especially rib fractures are common after CPR. In patients with good neurological recovery, lengthy ICU and hospital stay as well as high pneumonia rates remain. It remains to be evaluated if restoring chest wall integrity and respiratory mechanics through surgical stabilization of rib fractures (SSRF) might improve these outcomes.

Chapter 5 determined long-term outcomes after rib fractures and the effect of chest wall injury severity (one or two, ≥3 rib fractures, or a flail chest) or treatment modality (SSRF or nonoperative treatment) on these outcomes. In total, 300 patients were included with a median time from injury of 39 months (P_{25}-P_{75} 18-65). At follow-up, spirometry values of Forced Vital Capacity and Forced Expiratory Volume at 1 second had returned to 85% and 86% of the predicted reference values. Quality of life (Short Form-12 version 2 and EuroQol-5 Dimension questionnaires) indicated scores within normal US population ranges. Subjective complaints such as moderate to severe thoracic pain (Numeric Rating Scale >3), dyspnea in rest or during mild effort (*e.g.,* work), and chest tightness were experienced by 21%, 23%, and 16% of patients, respectively. The outcomes were similar across chest wall injury severity and treatment groups.

Overall, in the long-term, pulmonary function and quality of life recover to values considered normal. Rib fractures do however clinically impact the patient's wellbeing in the long-term as subjective complaints remain frequently present. No effect of initial chest wall injury severity or benefit of SSRF was demonstrated for these outcomes.

A systematic review and meta-analysis of comparative studies on SSRF versus non-operative treatment on in-hospital outcomes in patients with a non-flail fracture pattern is presented in **Chapter 6**. Fourteen studies of 13 cohorts were identified, totaling 4565 patients. Only two studies completely consisted of patients with a non-flail rib fracture pattern while this ranged from 54% to 97% in the other studies. Most studies (n=9) were retrospective. Meta-analysis showed a significant decrease in risk of pneumonia (relative risk [RR] 0.66, 95% CI 0.49-0.90; p=0.008) and mortality (RR 0.32, 95% CI 0.19-0.54; p<0.001), and shorter hospital stay (mean difference -5.8 days, 95% CI -10.4 to -1.2; p=0.01) in favor of SSRF. No effect of SSRF was demonstrated for duration of mechanical ventilation or ICU stay.

Altogether, SSRF was associated with improved in-hospital outcomes. However, due to the heterogeneous populations and low quality of the currently available literature, these results must be interpreted with caution and warrant high-quality prospective studies.

Chapter 7 describes the study protocol of a multicenter randomized controlled trial on the effect of SSRF versus nonoperative management in patients with a multiple simple rib fractures up to one year after injury. This study includes patients with ≥3 rib fractures of which at least one fracture is bicortically displaced. The primary outcome is pneumonia while secondary outcomes include in-hospital outcomes, thoracic complications and secondary interventions, analgesics use, spirometry, quality of life, and cost-effectiveness. These outcomes are assessed at follow-up visits during the first year after trauma. At the time of this thesis' print, 136 patients of the targeted 180 patients have been included.

The effect of increasing years of experience with SSRF on patient selection, (intra) operative characteristics and in-hospital outcomes is determined in **Chapter 8**. From 2010 through 2020, 222 patients underwent SSRF at a level I trauma center. Across the study years, patient selection in terms of age, ISS, rate of patients with a flail segment or ≥3 bicortically displaced rib fractures remained similar. In multivariable analysis, increasing study year was significantly associated with a reduced time from injury to SSRF and increase in operative time. In addition, each increasing study year was associated with a significantly reduced odds of complications (odds ratio [OR] 0.76; 95% CI 0.63-0.92; p=0.005), ventilator-free days < 28 days (OR 0.77; 95% CI 0.65-0.92; p=0.003), Intensive Care Unit (ICU)-free days < 24 days (OR 0.77; 95% CI 0.66-0.91; p=0.002), and hospital-free days < 18 days (OR 0.64; 95% CI 0.53-0.76; p<0.0001).

