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## **TRAUMA IN A SCANDINAVIAN URBAN REGION**

### **EPIDEMIOLOGICAL ASPECTS ON RISK FACTORS AND OUTCOME**

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M.D.



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*To Kristina and Andreas*

The scientist is not a person who gives the right answers,  
he's one who asks the right questions  
- Claude Lévi-Strauss

## ABSTRACT

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Trauma as a disease is a global health problem and for patients surviving the initial injury and early resuscitation phase, later complications contribute largely to morbidity and mortality. Awareness of risk factors, early recognition and appropriate treatment of complications are likely to have a significant influence on outcome. Early identification of patients at risk may contribute to optimising initial resuscitation, intensive care and long-term outcome. This thesis is based on four studies using epidemiological data from local and national registries. The aims of this thesis were to study incidence and risk factors for complications and mortality in severe trauma and the influence of socioeconomic factors and comorbidity on the risk of becoming a trauma victim.

*Study I* was a cohort study of 164 trauma patients admitted to the central intensive care unit at the Karolinska University Hospital, Stockholm. We found an incidence of multiple organ failure, acute lung injury and severe sepsis of 40.2%, 25.6% and 31.1% respectively. 30- and 90-day post-injury mortality was 10.4 %. Intensive care unit-complications and death were not uniformly affected by the different risk factors.

In *study II* we investigated the influence of gender and comorbidity on 30- and 360-day survival of individuals registered in the trauma registry at Karolinska University Hospital, Stockholm between January 2005 and August 2008. In addition we evaluated survival over time in relation to the general population. The influence of gender and comorbidity on outcome after trauma differed over time. Male gender was an independent risk factor for mortality at one year but not at 30-days post injury and the effect of gender seemed to be restricted to elderly patients. The presence of comorbidity became a significant risk factor beyond 30 days after trauma. A persistent excess mortality in comparison to the general population was seen among men one year after trauma, standardized mortality ratio 3.8 (95% CI 2.8 -5.1).

Our aim of *study III* was to report the overall incidence of pneumonia in intensive care unit-treated trauma patients and to investigate risk factors for development post injury pneumonia following severe trauma. The study cohort consisted of 322 trauma patients admitted to the central intensive care unit at the Karolinska University Hospital, Stockholm between February 2007 and July 2011. The incidence of pneumonia was 26% during their first 10 days in the ICU. Reduced consciousness was an independent risk factor for development of pneumonia after severe injury.

*Study IV* was a case-control study, cases ( $n = 7382$ ) were defined as all patients 15 years or older registered in the trauma registry with a first trauma admission between January 2005 and December 2010. A random selection of 36760 age, gender and municipality matched controls were extracted from the Total population registry. Our aim was to study the influence of socioeconomic factors and comorbidity on the risk of becoming a trauma victim. Level of education and income as well as substance abuse, psychiatric, and somatic comorbidity were all independent risk factors for trauma. Active substance abuse strongly influenced the risk for trauma and had a time dependent pattern.



## LIST OF PUBLICATIONS

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This thesis is based on the following papers, which will be referred to by their Roman numerals as indicated below:

- I. **Early predictors of morbidity and mortality in trauma patients treated in the intensive care unit**  
Brattström O, Granath F, Rossi P, Oldner A  
*Acta Anaesthesiol Scand* 2010; 54: 1007–1017
- II. **Time dependent influence of host factors on outcome after trauma**  
Brattström O, Larsson E, Granath F, Riddez L, Bell M, Oldner A  
*Eur J Epidemiol* (2012) 27:233–241
- III. **High incidence of post-injury pneumonia in intensive care-treated trauma patients**  
Hyllienmark P, Brattström O, Larsson E, Martling C-R, Petersson J, Oldner A  
*Acta Anaesthesiol Scand* 2013; 57: 848–854
- IV. **Socioeconomy and comorbidity as risk factors for trauma**  
Brattström O, Eriksson M, Larsson E, Oldner A  
*Manuscript*

*När det otänkbara händer  
Som ingen människa kan förutse  
När ödet ger dig en hand  
du aldrig ville se  
Kan någon se nån mening  
i något av det som sker  
Varför drabbades just du  
Varför just här och nu  
- Mauro Scocco*



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## **LIST OF ABBREVIATIONS**

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AIS	Abbreviated injury scale
ALI	Acute lung injury
APACHE II	Acute physiology and chronic health evaluation II
ARDS	Acute respiratory distress syndrom
ASA-PS	American society of anesthesiologists physical status
CDC	Centers for disease control an prevention
CI	Confidence interval
CNS	Central nervous system
DALY	Disability adjusted life years
DAMP	Damage associated molecular patterns
GCS	Glasgow coma scale
HR	Hazards ratio
ICD-10	International classification of diseases – tenth revision
ICU	Intensive care unit
IQR	Interquartile ranges
ISS	Injury severity score
LISA	The Longitudinal integration database for health insurance and labour market studies
NBHW	Swedish national board of health and welfare
NIOSH	The national institute for occupational safety an health
NISS	New injury severity score
OR	Odds ratio
PAMP	Pathogen-associated molecular patterns
RCT	Randomized control trials
RTS	Revised trauma score
SAP	Systolic arterial blood pressure
SES	Socioeconomic status
SIRS	Systemic inflammatory response syndrome
SMR	Standardized mortality ratio
TARN	Trauma audit & research network
TR-DGU	The trauma register- deutsche gesellschaft für unfallchirurgie
TRISS	Trauma score – injury severity score
YLL	Years of life lost



## INTRODUCTION

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An event leading to a severe injury may lead to major changes in life for the person who is injured and the family involved. The risk of becoming the victim of a trauma differs between individuals and so does the capacity to cope with a traumatic event both from a somatic and psychological perspective. Despite that our ability to treat the severely injured patient has improved, several challenges remain when striving for best care.

Improvement of the organisation of trauma care through implementation of a trauma system that address all aspects of care – from the prehospital setting, initial resuscitation in the hospital, to longer term definitive care, as well as on-going education and research is crucial in order to improve the care of the injured patient.

This thesis is based on four studies using epidemiological data from local and national registries allowing us to study incidence and risk factors for complications and mortality in severe trauma. In *study I* we investigated the incidence of complications and post-injury mortality in trauma patients treated in the intensive care unit (ICU) as well as possible risk factors for these events. In *study II*, we studied the influence of comorbidity and gender and their impact on mortality at 30-and 360-days. We also investigated whether there was a difference in survival over time in the trauma population in comparison with a general population. *Study III* describes pre-hospital and hospital parameters during the first 24 hours after admission and their possible association with later development of pneumonia in the ICU. In addition, we report pathogens identified in patients that developed pneumonia. *Study IV* was performed to investigate the influence of socioeconomic factors and comorbidity on the risk of becoming a trauma victim.



## BACKGROUND

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### HISTORICAL PERSPECTIVE

The management as well as development of new treatment options for the severely injured patient is largely based on experiences from wars during history. The modern treatment of the injured patient in a multi-professional way is considered to have started in Birmingham, UK in 1941 with the initiation of the first trauma centre.<sup>1,2</sup> The evolution of trauma care systems continued when two trauma centres in the United States were opened in San Francisco General Hospital and Cook County Hospital, Chicago in 1966. In the same year the National Academy of Sciences published a report, *Accidental Death and Disability: The neglected disease of modern society*, considered a landmark in the development of the emergency medical services system in the United States.<sup>3-5</sup> This has led to centralised care of the severely injured patients within a region by developing trauma care systems. A trauma care system is a pre-planned, organised and coordinated management of the trauma patient.