Thus, with increasing years of SSRF experience in-hospital outcomes improved while patient selection remained similar. Unexpectedly, operative time increased. The reason for this finding is likely multifactorial and might be related to uncaptured patient and fracture characteristics, onboarding of new surgeons, and minimally invasive exposures. Due to potential for confounding, study year should be accounted for when evaluating outcomes after SSRF.

The ideal time from injury to SSRF remains a matter of debate and **Chapter 9** presents the current literature on this topic. Nine studies addressed the effect of timing of SSRF on outcomes. Early SSRF (≤72h after trauma) was associated with improved in-hospital outcomes such as shorter ventilation duration, hospital and ICU length of stay, and complication rate. Also, two studies indicated that late SSRF was associated with outcomes inferior to nonoperative management. Since all studies were retrospective and none elaborated on why patients underwent early or late SSRF, the outcomes should be interpreted in the light of possible selection bias.

In selected stable patients, early SSRF is recommended as compared with late salvage SSRF. The earlier SSRF is performed the better, but preferably ≤72 hours after trauma.

The effect of SSRF and nonoperative management in patients with multiple rib fractures and moderate to severe TBI (GCS score ≤12), a traditional relative contra-indication to SSRF, is studied in **Chapter 10** (CWIS-TBI study). This study included 456 patients from 19 trauma centers worldwide of which 111 (24%) underwent SSRF. In one patient (0.9%), a complication related to the perioperative setting occurred in which intracranial pressure increased and medicinal intervention was required after which SSRF was completed. In multivariable analyses, the SSRF group had a significantly lower odds of developing pneumonia (OR 0.59; 95% CI 0.38–0.98; p=0.043) and 30-day mortality (OR 0.32; 95% CI 0.11–0.91; p=0.032). In a post-hoc subgroup analysis of the CWIS-TBI study, the study population was stratified for having sustained a non-flail fracture pattern or flail chest (**Chapter 11**). In patients with a non-flail fracture pattern, SSRF was associated with an over three times lower odds of pneumonia (OR 0.29; 95% CI 0.11-0.77; p=0.013). In patients with a flail chest, an approximate 3-day decrease in ICU LOS was observed in patients who underwent SSRF (beta -2.85; 95% CI -5.70 to -0.23; p=0.034).

In conclusion, before conducting expensive and potentially invasive scientific studies, this study establishes that there is at least equipoise between treatment modalities and SSRF does not hamper neurological recovery or harm the patient with multiple rib fractures and TBI. In the setting of TBI, the decision to perform SSRF should be carefully made, weighing the risks of surgery against the benefits of pulmonary and overall recovery. These data suggest a potential role for SSRF in select patients with TBI and severe rib fracture patterns.

In **Chapter 12** (CWIS-CPR), the hypothesis of **Chapter 4** whether SSRF might improve outcomes in patients with multiple rib fractures following CPR is tested. This international, retrospective study comprised patients who underwent SSRF or nonoperative management for multiple rib fractures following CPR. In total, 39 operative cases were matched to 69 nonoperative controls by cardiac arrest location, cause of arrest, rib fracture pattern (*i.e.,* unilateral or bilateral, flail sternum, flail chest), and age. Patients who underwent SSRF more often had ≥1 displaced rib fractures (n=28, 72% vs. n=31, 47%; p=0.015) and a higher median number of displaced ribs (2, P_{25}-P_{75} 0-3 vs. 0, P_{25}-P_{75} 0-3; p=0.014). In the nonoperative group, a rib fixation specialist was consulted in 14 patients (21%). The ICU LOS was significantly longer in the operative group (13 days, P_{25}-P_{75} 9-23 vs. 9 days, P_{25}-P_{75} 5-15; p=0.004). The number of mechanical ventilator-free days and other in-hospital outcomes were similar between the treatment groups.

Despite more consequential chest wall injury in the SSRF group, both treatment groups had relatively similar outcomes. Other variables than the included injury and radiographic

characteristics might result in rib fixation consultation in this population, highlighted by the low consultation in the nonoperative group. Careful patient selection and prospective studies are required before embedding or abandoning this procedure in these patients.

The anatomical positioning and biomechanical characteristics of five currently available fixation systems for SSRF are collectively studied in **Chapter 13**. Bilateral ribs number six to 10 of five postmortem human specimens were used to be fixated. Half of the ribs were fractured to represent acute rib fractures. Each fixated rib was subjected to a four-point bending test to determine its biomechanical characteristics. On an intact rib, the bending structural stiffness (EI; N/m^2), load to failure (Fmax; N), and relative difference in EI and Fmax as compared to a non-fixated intact rib was similar between the fixation systems. On a fractured rib, the relative difference in stiffness differed significantly between the clamping and plate and screw implants, ranging from -0.88 (SD 0.08) for the STRACOS™ system to +0.17 (SD 0.50) for the MatrixRIB™ system. Altogether, current fixation systems differ significantly in their biomechanical properties, especially when fixated on fractured ribs. Insight in these differences can help choosing an implant when considering rib fracture type and location, and preferred goal of fixation based on underlying pathology.

Finally, the general discussion and future perspectives are discussed in **Chapter 14**.

NEDERLANDSE SAMENVATTING EN CONCLUSIES

Hoofdstuk 1 is de algemene introductie van dit proefschrift. Het licht de epidemiologie, impact en uitkomsten van ribfracturen toe en identificeert bestaande lacunes in de huidige wetenschappelijke literatuur.

Hoofdstuk 2 behandelt populatie gebaseerde trends in de incidentie van ribfracturen in Nederland tussen 2015 en 2018 en geeft een overzicht van geassocieerde (in)directe kosten en gezondheidszorggebruik. Gedurende deze periode werden 32.124 patiënten met ribfracturen geregistreerd waarvan 19.885 (62%) opgenomen werden en 19.997 (59%) multipele ribfracturen hadden. De incidentie van ribfracturen was 47 per 100.000 persoonsjaren en deze nam sterk toe met het vorderen van de leeftijd. De gemiddelde ziekenhuisopnameduur was 7,7 dagen voor het gehele cohort en nam toe met de ernst van het letsel: van 5,6 dagen (één ribfractuur) tot 8,3 dagen (multiple ribfracturen) en 12,3 dagen (fladderthorax). De gemiddelde directe kosten van een patiënt met ≥1 ribfracturen waren €6.800 ($8.500) waarbij opgenomen patiënten verantwoordelijk waren voor 91% van deze kosten. De indirecte kosten bedroegen €15.500 ($18.500) waarbij 90% van de kosten werden gemaakt door opgenomen patiënten. Het werkverzuim was gemiddeld 44 dagen (65 dagen voor opgenomen patiënten en 8 dagen voor niet opgenomen patiënten).
Ribfracturen komen vaak voor en zijn geassocieerd met langdurige ziekenhuisopname, werkverzuim en hoge kosten. Deze uitkomsten lijken sterker geassocieerd te zijn met opnamestatus en leeftijd dan met het oplopen van één of meerdere ribfracturen.

In **Hoofdstuk 3** is het optreden van ribfracturen, ribfractuur type, en begeleidend (intra)thoracaal letsel vergeleken tussen patiënten van ≥50 jaar met normale of verminderde botmineraaldichtheid (BMD [osteopenie of osteoporose] T-score <-1.0) na stomp thoraxletsel. In totaal werden 119 patiënten geïncludeerd. Patiënten met verminderde BMD hadden vaker ribfracturen dan patiënten met normale BMD (n=43, 74% vs. n=31, 51%; p=0.011), maar het aantal ribfracturen, fladderthoraxen en de ernst van het (intra)thoracaal letsel was gelijk. Het ribfractuur type (simpel, wig of complex) was gelijk verdeeld tussen de groepen.
Bij patiënten van ≥50 jaar die een stomp thoraxtrauma hebben ondergaan, moet de aanwezigheid van een verminderde BMD en een mogelijk verhoogd risico op ribfracturen overwogen worden. Het maken van een DXA scan kan inzicht geven in de werkelijke prevalentie en het effect van verminderde BMD in deze populatie.