The idea of a trauma system is to develop and coordinate the medical care from dispatch and medical oversight of prehospital care, hospital care and rehabilitative services to medical care follow up. Trauma systems in Europe and Scandinavia show significant variation<sup>6,7</sup> and are yet less developed than in the United States

### TRAUMA

The definition of the word “trauma” vary depending on which profession you belong to and the context in which the word is used. In Greek it means *τράυμα* "wound". One way to define trauma is to refer only to the event and not the reaction. This should be reserved for major events that are somatic and psychologically overwhelming for an individual. In the current thesis the word trauma according to the definition from CDC / NIOSH; "*an injury or wound to a living body caused by the application of external force or violence*" was used.<sup>8</sup>

Trauma as a disease is a global health problem and in 2010 a tenth of the worlds 53 million deaths globally were related to injuries. Among trauma patients males, account for about two thirds of all injury-related deaths. A large proportion of people surviving their injuries incur temporary or permanent disabilities.<sup>9</sup> A measure of population health can be calculated as disability adjusted life years, DALYs. DALYs are the sum of two components: years of life lost due to premature mortality and years lived with disability.<sup>10,11</sup> Injuries collectively caused a tenth of the global burden of DALYs. Many different injuries contribute to these figures. The largest being road accidents accounting for 27%. Blunt trauma is the major type of injury in European countries with 90% of the patients in this

category.<sup>12,13</sup> Different patterns are seen in parts of the United States and South Africa, reporting proportions of penetrating injuries of 20-45% and 60% respectively.<sup>14-16</sup> In Sweden, 4000 people die from injury annually. It is the most common cause of death for individuals under the age of 45 (48%).<sup>17</sup>

## **TRAUMA AND ICU SCORING SYSTEM**

Description of injuries and diseases by type and severity are essential for patient management, research and quality improvement processes. A number of different scoring systems exist in order to facilitate injury comparison between patients in an objective manner. Some of these scoring systems are based on the anatomical nature of the injuries sustained (anatomical scores) and some are based on the physiological status of the patient (physiological scores).<sup>18,19</sup>

### *Abbreviated injury scale*

The abbreviated injury scale (AIS) is an anatomical scoring system and the first scale was first published in 1971.<sup>20</sup> An AIS code is a seven-digit number specifying the body region, specific structure, type and severity of injury. It is consensus derived and classifies each injury according to its relative importance on a 6-point scale. The AIS is monitored by a scaling committee of the Association for the Advancement of Automotive Medicine (AAAM).<sup>21</sup> Today, the AIS is the global system of choice for injury data collection and has become the basis for a number of derivative scales in use. The current version in use is AIS 2005 Update 2008 (Dec 2013).

### *Injury severity score*

Injury severity score (ISS) is an anatomical description of injury that is designed to quantify the total load of anatomical injury across body regions. The ISS is calculated by taking the sum of the squares of the AIS codes for the most severe injury in each of the three most severely injured ISS body regions. The maximum score of ISS is 75. The body regions are divided into; (1) head and neck, (2) face, (3) chest (thorax), (4) abdominal and pelvic contents, (5) extremities and bony pelvis and (6) external.<sup>22</sup>

### *New injury severity score*

The new injury severity score (NISS) is calculated as the sum of squares of the AIS codes of the three most severe injuries, regardless of body region. The same body regions as ISS are used.<sup>23</sup>



## OUTCOME PREDICTION AND PHYSIOLOGICAL SCORING

In the context of quality monitoring and research regarding the severely injured patient, we need to take into consideration different risk factors in order to evaluate outcome and predict mortality. Prediction models take into account some of the case mix variation occurring in a trauma or ICU population such as age, degree of injury, physiology, comorbidity etc. Several different prediction models are in use. One of the oldest and most commonly used is TRISS. Other examples of prediction models are the British TARN Outcome Prediction Model; Ps12n <sup>24</sup> and the German TR-DGU Registry; RISC (Revised Injury Severity Classification) <sup>25</sup>

### *Revised trauma score*

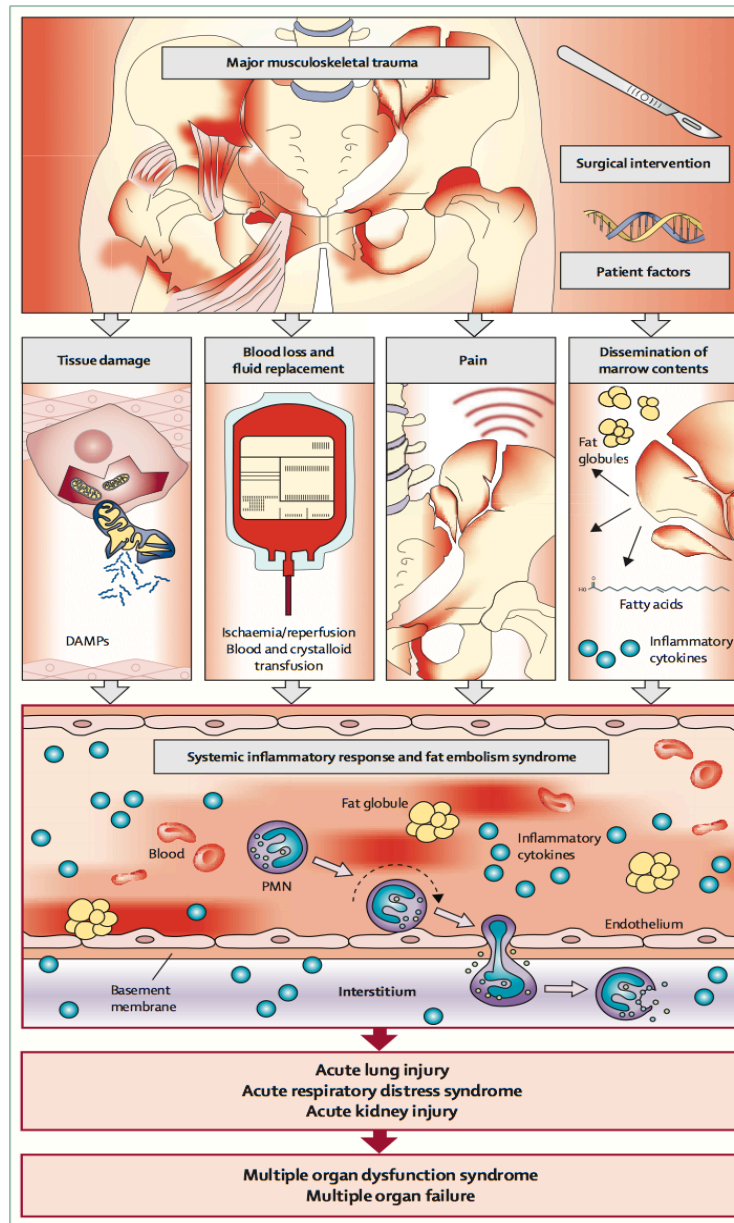
Revised trauma score (RTS) is a physiological scoring system that substituted the trauma score in 1990<sup>26</sup> and according to the trauma score – injury severity score (TRISS) definition the first set of data obtained on arrival at the hospital are used. RTS includes values of the Glasgow coma scale (GSC), systolic pressure and respiratory rate. In Europe, patients are mainly assigned GCS and respiratory rate scores recorded immediately before intubation, either on scene of the injury, or in the emergency department/trauma unit according to the European consensus agreement.<sup>27</sup>

For over 30 years TRISS has been the prediction model commonly used for outcome analysis of trauma patients.<sup>28,29</sup> TRISS attempts to predict the probability of patient survival based on physiology (RTS), injury severity (ISS), age and type of trauma (blunt or penetrating). Originally, physiological derangement was scored via the trauma score.<sup>30</sup>

## EFFECTS OF TRAUMA

For trauma patients surviving the initial injury and early resuscitation phase, later complications contribute largely to morbidity and mortality.<sup>31,32,33-35</sup> Awareness of risk factors, early recognition and appropriate treatment of complications are likely to have a significant influence on outcome. Early identification of patients at risk may contribute to optimising initial resuscitation and ICU care. Multiple organ failure (MOF), acute lung injury (ALI), sepsis and pneumonia are among the most common causes of morbidity and mortality for trauma patients surviving the initial phase.<sup>34,36-39</sup> The development of these post-injury complications may depend on several mechanisms.

**Figure 1:** Secondary organ injury after major trauma



*Injury severity, genetic predisposition, and surgical intervention are the key determinants of the magnitude of inflammatory response, which is mediated through (1) tissue damage and hypoxia causing release from necrotic cells of intracellular trauma alarmins, such as mitochondrial DNA and nuclear HMGB1 proteins; (2) transfusion of allogenic blood and blood components; (3) pain through putative descending neurological mechanisms; and (4) fat emboli causing local hypoxia, and platelet and endothelial activation. ALI=acute lung injury. DAMPs=danger-associated molecular patterns. From Balogh ZJ et al <sup>40</sup>, reproduced with permission.*

Systemic inflammatory response syndrome (SIRS) can be induced by injury and in the complex pathophysiology of the poly-traumatised patient there is a growing understanding of the multi-faceted deterioration in the immune response after multiple trauma (fig 1). Dysregulation of the immune response has been suggested to contribute to many of the complications seen after a severe

trauma.<sup>40-42</sup> Infection is one way where innate immunity is activated by pathogen-associated molecular patterns (PAMP) expressed by invading microorganisms. PAMPs are a diverse set of microbial molecules that alert the organism to intruding pathogens. However, even without shock or infection, tissue injury can lead to release of endogenous damage-associated molecular patterns (DAMPs) that activate innate immunity and lead to SIRS.<sup>42,43</sup> DAMPs are the equivalent of PAMPs but are endogenous molecules e.g. high mobility group box 1, S100 proteins and mitochondrial DNA.<sup>44</sup>

### Multiple organ failure

Despite an improved survival in general for the severely injured patient, MOF remains the leading cause of late post-injury mortality, morbidity and extended intensive care length of stay. The incidence of MOF after trauma varies considerably in the literature. Numbers between 15-47% are reported in the literature.<sup>31,36,45-47</sup> These discrepancies may to a large extent be explained by different definitions of organ failure and MOF.<sup>48</sup> Two of the most common scoring systems for organ failure are displayed in table 1 and 2.

**Table 1.** Sequential organ failure assessment score (SOFA).<sup>49</sup>

SOFA score	0	1	2	3	4
<b>Respiratory</b>					
PaO <sub>2</sub> /FiO <sub>2</sub> (mmHG)	> 400	≤ 400	≤ 300	≤ 200 with respiratory support	≤ 100 with respiratory support
<b>Coagulation</b>					
Platelets x 10 <sup>3</sup> /mm <sup>3</sup>	> 150	≤ 150	≤ 100	≤ 50	≤ 20
<b>Liver</b>					
Bilirubin (mg/dl)	< 1.2	1.2-1.9	2.0-5.9	6.0-11.9	≥ 12.0
(umol/l)	< 20	20-32	33-101	102-204	>204
<b>Cardiovascular</b>	No hypotension	MAP < 70 mm Hg	Dopamine ≤ 5* or dobutamine##	Dopamine > 5* or epinephrine ≤ 0.1* or norepinephrine ≤ 0.1*	Dopamine > 15* or epinephrine > 0.1* or norepinephrine > 0.1* or levosimendan# or vasopressin#
<b>Central Nervous System</b>					
Glasgow Coma Scale	15	13-14	10-12	6-9	< 6
<b>Renal</b>					
Creatinine (mg/dl)	< 1.2	1.2-1.9	2.0-3.4	3.5-4.9	> 5.0
(umol/l)	< 110	110-170	171-299	300-440	> 440
or urine output				or < 500 ml/day	or < 200 ml/day

SOFA score according to the guidelines from Swedish intensive care registry.<sup>50</sup> \*Doses given are in ug/kg per min  
# Any dose.

In this thesis organ failure was defined as a SOFA score  $\geq 3$  in one domain during at least one day during the ICU stay. MOF was defined as organ failure in two or more organ systems simultaneously during at least one day during the ICU stay.

**Table 2.** Denver post-injury multiple organ failure score.<sup>51,52</sup>

Dysfunction	Grade 0	Grade 1	Grade 2	Grade 3
A: pulmonary P/F ratio	$X > 250$	$250 \geq X > 200$	$200 \geq X > 100$	$X \leq 100$
B: renal creatinine level, mg/dL	$X \geq 1.8$	$1.8 < X \leq 2.5$	$2.5 < X \leq 5.0$	$X > 5.0$
C: hepatic bilirubin level, mg/dL	$X \leq 2.0$	$2.0 < X \leq 4.0$	$4.0 < X \leq 8.0$	$X > 8.0$
D: cardiac	No inotropes	Minimal inotropes	Moderate inotropes	High inotropes

**MOF score** = A + B + C + D not caused by chronic disease. Pulmonary score is based on PaO<sub>2</sub> to FiO<sub>2</sub> ratio with values adjusted for altitude. Cardiac score: minimal inotropes = dopamine level less than 5 ug/kg/min; moderate inotropes = dopamine 5-15 ug/kg/min; high inotropes = dopamine greater than 15 ug/kg/min. **MOF** = MOF score  $> 3$ .

### Acute lung injury

Pulmonary complications represent an important burden after major trauma, accounting for one third of all disease complications and leading to incremental risk of mortality.<sup>53,54</sup> In the trauma setting the pathogenesis may stem from direct injury to the lung from severe contusions or indirect mechanisms by means of systemic inflammation and sepsis.

### Sepsis

Together with organ dysfunction, sepsis has been advocated as a major contributor to post-injury ICU-related morbidity and mortality.<sup>38,55</sup> Trauma-induced changes in immune response, contamination of wounds, physiological derangement, excessive surgery and invasive procedures may all contribute to post injury infections and sepsis. Data on post-injury sepsis is limited in the literature and the reported incidence varies notably, partly due to differences in definitions of sepsis. Figures from a few percent up to 25% are described.<sup>36,38,56</sup> Despite variations in incidence and definitions a consistent finding in these studies is that sepsis markedly affects the clinical course and mortality.

### Pneumonia

Trauma patients are highly susceptible for post-injury infections, which are a major threat to recovery for this patient group.<sup>34,39,57</sup> Pneumonia is more common among trauma patients requiring ICU treatment than among other ICU patients, despite trauma patients being younger and healthier.<sup>58</sup> Furthermore, pneumonia is a common infectious complication in multiple injured patients with an incidence reaching 30%.<sup>59-61</sup> Previous studies have also shown that post-injury

pneumonia results in prolonged ICU and hospital stay, increased health care costs and delayed recovery.<sup>57,62,63</sup>

## HOST FACTORS

### *Comorbidity*

Comorbidity has been advocated as an important risk factor for post-injury morbidity and mortality but the strength of this association seems to vary depending on injury severity, age and time since admission.<sup>64-66</sup> The prevalence of comorbidity among patients treated after trauma varies in the literature; figures between 30–50% are reported. The description and measurement of preexisting conditions varies in the literature and some examples are; status by the absence/presence of any of a list of predefined diseases, the total number of preexisting conditions present and the Charlson comorbidity Index.<sup>65,67,68</sup>

### *Gender*

The impact of gender on post-injury complications and mortality has been debated. Divergent results concerning the influence of gender on patient outcome after trauma have been reported in previous clinical studies.<sup>69-73</sup> Experimental studies show more consistent results with superior survival for female gender, an effect that has been suggested to be linked to female vs. male sex steroids.<sup>74-76</sup>

### *Socioeconomic status*

The correlation between disparities in health and socioeconomy are well known<sup>77-79</sup> and constitute a challenge for public health systems. The distribution of comorbid conditions in trauma populations has previously been addressed<sup>65,80</sup> but not the strength of association between comorbidity and the risk for trauma. Psychiatric disorders and substance abuse (alcohol or drugs) have been shown to increase the risk for mortality and morbidity after trauma but not to which extent they together with socioeconomic status (SES) influence the risk of becoming a trauma victim.



## **AIMS OF THE STUDY**

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General aim:

To investigate risk factors for adverse outcome in a Scandinavian urban trauma population and risk factors for becoming a trauma victim.

Our specific aims were:

- To describe the incidence and severity of post-injury complications and mortality as well as to identify and differentiate risk factors for these events in ICU-treated trauma patients.
- To investigate the influence of gender and comorbidity on 30-and 360-day survival in a Scandinavian trauma cohort and to evaluate survival over time in relation to the general population
- To report the overall incidence of pneumonia in ICU-treated trauma patients and to investigate risk factors for development post-injury pneumonia following severe trauma.
- To study the influence of socioeconomic factors and comorbidity on the risk of becoming a trauma victim.





## MATERIAL AND METHODS

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### REGISTRIES

#### *Registries at the Karolinska University Hospital*

In January 2005 the trauma registry at Karolinska was established and data has been consecutively collected on patients that meet the criteria for inclusion, which are trauma team activation as well as patients admitted without trauma team activation but found to have an injury severity score >9. Patients classified as dead after brief resuscitation following arrival are also included. Isolated fractures of the upper or lower extremity, chronic subdural hematoma, drowning, burn injury, and hypothermia without concomitant trauma are not recorded in the trauma registry. Entered data includes variables to describe patient characteristics, injury severity (ISS, NISS) process data (prehospital and hospital) e.g. prehospital transport times and time to first computed tomography scan, system characteristics such as; type of transportation, type of first key emergency intervention at hospital and inter-hospital transfer etc. and outcome variables e.g. Glasgow outcome scale at discharge from hospital and survival status 30 days after injury.

Since March 2007, trauma patients treated in the central ICU for more than 24 hours have been registered in a trauma ICU database. During the ICU stay all relevant data needed to score patients into different scoring systems e.g. Acute physiology and chronic health evaluation II (APACHE II), SOFA and organ dysfunction such as ALI are entered once daily.