De prevalentie van thoraxwandletsel en het effect daarvan op uitkomsten tijdens ziekenhuisopname door reanimatie vanwege een hartstilstand buiten het ziekenhuis

is onderzocht in **Hoofdstuk 4**. In totaal werden 344 patiënten geanalyseerd waarvan 291 (85%) reanimatie-gerelateerd thoraxwandletsel hadden. Ribfracturen kwamen het vaakst voor (n=285, 83%) en deze patiënten hadden een mediaan van 8 gebroken ribben (P_{25}-P_{75} 4-10) welke voornamelijk niet-gedisloceerde, simpele, anterieure fracturen waren van rib 2 tot 7. Het oplopen van ≥6 ribfracturen of ≥1 gedisloceerde ribfractuur was geassocieerd met een langere ziekenhuis- en Intensive Care (IC)-opnameduur in patiënten met goed neurologisch herstel (motor Glasgow Coma Scale [GCS] score, 5-6). De prevalentie van een pneumonie was 31% vs. 9% in patiënten met respectievelijk zonder ribfracturen en goed neurologisch herstel (p=0.077).

Samenvattend, thoraxwandletsel en vooral ribfracturen komen vaak voor na reanimatie. Patiënten met ribfracturen en goed neurologisch herstel ontwikkelen vaak een pneumonie en hebben lange ziekenhuis- en IC opnames. Het is derhalve zinvol om te onderzoeken of herstel van de thoraxwandstabiliteit middels ribfixatie deze uitkomsten kan verbeteren.

Hoofdstuk 5 heeft de lange termijn uitkomsten na ribfracturen en het effect van letselernst (één of twee, ≥3 ribfracturen of een fladderthorax) en behandeling (operatief of niet-operatief) onderzocht. In totaal werden 300 patiënten met een mediaan van 39 maanden (P_{25}-P_{75} 18-65) na trauma gezien tijdens een eenmalige follow-up. Tijdens follow-up bleken de spirometrie waarden Forced Vital Capacity en Forced Expiratory Volume at 1 second tot 85% en 86% van de voorspelde referentiewaarden te zijn hersteld. Kwaliteit van leven scores (op basis van Short Form-12 versie 2 en EuroQol-5 Dimension vragenlijsten) vielen ook binnen de Amerikaanse populatienormen. Subjectieve klachten zoals matig tot ernstige thoracale pijn (Numeric Rating Scale >3), kortademigheid in rust of bij milde inspanning, en een strak gevoel van de borstkas werden nog ervaren door respectievelijk 21%, 23% en 16% van alle patiënten. Langetermijn uitkomsten waren gelijk voor de groepen op basis van thoraxwandletsel ernst en behandeling.

Op de lange termijn normaliseren longfunctie en kwaliteit van leven scores maar subjectieve thoracale klachten en pijn blijven vaak aanwezig. De initiële ernst en behandeling van het thoraxwandletsel lijken niet geassocieerd te zijn met deze uitkomsten.

Een systematisch literatuurreview en meta-analyses van vergelijkende studies over het effect van ribfixatie versus een niet-operatieve behandeling op klinische uitkomsten in patiënten zonder fladderthorax wordt gepresenteerd in **Hoofdstuk 6**. Veertien studies van 13 cohorten werden geïdentificeerd met in totaal 4565 patiënten. Slechts twee studies bestonden volledig uit patiënten zonder fladderthorax, terwijl dit verschilde van 54 tot 97% voor de andere studies. De meeste studies (n=9) waren retrospectief

van aard. Meta-analyse toonde een significante afname in het risico op een pneumonie (relatief risico [RR] 0.66, 95% BI 0.49-0.90; p=0.008) en mortaliteit (RR 0.32, 95% BI 0.19-0.54; p<0.001) en kortere ziekenhuisopnameduur (gemiddeld verschil -5.8 dagen, 95% BI -10.4 tot -1.2; p=0.01) ten faveure van ribfixatie. Er was geen verschil voor de duur van beademing en IC opname.

Concluderend bleek ribfixatie geassocieerd te zijn met gelijke of betere klinische uitkomsten dan niet-operatieve behandeling. Echter, vanwege de heterogene patiënt-populatie en lage methodologische kwaliteit moeten de resultaten van de huidige studies met enige terughoudendheid worden geïnterpreteerd en geven ze de noodzaak aan van prospectief en kwalitatief sterk onderzoek.

In **Hoofdstuk 7** is het studieprotocol beschreven van een multicenter gerandomiseerde studie betreffende het effect van ribfixatie en niet-operatieve behandeling van multipele enkelvoudige ribfracturen. Deze trial includeert patiënten met ≥3 enkelvoudige ribfracturen waarvan minimaal één fractuur bicorticaal gedisloceerd is. De primaire uitkomstmaat is de pneumonie prevalentie en secundaire uitkomsten zijn onder andere klinische uitkomsten, thoracale complicaties of secundaire interventies, pijnmedicatie gebruik, longfunctie, thoracale pijn, kwaliteit van leven en kosteneffectiviteit. Deze uitkomsten worden geëvalueerd gedurende het eerste jaar na trauma. Ten tijde van het drukken van dit proefschrift waren 136 van de beoogde 180 patiënten geïncludeerd.

De invloed van toenemende jaren van ervaring met ribfixatie op patiëntselectie, (intra) operatieve eigenschappen en klinische uitkomsten wordt bepaald in **Hoofdstuk 8**. Tussen 2010 en 2020 ondergingen 222 patiënten ribfixatie in een Level-I traumacentrum. Gedurende de jaren bleef patiëntselectie op basis van leeftijd, letselernst score (ISS) en de prevalentie van patiënten met een fladderthorax of ≥3 gedisloceerde ribfracturen gelijk. Elk toenemend studiejaar was in multivariate analyse significant geassocieerd met een afname in tijd van trauma tot ribfixatie en toename in operatieduur. Bovendien was elk toenemend studiejaar geassocieerd met een reductie in de kans op complicaties (odds ratio [OR] 0.76; 95% BI 0.63-0.92; p=0.005), beademingsvrije dagen <28 (OR 0.77; 95% BI 0.65-0.92; p=0.003), IC-vrije dagen < 24 (OR 0.77; 95% BI 0.66-0.91; p=0.002), en ziekenhuisvrije dagen < 18 (OR 0.64; 95% BI 0.53-0.76; p<0.0001).

Terwijl patiëntselectie gelijk bleef, verbeterden de klinische uitkomsten na ribfixatie met elk toenemend jaar aan ervaring. De operatieduur steeg onverwacht. Dit is waarschijnlijk multifactorieel en mogelijk gerelateerd aan specifieke patiënt- en fractuurkarakteristieken, de komst van nieuwe chirurgen en minimaal invasieve benaderingen. Vanwege het effect van studiejaar wordt aangeraden om hiervoor te corrigeren in ribfixatie studies.

De optimale tijd van trauma tot ribfixatie staat ter discussie. De negen studies die het effect van tijd tot ribfixatie op uitkomsten beschreven, worden gepresenteerd in **Hoofdstuk 9**. Vroege ribfixatie (≤72 uur na trauma) was geassocieerd met betere klinische uitkomsten zoals kortere beademings-, IC- en ziekenhuisopnameduur en minder pulmonale complicaties. Bovendien lieten twee studies zien dat late ribfixatie geassocieerd was met slechtere uitkomsten dan vroege ribfixatie of zelfs een niet-operatieve behandeling. Echter, aangezien alle studies retrospectief waren en geen inzicht gaven in de onderliggende reden voor een vroege of late ribfixatie, moeten de resultaten in het licht van mogelijke selectiebias worden gezien.