#### *The Swedish national inpatient register*

The Swedish national inpatient register (IPR) is part of the National Patient Register. It was launched in 1964 (psychiatric diagnoses from 1973) with complete coverage since 1987. Currently, more than 99% of all somatic (including surgery) and psychiatric hospital discharges are registered in the IPR. The information in IPR consists of several variables, which can be divided into four groups; patient related data, data about the caregiver, administrative and medical data. Diagnoses in the IPR are coded according to the Swedish version of WHO's International Classification of Disease (ICD) system, first introduced in 1964. ICD 10 was introduced in 1997. The long follow up makes the register particularly suitable for large-scale population-based research.<sup>81,82</sup>

#### *The cause of death register*

The causes of death are classified according to the English version of the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10), including the official updates published on the World

Health Organization's (WHO) website. It contains dates and causes including all deaths among Swedish residents.<sup>17</sup>

### *Total population register*

Statistics Sweden is responsible for official statistics regarding the Swedish census and manages the total population register. It is the register for the population of Sweden, and contains information about persons who live in the country and where they live. Name, identity and family relationships are also registered.<sup>83</sup>

### *The longitudinal integration database for health insurance and labour market studies (LISA)*

Statistics Sweden's database the longitudinal integration database for health insurance and labour market studies (LISA) includes all individuals 16 years of age and older that were registered in Sweden as of December 31 for each year. The database integrates existing data from the labour market, educational and social sectors and is updated each year with a new annual register. The individual is the primary object in LISA, but connections to family, companies and places of employment are also available.<sup>84</sup>

## STUDY DESIGN AND OUTCOME MEASURES

Study design as well as outcome measures are summarised in table 3.

**Table 3.** Study design and outcome measures.

Study	I	II	III	IV
Design	Observational cohort study	Observational cohort study	Observational cohort study	Observational case – control study
Study population	Cohort of ICU-treated trauma patients February 2007-November 2008	Prospectively registered trauma cohort January 2005-August 2008	Cohort of ICU-treated trauma patients February 2007-July 2011	Prospectively registered trauma cohort 2005-2010
Sample size	164	4051	322	Cases 7382 Controls 36760
Registry used	ICU-trauma database Trauma registry	Trauma registry Cause of death registry Inpatient registry Statistic Sweden	ICU-database Local infection surveillance database Trauma registry	Trauma registry Cause of death registry Inpatient registry LISA Total population register
Follow up	30 days	360 days	10 days	-
Outcome measures	Risk factors for ICU complications	Risk factors for 30 and 360 day mortality SMR.	Risk factors for pneumonia	Event: Trauma Exposure: SES, comorbidity

*Study I*

This study was conducted on trauma patients admitted to the central ICU at the Karolinska University Hospital, Solna following initial resuscitation and, where indicated, interventional surgery in the trauma unit. Patients 15 years or older with an expected ICU stay of more than 24 hours were included between February 2007 and November 2008. Pre-hospital and baseline data from the trauma unit were collected retrospectively from the trauma registry and patient records. During the ICU stay all relevant data needed to score patients into different scoring systems and definitions were entered once daily into a database by a research nurse. Data were collected until ICU discharge or death which ever occurred first. For patients discharged alive from the ICU data on 30- and 90-day mortality were taken from patient records.

*Study II*

The study population consisted of individuals registered in the trauma registry between January 2005 and August 2008. Patients 15 years or older were included. Data from the trauma cohort were linked to The Swedish National Inpatient Register and The Cause of Death Register. The total study population included 4051 patients. All included patients had complete data on 30- and 90-day survival. Information on date of death was retrieved from the national registry four months after the end of the study period, yielding complete data on 360-day survival for 3242 patients. Age and sex specific mortality rates were obtained from Statistics Sweden regarding the general population and standardised mortality ratio (SMR) was used in order to evaluate survival in relation to the general population

*Study III*

The study cohort consisted of trauma patients admitted to the central ICU at the Karolinska University Hospital, Stockholm between February 2007 and July 2011. Patients admitted from other units than the Karolinska trauma unit were excluded. No other exclusion criteria were applied. Pre-hospital and baseline patient data were retrieved from the trauma registry and patient records. During the ICU stay all relevant data needed to assess patients in different scoring systems were entered once daily into a database by a research nurse. In addition, data necessary to identify pneumonia cases during there first 10 days in the ICU were retrieved from a local infection surveillance database. Data were collected until ICU discharge or death. Mortality for patients discharged alive was assessed at 30 days post injury. Pneumonia was defined in accordance with criteria used by the Swedish intensive care registry.

#### Study IV

In this case-control study, cases (n = 7382) were defined as all patients 15 years or older registered in the trauma registry with a first trauma admission between January 2005 and December 2010, and with a valid personal identity number. A random selection of 36760 age, gender and municipality matched controls were extracted from the total population registry. Data were linked to the Swedish national inpatient register, the cause of death register and LISA.

#### STATISTICAL ANALYSIS

P-values < 0.05 were considered statistically significant. Comparisons of continuous variables were performed with the Mann Whitney U-test in *study I and II*. Differences between categorical variables were evaluated with the Pearson Chi-square test in *all studies*.

In *study I and II* data were analysed by univariate and multivariable logistic regression in order to adjust for possible confounders and to identify independent risk factors for complications in the ICU and death. Results are presented as odds ratios (OR) with corresponding 95 % confidence intervals.

Risk factors for 30- and 31-360-day post-injury mortality were evaluated using multivariable logistic regression models and multivariable Cox regression models in order to adjust for possible confounders in *study II*, results are presented ORs or hazards ratios (HR) with corresponding 95 % confidence intervals. In the *same study* standard mortality ratio was calculated as the ratio between the observed number of deceased persons in the study population and the expected number of deaths up to one year post injury. In order to investigate the proportional hazard assumption we divided the follow up time into different intervals (31-90 days, 91-180 days and 181-360 days post injury). We could not find any significant differences in the hazards ratios between the time intervals using the Wald test (*study 2*).

The relative risk of trauma in relation to education, income and comorbidity was estimated in *study IV* by conditional logistic regression and expressed as ORs with corresponding 95% confidence intervals.

## RESULTS

### Study I

During the 21 month period a total of 164 patients were included in the study. General characteristics of the patient cohort are shown in table 4.

**Table 4.** General characteristics of the patient cohort

Parameter	
Age, years	40 (26-58)
Female/male, n	30/134
History of comorbidity, %	43.8
Mechanism of injury, %	
Transport total	52.4
Fall	21.3
Machinery	7.9
Violence	9.8
Self inflicted	7.3
Others	1.2
Penetrating trauma, n (%)	15/164 (9.1)
ISS, score	24 (17-33)
NISS, score	29 (22-43)
Rescue time, minutes	47 (36-58)
Admission SAP, mmHg	129 (107-150)
Admission GCS, score	14 (8-15)
Admission plasma glucose, mM	8.5 (7.0-10.4)
Intoxicated by ethanol, n (%)	51/158 (32.2)
Massiv transfusion ( $\geq 10$ blood units/24) n (%)	23 (14.0)
Fluid load 24h, litres	5.5 (4.0-7.2)
APACHE II, score	15 (10-21)
SOFA max, score	7 (5-10)
Duration of mechanical ventilation, days	2 (0-6)
ICU length of stay, days	3.1 (1.9-6.5)
30 day post-injury mortality, count (%)	17/164 (10.4)

*Injury severity score (ISS), new injury severity score (NISS), systemic arterial blood pressure (SAP), millimolar (mM), Glasgow Coma Scale (GCS). Data presented as median (25<sup>th</sup>-75<sup>th</sup> percentile) or count (n) and percent as depicted in the table.*

A main finding was that the outcome parameters were not uniformly affected by the different risk factors. The incidence of MOF was found to be 40.2 % and the most frequent organ system failing was respiration followed by circulation and CNS. Age, alcohol, massive transfusion, ISS > 24 and significant head injury (AIS  $\geq 3$ ) were found to be independent risk factors. MOF was the only of the studied outcome parameters where alcohol was an independent risk factor. For patients who developed ALI (25.6%) a subgroup of these patients (33/164, 20.1%) also

fulfilled the criteria of acute respiratory distress syndrome (ARDS). Massive transfusion and severe injury were found to be independent risk factors for ALI. One third of the patients developed severe sepsis and among them, age, aggressive fluid load and high ISS were independent risk factors. The mortality at 30 days post injury was 10.4% and age, prolonged rescue time as well as significant head injury (AIS  $\geq 3$ ) proved to be independent risk factors. No deaths were noted between 30 and 90 days post injury *in study I*.

**Table 5.** Demographic, admission and initial management parameters in relation to multiple organ failure and acute lung injury.

	all	Multiple organ failure		Acute lung injury	
	n (%)	n (%)	p	n (%)	p
count	164	66/164 (40.2)		42/164 (25.6)	
Age > 55	46/164 (28.0)	26/46 (56.5)	.008	15/46 (32.6)	.200
Female gender	30/164 (18.3)	11/30 (36.7)	.658	5/30 (16.7)	.214
Ethanol > 0 mmol/L	51/158 (32.2)	29/51 (56.9)	.006	15/51 (29.4)	.493
Rescue time > 60 min	33/156 (21.1)	17/33 (51.5)	.012	10/33 (30.3)	.490
GCS 9-13	22/164 (13.4)	8/22 (36.4)	.000	9/22 (40.9)	.072
GCS 3-8	53/164 (32.3)	38/53 (71.7)		16/53 (30.2)	
SAP < 90 mmHg	20/164 (12.2)	14/20 (70.0)	.004	8/20 (40.0)	.116
$\geq 10$ blood units	23/164 (14.0)	14/23 (60.9)	.030	10/23 (43.5)	.034
Fluid load >5-10 L	73/164 (44.5)	35/73 (47.9)	.032	20/73 (27.4)	.049
Fluid load > 10 L	14/164 (8.5)	8/14 (57.1)		7/14 (50.0)	
ISS >24	80/164 (48.7)	46/80 (57.5)	.000	31/80 (38.8)	.000
Head injury AIS $\geq 3$	59/164 (36.0)	35/59 (59.3)	.000	20/59 (33.9)	.068
Dead at 30 days	17/164 (10.4)	15/17 (88.2)	.000	6/17 (35.3)	.334

*Categorical parameters in relation to the total cohort for multiple organ failure, acute lung injury. Fluids and blood transfusions are the cumulative amount administered during the initial 24 hours after trauma.*

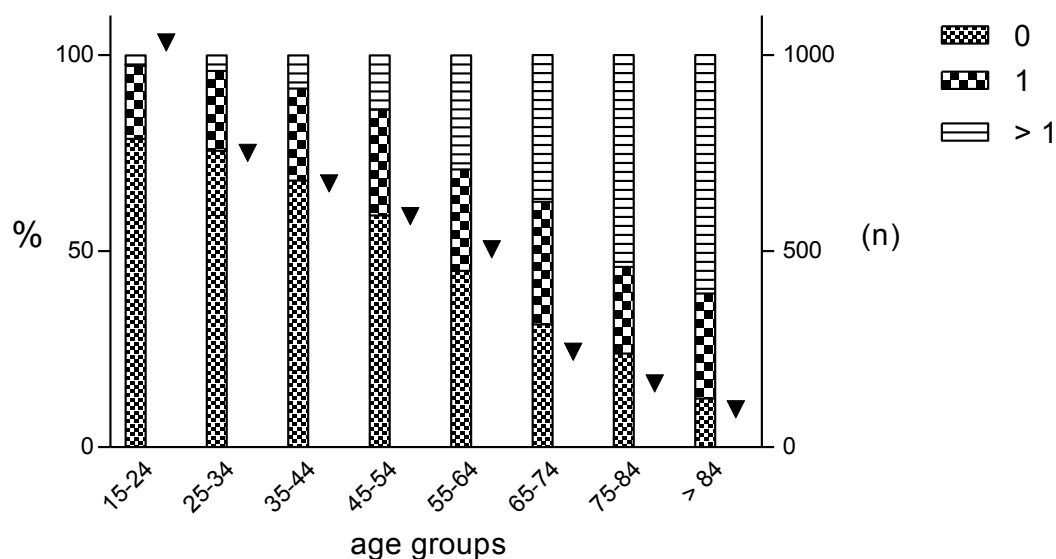
**Table 6.** Demographic, admission and initial management parameters in relation to severe sepsis and 30 day post-injury mortality.

	all	Severe sepsis	30 day mortality		
	n (%)	n (%)	p	n (%)	p
count	164	51/164 (31.1)		17/164 (10.4)	
Age > 55	46/164 (28.0)	20/46 (43.5)	.032	10/46 (21.7)	.003
Female gender	30/164 (18.3)	7/30 (23.3)	.309	7/30 (23.3)	.010
Ethanol > 0 mmol/L	51/158 (32.2)	18/51 (35.3)	.496	4/51 (7.8)	.511
Rescue time > 60 min	33/156 (21.1)	14/33 (42.4)	.083	7/33 (21.2)	.032
GCS 9-13	22/164 (13.4)	5/22 (22.7)	.009	1/22 (4.5)	.002
GCS 3-8	53/164 (32.3)	25/53 (47.2)		12/53 (22.6)	
SAP < 90 mmHg	20/164 (12.2)	12/20 (60.0)	.003	3/20 (15.0)	.468
≥ 10 blood units	23/164 (14.0)	13/23 (56.6)	.004	4/23 (17.4)	.233
Fluid load >5-10 L	73/164 (44.5)	30/73 (41.1)	.000	6/73 (8.2)	.691
Fluid load > 10 L	14/164 (8.5)	9/14 (64.3)		2/14 (14.3)	
ISS >24	80/164 (48.7)	39/80 (48.8)	.000	13/80 (16.2)	.016
Head injury AIS ≥ 3	59/164 (36.0)	23/59 (39.0)	.102	12/59 (20.3)	.002
Dead at 30 days	17/164 (10.4)	9/17 (52.9)	.040		

*Categorical parameters in relation to the total cohort for severe sepsis and mortality. Fluids and blood transfusions are the cumulative amount administered during the initial 24 hours after trauma.*

## Study II

In the cohort of 4051 trauma patients treated between January 2005 and August 2008 the median age was 38 years and a pre-injury history of comorbidity was noted in 37.3% of the patients. The proportion of comorbidities increased with age (figure 2). Mortality at 30-, 90- and 360-day after injury were 5.2%, 6.1% and 9.3%, respectively. Analyses with multivariable logistic regression for death at 30-day post injury revealed that age over 55 was an independent risk factor, with a marked increase for the oldest patients (OR 227.5 for patients > 84 years). In addition, penetrating injury, SAP < 90mmHg, injury severity and low GCS on admittance were independent risk factors but not gender.

**Figure 2.** Distribution of comorbidities in different age groups.

Black triangles depict the number of patients within each age group. The bars represent the distribution of comorbidities within each age group. 0 = no comorbidities, 1 = one comorbidity, > 1 = more than one comorbidity.

In the analysis of patients surviving beyond 30-days post injury, male gender and comorbidity proved to be independent risk factors. Adjusted HR for male gender and comorbidity regarding the time period 31-360 days post injury were 3.0 (95 % CI 1.7-5.3) and 3.4 (95% CI 1.9-6.1) respectively (table 7). In the age stratified analysis, the Cox regression model revealed a significant influence of male gender only among patients 55 years or older. The influence of comorbidity was significant in both age groups (table 7). SMR was markedly increased for both women and men during the first 30 days 64.4 (95% CI 50.1-81.6) vs. 80.8 (95% CI 68.5-94.7). For the time period 31-90 days post-injury SMR began to decline for both women and men 4.7 (CI 2.1-9.3) vs. 11.3 (CI 7.8-15.9). In the later phase, 91-360 days post-injury SMR was normalised for women but still significantly increased for men 1.2 (95% CI 0.6-2.3) vs. 3.8 (95% CI 2.8-5.1).