Vroege ribfixatie wordt aanbevolen voor geselecteerde stabiele traumapatiënten ten opzichte van late ribfixatie: des te eerder des te beter, bij voorkeur binnen 72 uur na trauma.

Van oudsher wordt matig tot ernstig hersenletsel (GCS score ≤12) beschouwd als een relatieve contra-indicatie voor ribfixatie. Het effect van operatieve versus niet-operatieve behandeling van multipele ribfracturen in deze patiëntengroep is geëvalueerd in **Hoofdstuk 10** (CWIS-TBI studie). Deze studie bestond uit 456 patiënten uit 19 trauma-centra wereldwijd waarvan 111 (24%) ribfixatie ondergingen. Eén patiënt (0.9%) ontwikkelde een complicatie in de perioperatieve setting waarbij de intracraniële druk toenam en medicatie nodig was om de ribfixatie te kunnen voltooien. In multivariate analyse bleek ribfixatie geassocieerd met een significant lagere kans op een pneumonie (OR 0.59; 95% BI 0.38–0.98; p=0.043) en 30-dagen mortaliteit (OR 0.32; 95% BI 0.11–0.91; p=0.032). Ook zijn de patiënten gestratificeerd voor het hebben van een fladderthorax of niet in een post-hoc subgroep analyse van de CWIS-TBI studie (**Hoofdstuk 11**). In patiënten met matig tot ernstig hersenletsel zonder fladderthorax had de ribfixatie groep een meer dan drie keer zo laag risico op het ontwikkelen van een pneumonie (OR 0.29; 95% BI 0.11-0.77; p=0.013). In patiënten met matig tot ernstig hersenletsel en een fladderthorax werd een ongeveer drie dagen kortere IC-opnameduur gezien in de patiënten die ribfixatie hadden ondergaan (beta -2.85; 95% BI -5.70 tot -0.23; p=0.034).

Deze studie laat zien dat ribfixatie het neurologisch herstel niet hindert in patiënten met hersenletsel en ribfracturen en mogelijk zelfs baat heeft. In de setting van matig tot ernstig hersenletsel moet het besluit tot ribfixatie zorgvuldig genomen worden, terwijl de risico's van de operatie en de voordelen van pulmonaal en algeheel herstel worden afgewogen.

De hypothese uit **Hoofdstuk 4**, in hoeverre ribfixatie de uitkomsten in patiënten met multipele ribfracturen na reanimatie verbetert, is getest in **Hoofdstuk 12** (CWIS-CPR). Deze internationale, retrospectieve studie bevatte patiënten die ribfixatie of niet-

operatieve behandeling ondergingen voor multipele ribfracturen na reanimatie. In totaal werden 39 operatieve patiënten gekoppeld aan 69 niet-operatieve controles op basis van locatie van de hartstilstand, oorzaak van arrest, ribfractuurpatroon (unilateraal of bilateraal, fladdersternum, fladderthorax) en leeftijd. Patiënten die ribfixatie ondergingen hadden vaker ≥1 gedisloceerde ribfracturen (n=28, 72% vs. n=31, 47%; p=0.015) en een hogere mediaan gedisloceerde ribfracturen (2, P_{25}-P_{75} 0-3 vs. 0, P_{25}-P_{75} 0-3; p=0.014). In het niet-operatieve cohort werd een rib fixatie specialist geconsulteerd in 14 patiënten (21%). De IC-opnameduur was significant langer in de operatieve groep (13 dagen, P_{25}-P_{75} 9-23 vs. 9 dagen, P_{25}-P_{75} 5-15; p=0.004), terwijl het aantal invasieve beademingsvrije dagen en andere klinische uitkomsten gelijk waren tussen de behandelgroepen.