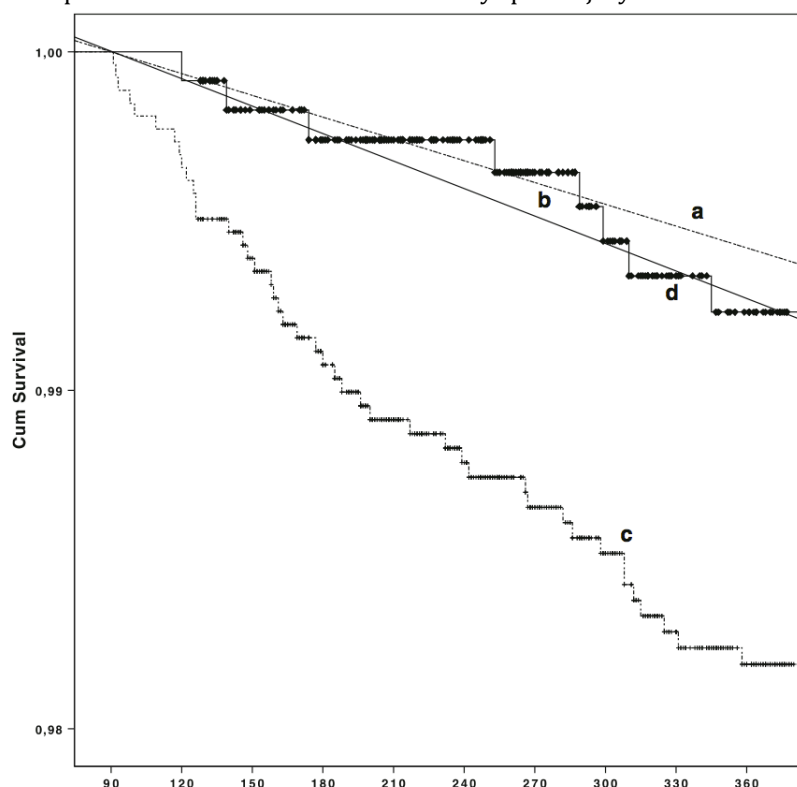
**Table 7.** Cox regression analysis of 31-360 day survival.

Hazard Ratios (95% CI)				
	Unadjusted		Adjusted	
<b>Gender</b>	<b>All</b>		<b>All</b>	
Female	ref		ref	
Male	2.2 (1.3-3.9)		3.0 (1.7-5.3)	
	<b>&lt; 55 year</b>	<b>≥55 year</b>	<b>&lt;55 year</b>	<b>≥55 year</b>
Female	ref	ref	ref	ref
Male	2.8 (0.8-9.6)	2.4 (1.3-4.5)	2.5 (0.7-8.6)	3.2 (1.6-6.2)
<b>Comorbidity</b>	<b>All</b>		<b>All</b>	
No	Ref		ref	
Yes	8.2 (4.8-14.1)		3.4 (1.9-6.1)	
	<b>&lt; 55 year</b>	<b>≥55 year</b>	<b>&lt;55 year</b>	<b>≥55 year</b>
No	ref	ref	ref	ref
Yes	4.7 (2.0-11.1)	4.5 (2.1-9.4)	3.6 (1.5-8.8)	3.4 (1.6-7.2)

*Hazard Ratios for male gender and comorbidity unadjusted and adjusted for age, type of violence, systemic arterial blood pressure (SAP), injury severity score (ISS) and Glasgow coma scale (GCS). Data presented as hazard ratios with 95% confidence intervals (CI). Analysis of all patients and stratified by age (< 55 and ≥ 55 years respectively).*

The relation between the study population and an age matched general population for survival for both genders over time beyond 90 days is displayed in figure 3.

**Figure 3.** Kaplan-Meier survival curves 91-360 days post injury.



*Reference lines of survival over time for an age matched male (a) and female (b) general population. Kaplan-Meier survival curves from 91 to 360 days post injury for male (c) and female (d) trauma patient. Short vertical lines depict censored cases.*

### Study III

322 patients admitted to the ICU were included in the study. A majority of the patients were male (78%) and the median age was 41 years. One fifth of the patients were intubated in the field. On admission to the trauma unit 52 (16%) patients were in shock with a systolic blood pressure < 90mmHg. The overall degree of injury was high with a median ISS of 24, and more than half of the patients presented with major chest trauma (AIS  $\geq$  3). Median ICU and hospital length of stay were three and 16 days respectively, whereas 30-day post-injury mortality was 9%. Eighty-five (26%) patients developed pneumonia in the ICU within 10 days after injury. VAP occurred in 45 (14%) of the patients. The clinical course was markedly different between patients with and without pneumonia. For patients with pneumonia, ICU and hospital length of stay were nearly four and two times longer, respectively. 30-day mortality did not differ statistically between the two groups. Multivariable logistic regression revealed that GCS 3-8 was identified as an independent risk factor (table 8).

**Table 8.** Logistic regression analysis of risk factors for post-injury pneumonia within 10 days after trauma.

	Post-injury pneumonia	
	OR (95% CI)	
	Univariate	Multivariable
Age > 55	1.3 (0.7-2.2)	1.6 (0.9-3.0)
Male gender	1.3 (0.7-2.4)	1.5 (0.8-3.0)
Intubated at scene	1.9 (1.1-3.4)	1.0 (0.5-2.3)
SAP < 90 mmHg	2.0 (1.1-3.7)	1.1 (0.5-2.3)
GCS 3-8	2.8 (1.6-4.8)	2.4 (1.2-4.9)
Major surgery	2.1 (1.2-3.7)	1.6 (0.8-3.4)
Massive transfusion	1.8 (1.0-3.3)	1.2 (0.6-2.5)
ISS > 24	2.5 (1.2-5.3)	1.9 (0.8-4.2)

In 42 of the 85 cases of pneumonia the diagnosis was defined by significant growth of at least one pathogen in a sample from the lower respiratory tract. *Enterobacteriaceae* and *Staphylococcus aureus* were the most common pathogens for both early and late pneumonia. Three out of four isolates of *Streptococcus pneumoniae* were obtained within the first 48 hours after admission, whereas all isolates of *Pseudomonas spp.* and *Acinetobacter spp.* were obtained after > 48 h of admission.

## Study IV

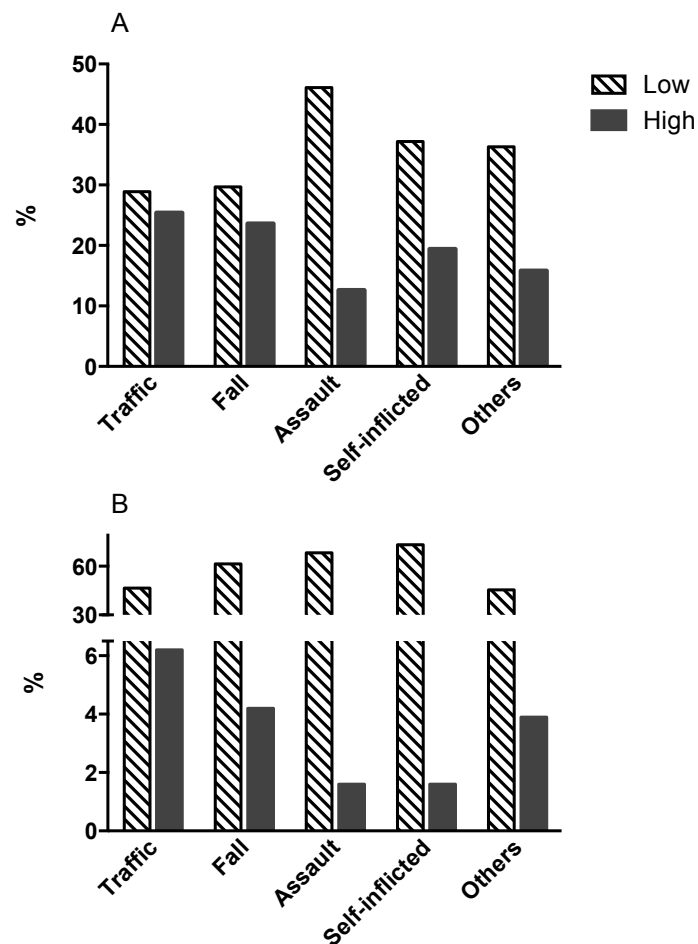
Characteristics of the population are shown in table 9.

**Table 9.** Characteristics for study population. All patients.

	All	
	Trauma (n= 7382)	Controls (n=36760)
Sex		
Female n (%)	2297 (31.1)	11436 (31.1)
Male n (%)	5085 (68.9)	25324 (68.9)
Age, years, median (IQR)	39 (25-55)	39 (25-55)
ISS, median (IQR)	5 (2-14)	
Level of education		
Low n (%)	2120 (31.6)	7932 (23.4)
Medium n (%)	3049 (45.5)	14592 (43.0)
High n (%)	1534 (22.9)	11407 (33.6)
Income		
Low n (%)	3818 (54.3)	16636 (47.2)
Medium n (%)	2878 (40.9)	15687 (44.5)
High n (%)	341 (4.8)	2896 (8.2)
History of comorbidity, count (%)	2869 (38.9)	9115 (24.8)
Comorbidity		
Psychiatric diagnosis	989 (13.4)	2017 (5.5)
Substance abuse diagnosis	1029 (13.9)	1053 (2.9)
Somatic diagnosis	1805 (24.5)	7142 (19.4)

A lower proportion of the trauma patients had achieved a university education compared with the controls, one fifth compared to one third. There was a higher proportion of individuals with low income and comorbidities among trauma patients, this relationship remained unchanged when the study population was restricted to individuals with an ISS score of more than 15 ( $p < .0001$  and  $p < .0001$  respectively). Trauma patients had been treated for psychiatric, substance abuse and somatic diagnoses to a higher extent than the controls. The distribution pattern of injury mechanisms differed largely with the level of education and income (figure 4). Low education and income were commonly noted among victims of assault.