De behandelgroepen hadden relatief gelijke klinische uitkomsten ondanks ernstiger thoraxwandletsel in de ribfixatie groep. Mogelijk spelen andere variabelen dan de geïncludeerde letsel en radiologische karakteristieken een rol in het overwegen van rib fixatie in deze populatie, uitgelicht door het lage percentage consulten voor ribfixatie in de niet-operatieve groep. Zorgvuldige patiëntselectie en prospectieve studies zijn nodig voor het integreren of juist afstand doen van ribfixatie in deze patiënten.

De anatomische positionering en biomechanische eigenschappen van vijf verschillende ribfixatiesystemen worden geëvalueerd in **Hoofdstuk 13**. Hiertoe werden de ribben zes tot tien van vijf overleden personen gefixeerd nadat in de helft van de ribben een fractuur was gemaakt. Middels een vierpunts buigproeftest werden de biomechanische eigenschappen van iedere rib bepaald. Voor de intacte rib, ten opzichte van een niet gefixeerde rib, bestond geen verschil tussen de diverse ribfixatiesystemen voor wat betreft stijfheid (EI; N/m^2), breukbelasting (Fmax; N) en het relatieve verschil in EI en Fmax. Voor de gefixeerde gebroken rib bestond een significant verschil in relatieve stijfheid ten opzichte van een niet gefixeerde rib tussen systemen die gebruik maken van een klemmend implantaat en plaat-schroef implantaten, variërend van -0.88 (SD 0.08) voor het STRACOS™ systeem tot +0.17 (SD 0.50) voor het MatrixRIB™ systeem. De huidige ribfixatiesystemen verschillen significant in hun biomechanische eigenschappen. Deze kennis is relevant en essentieel om, afhankelijk van anatomische locatie en fractuurtype, het beste implantaat te kunnen kiezen in een klinische situatie.
Tenslotte worden de algemene discussie en toekomstperspectieven besproken in **Hoofdstuk 14**.

CHAPTER 15

APPENDICES

List of publications
Other publications
Contributing authors
PhD portfolio
Dankwoord
About the author

LIST OF PUBLICATIONS

This thesis

Early fixation versus conservative therapy of multiple, simple rib fractures (FixCon): protocol for a multicenter randomized controlled trial
M.M.E. Wijffels*, **J.T.H. Prins***, S. Polinder, T.J. Blokhuis, E.R. De Loos, R.H. Den Boer, E.R. Flikweert, A.F. Pull ter Gunne, A.N. Ringburg, W.R. Spanjersberg, P.J. Van Huijstee, G. Van Montfort, J. Vermeulen, D.I. Vos, M.H.J. Verhofstad, E.M.M. Van Lieshout
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Eur J Trauma Emerg Surg. 2021 Apr. DOI: https://doi.org/10.1007/s00068-021-01662-8

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Submitted to J Trauma Acute Care Surg (2022 March)

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Other publications

Outcome after surgical stabilization of symptomatic rib fracture nonunion: a multicenter retrospective case series
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	Year	Workload (ECTS)

1. PhD training

General courses

	Year	Workload (ECTS)
Basiscursus Regelgeving Klinisch Onderzoek (BROK)	2019	1.5
CPO-course: Patient Oriented Research	2019	0.3
Biostatistical Methods I: Part A	2019	2.0
Biomedical English Writing	2020	2.0
Research Integrity	2021	0.3

Specific courses

	Year	Workload (ECTS)
Basiskwalificatie Onderwijs (BKO):		
- Teach the Teacher (TtT) II	2019	
- Feedback geven	2019	
- Hoorcollege geven	2019	
Fundamental Critical Care Support Course	2021	
Advanced Trauma Life Support (ATLS)	2021	