**Figure 4A and 4B.** Proportions of low and high levels of education (a) and income (b) in relation to mechanisms of injury.



Striped bars represent low level and filled bars high level of education and income respectively. Distribution of proportions significantly different by chi-square test.  $p = <0.001$  and  $p = <0.001$  respectively.

In the conditional logistic regression analysis of the total cohort, level of education, income and comorbidity (divided in to psychiatric, substance abuse and somatic diagnoses) were all independent risk factors for trauma (table 10). When analysing the severely injured patients separately the results did not alter except for somatic diagnoses not being a risk factor (table 10). Substance abuse increased the risk for trauma more than three times in the severely injured.

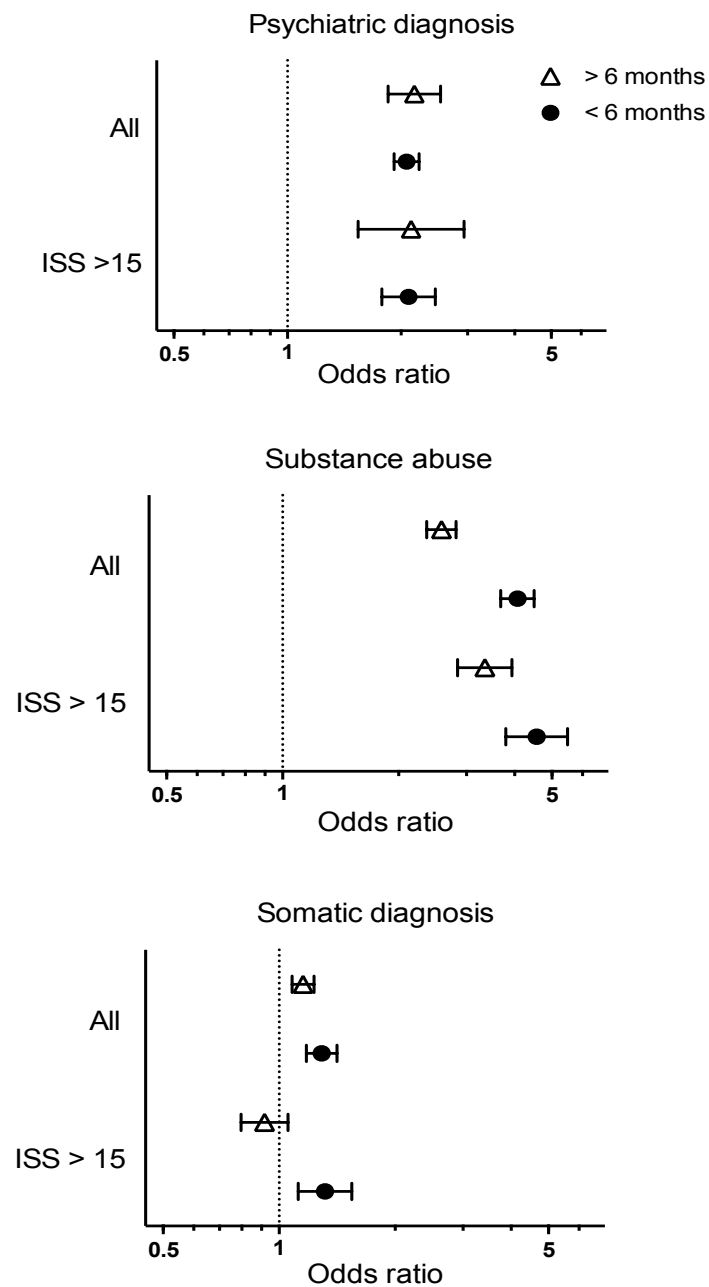
**Table 10.** Conditional logistic regression analysis of level of education, income and comorbidity as risk factors for trauma.

	Odds Ratio (95% CI)		Odds Ratio (95% CI)	
	All		ISS >15	
	unadjusted	adjusted	unadjusted	adjusted
Level of education				
Low	1.8 (1.7-1.9)	1.5 (1.4-1.6)	1.7 (1.5-1.9)	1.4 (1.2-1.6)
Medium	1.5 (1.4-1.5)	1.3 (1.3-1.4)	1.5 (1.3-1.7)	1.3 (1.1-1.5)
High	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Income				
Low	1.8 (1.6-2.0)	1.2 (1.1-1.3)	2.0 (1.6-2.6)	1.3 (1.1-1.7)
Medium	1.5 (1.3-1.6)	1.2 (1.1-1.4)	1.7 (1.3-2.2)	1.4 (1.1-1.8)
High	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Comorbidity				
Psychiatric diagnosis	2.1 (2.0-2.3)	1.5 (1.4-1.6)	2.1 (1.8-2.4)	1.4 (1.2-1.6)
Substance abuse diagnosis	3.3 (3.1-3.5)	2.6 (2.4-2.8)	3.9 (3.4-4.4)	3.4 (3.0-4.0)
Somatic diagnosis	1.3 (1.2-1.3)	1.1 (1.1-1.2)	1.2 (1.1-1.3)	1.0 (0.9-1.1)

*Data presented as odds ratios with 95% confidence intervals (CI). Analysis of all patients and stratified for injury severity (ISS > 15).*

In addition, we analysed the impact of recent (six months prior to injury) treatment for comorbid conditions (figure 5). A recent treatment for substance abuse or a somatic disorder significantly increased the risk of trauma.

**Figure 5.** Impact of treatment for a psychiatric, substance abuse or somatic disorder within six months on the risk of trauma.



*The figure displays how the adjusted odds ratio (95% CI) for trauma is affected by having the most recent treatment within six months (open triangles) as compared with before six months (closed circles) of the time of injury for all and severely injured (ISS > 15) patients respectively.*





## DISCUSSION

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The global burden of injuries is considerable and there are large regional differences in the world in terms of morbidity and mortality. Developing countries account for a high proportion but also in the developed countries significant numbers of complications and regional differences are noted.<sup>9,85</sup> Trying to describe and study these differences and subsequently analyse their nature is one of the cornerstones in epidemiologic research. But what is epidemiology?

The word epidemiology comes from the Greek words epi, meaning "on or upon," demos, meaning, "people," and logos, meaning "the study of." One useful and distinct definition of epidemiology is, *the study of the distribution and determinants of disease frequency in a human population*.<sup>86</sup>

### *Study design*

There are several types of design strategies used in epidemiology research. They can be divided in to two main types, intervention (experimental) or observational studies. In an intervention study the investigator has the opportunity to modulate the exposure assigned to study participants, in the clinical setting most often represented by randomized control trials (RCTs).<sup>87</sup> Ecological, cross-sectional, cohort and case-control studies represent different observational study designs. RCTs are often considered to be the gold standard of clinical and epidemiological studies and considered as providing the most valid scientific results. However, it has been shown that well-designed observational studies can be at least as valid as randomised trials.<sup>88,89</sup>

In the studies in this thesis, data from both local and national registries were used to investigate risk factors to become a trauma victim and various risk factors for complications and death after trauma. We had the opportunity to use the Swedish personal identity number, which provides a unique tool for linking data from the trauma registry to validated national registries in order to get a data set including information on e.g. income, level of education, pre-existing medical conditions and long term outcome.<sup>90</sup> All of the studies in the thesis are observational studies, *study I-III* were based on cohort design and *study IV* was a case-control design. In *study I and III* we used data on trauma patients admitted to the central ICU during different time periods. *Study II and IV* are based on patients registered in Trauma registry of Karolinska Hospital, Stockholm, but diverse time periods.

## *Validity*

In an epidemiological study, we do not have the opportunities that exist in a laboratory setting to control for factors that may influence the results. Do we measure what we want to measure? Are the study results assignable to another populations? In an epidemiologic investigation, evaluation of validity, both internal and external, requires consideration of the role of bias, confounding and chance as alternative explanation for the study findings.