Presentations

	Year	Workload (ECTS)
FixCon RCT presentation at including hospitals	2019	2.0
	2021	
Assistentensymposium Traumachirurgie (NVT)	2019	1.0
Science Day Department of Surgery, Erasmus MC	2019	1.0
European Congress of Trauma & Emergency Surgery	2019	1.0
Traumadagen (NVT)	2019	1.0
Chest Wall Injury Society Research Symposium	2020	1.0
Science Day Dept. of Surgery, Denver Health, CO, USA	2021	1.0
Chest Wall Injury Society Hybrid Summit 2021	2021	2.0

Surgical Infection Society 40th Annual Meeting	2021	1.0
Southwestern Surgical Congress Annual Meeting	2021	1.0
German Congress of Orthopaedics and Traumatology	2021	1.0
ACE Bone & Joint Meeting, Erasmus MC	2021	1.0
Assistentensymposium Traumachirurgie (NVT)	2022	1.0
Chest Wall Injury Society Summit 2022	2022	3.0

(Inter)national Conferences

Assistentensymposium Traumachirurgie (NVT)	2020	0.3
Chest Wall Injury Society Summit 2020	2020	0.6
Traumadagen (NVT)	2021	0.6

2. Teaching activities

Supervising Master students

- S.M. Wooldrik	2020	2.0

Supervising Bachelor research student

- H.C.G. Overtoom	2020	2.0
- Y.S. Tekin	2020	2.0
- Bachelor students TU Delft	2020	2.0

ABOUT THE AUTHOR

Jonne Thomas Hendrik Prins was born on November 8th, 1991 in Amsterdam, the Netherlands as the oldest son of Pier Prins and Noëlle Pameijer and brother of Kyra. He completed the Gemeentelijk Gymnasium Hilversum in 2010.
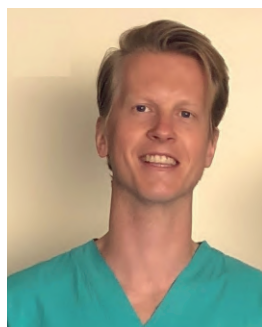
In 2010, he was awarded a Fulbright scholarship and went to the private liberal arts college Denison University, Granville, OH, USA. Here, he completed a year of pre-medical courses and played on the varsity soccer team, NCAC Division III. After being drawn out for Medical school upon returning to The Netherlands, he studied a year at Amsterdam University College. In 2012, he started Medical school at the Erasmus University Medical School in Rotterdam. During Medical School, he joined the student team 'Les Forgerons' at the Emergency Department of the Ikazia Hospital, Rotterdam which sparked his interest in surgery. In November 2018, he obtained his medical degree.

In January 2019 he started as a PhD candidate at the Trauma Research Unit Department of Surgery of the Erasmus MC under supervision of prof. dr. M.H.J. Verhofstad, focusing on thoracic trauma. From January-March 2021 he worked as a research fellow at the Department of Surgery at the Denver Health Hospital, Denver, CO, USA under dr. F.M. Pieracci. In January 2022, he started as a senior house officer at the Department of Surgery of the Ikazia Hospital, Rotterdam.

DANKWOORD

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my time at Denver Health unforgettable. From seeing you operate ribs to playing top golf to skiing down the slopes, the Denver experience was amazing. I am honored to have been able to be the first research fellow to visit. Your scientific insights and feedback as well your tireless enthusiasm and time as a family man have intrigued me and are an example to me. I hope to keep working together and see you soon!

Mijn paranimfen, Gijs en Satchel, het is geweldig dat jullie naast mij staan op deze dag. Gijs, de Rue de Jean Noir en de Goof, maar ook de vakantie in de Dordogne, we kunnen een boekje vullen met anekdotes. Een van de hoogtepunten was toch wel de lockdown begin 2020, toen we naar eigen zeggen erg hard werkten maar wel binnen enkele weken zeven seizoenen Walking Dead hadden afgerond. De middagen bestonden uit sporten of meeluisteren met de Teams-meeting van de ander als deze er van langs kreeg. Dank dat jij er altijd bent en op deze dag mijn paranimf wil zijn.
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