Internal and external validity are the two primary types of validity. Internal validity is a prerequisite, but does not guarantee, external validity. Validity refers to the accuracy of a measure. In general, a measure is valid when it measures what it is designed to measure. Internal validity is the degree to which an observation is correct for the particular group being studied. External validity or generalizability refers to the validity of the inferences drawn to individuals not included in the study.

## *Generalizability*

Are our results applicable to other trauma populations? Our studies are single centre studies that can be considered to reduce the generalizability, nevertheless the trauma cohorts in these studies are largely similar to those described in other studies. In *study I and III*, the cohorts consisted of ICU-treated trauma patients, as expected, with a higher proportion of severely injured patient compared with the cohorts in *study II and IV*. In *study I and III*, one fifth of the patients were females and ninety percent had blunt trauma as the major type of injury. The patients were relatively severely injured with a median ISS of 24, this is of the same magnitude as in other similar studies.<sup>47,61,91,92</sup> In the cohorts of trauma patients in *study II and IV*, there were a dominance of male gender and a majority of younger patients with an mean age of approximately 40 year and one third of the patients exhibiting some pre-existing medical condition. Thus, the demography is much in line with several other trauma studies.<sup>13,93-95</sup>

## *Bias*

Bias may be defined as a systematic error that results in an inappropriate estimate of the association between exposure and outcome.<sup>86</sup> Two general classes of systematic error are selection and information bias. Selection bias refers to any error that arises in the process of identifying the study population and information bias is the systematic errors in the measurements of information on exposure or outcome. Selection bias can be an issue in case-control studies. Public health care in Sweden is accessible for all resident and no trauma patients are treated in the private sector. In addition, we have unique opportunities to generate matched controls from the general Swedish population. In all of the studies in this thesis we have to take into account the risk of misclassification, a

type of information bias. The Swedish inpatient register has complete nation-wide coverage since 1987. The definition of comorbidity in trauma research has been a subject of debate. However, it is unlikely that different definitions would influence the estimates of interest in this thesis. In *study II* additional analysis using different stratifications and weighted comorbidity index was done to determine if it made any difference in the final estimate. We could not find such a difference.

### *Confounding*

Confounding can be explained as mixing of effects and could also be referred to as a systematic error. A confounder is associated with the disease as well as with the exposure, but not an intermediate factor in the causal pathway. In the studies in this thesis confounding was controlled for by using appropriate regression models. *A priori* clinically relevant variables were selected. Even though confounding was well accounted for, there is always a possibility of residual confounding.

### *Chance*

The error that remains after accounting for the systematic errors is referred to random error, variability in the data that we cannot readily explain. Confidence intervals and p-values are used to statistically describe random error in a study. The confidence interval reflects a range, with a certain degree of uncertainty, within the true magnitude of effect. The p-value is a function of the strength of the association and sample size and should be used with caution; a non significant p-value is not equivalent to a true null hypothesis. In *study I* random variability may affect the results due to the limited number of patients included. The large size of *study II and IV* provides a good basis to minimize the likelihood of random errors.

## **POST-INJURY MORBIDITY AND RISK FACTORS**

### *Multiple organ failure*

Multiple organ failure occurred in 40% of the patients during the ICU stay in *study I*. Although the incidence of MOF after trauma varies notably in the literature, this figure may appear relatively high. <sup>36,45,46,96</sup> Ciesla *et al* reported a 25% incidence of MOF in a US trauma patient cohort with a mean ISS of 29. <sup>96</sup> In a European study an incidence of only 12% was noted in patients with a mean ISS of 31.<sup>36</sup> As commonly found in the literature, respiratory, circulatory and CNS failure were the most frequently noted organ systems failing. <sup>97</sup> The presence of MOF markedly affected the clinical course with evident effects on ICU stay and invasive ventilator days. Even though mortality related to post-injury MOF has been shown to decrease with improved treatment, mortality was ten times higher in MOF patients compared to non MOF patients. <sup>32,36</sup> In this study we defined organ failure

according to the SOFA score definitions that previously has been validated in trauma patients.<sup>97</sup> A recent Scandinavian study also using the SOFA based MOF definitions reported a similar incidence (47%) as in our study.<sup>46</sup> The ability to detect organ failure and MOF will be dependent on the scoring system used.<sup>98</sup> A major problem today is the divergent definitions of organ failure and multiple organ failure and the current lack of a consensus on how to define these manifestations. When to start assessing post injury organ failure is another subject of debate, some argue organ failure within 48 hours after the trauma is a direct result of the trauma itself rather than “true organ failure.”<sup>32,48</sup> Including CNS in a MOF score has been debated and even said to be misleading.<sup>99</sup> The use of Marshal score (six domains including CNS) and Denver score (four domains not including CNS) were recently evaluated.<sup>48</sup> No significant differences were found between these scores in predicting mortality, ICU stay or ventilator-free days. Whether or not to include GCS/CNS is debatable and GCS is frequently used in MOF assessment in trauma studies.<sup>46,100-102</sup> In the current thesis we included GCS (as part of SOFA score) since we believe this domain to be of importance. GCS obtained prior to sedation/induction was used until further proper evaluations could be done. In *study I* we found that age, alcohol, massive transfusion, high ISS and head injury were independently associated with MOF. Transfusions have been advocated as a risk factor for post-injury MOF. Moore *et al* showed a dose response relationship between blood transfusions and later development of MOF in ICU admitted trauma patients.<sup>103</sup> This may be explained by immunosuppressive and/or neutrophil priming properties in stored blood.<sup>103</sup> Chronic alcohol abuse has been associated with an increased risk of ARDS and organ dysfunction.<sup>104,105</sup> In both clinical and experimental studies prolonged alcohol exposure prior to trauma and haemorrhage results in an increased pro-inflammatory response. Endogenous scavengers have been suggested to affect by alcohol exposure.<sup>104,106</sup> Moreover, acute alcohol intoxication has been shown to reduce tolerance to haemorrhagic shock in animals.<sup>107</sup>

### *Acute lung injury*

Acute lung injury constitutes a major clinical problem and the mortality is in the range of 38-68% in recent studies.<sup>108-110</sup> The pathogenesis of ALI among trauma patients may stem from direct injury to the lung from severe contusions or indirect mechanisms by means of systemic inflammation and sepsis. In *study I*, one quarter of the patients developed ALI during their ICU stay. This finding is consistent with other reports both in civilian trauma and at a combat support hospital.<sup>96,111</sup> Injury severity and the amount of fluid given the first 24 hours influenced the development of ALI and the clinical course was affected by the presence of ALI with a longer ICU stay and a five-fold increase in invasive ventilator days whereas no significant effect on mortality was seen. Injury severity

and massive transfusion proved to be independent risk factors in *study I*. These results are fairly consistent with other authors investigating risk factor or post-injury ARDS and ALI development.<sup>37,111,112</sup>

Pro-inflammatory substances can be administered with blood transfusions that accumulates in stored blood even after leukoreduction and this can be enhanced by transfusion of plasma-rich blood products e.g. plasma and platelets.<sup>113-115</sup> In the strategies of damage control resuscitation, with early and aggressive blood, plasma and platelet transfusion, there is an increased risk of another form of ALI, transfusion-related acute lung injury.<sup>116</sup>

The majority of the patients in *study I* developed ALI before day four. The mechanism behind this are more likely to be related to direct injury, massive transfusion or fluid administration in contrast to ALI patients with late onset (38%) day four or later, suggesting the presence of an indirect mechanism such as systemic inflammation or infection.

### *Severe sepsis*

Trauma itself can lead to contamination of wounds, physiological derangement, changes in immune response and along with excessive surgery and invasive procedures, all can contribute to post-injury infections and sepsis. During the ICU stay in *study I*, one third of the patients developed severe sepsis. A third of this group had a late onset, day four or later, whereas a majority were diagnosed on day three post injury. Development of severe sepsis had an impact on the clinical course with a several fold increase in invasive ventilator days and ICU stay as well as mortality.

Data on post-injury sepsis is limited in the literature and the reported incidence varies notably, partly due to differences in definitions of sepsis. Figures from few percent up to 25% are reported in recent studies.<sup>38,56</sup> Despite variations in incidence and definitions, a consistent finding in these studies is that sepsis markedly affects the clinical course and mortality. Age, fluid load and severe injury were found to be independent risk factors for later development of severe sepsis in *study I*. Previous studies have shown, in line with our findings, that age and severe injury are predisposing factors for post injury sepsis.<sup>38,56</sup> In contrast to the findings in our study, male gender and massive blood transfusions have previously been shown to be independent risk factors for sepsis.<sup>38,56,101</sup> Massive transfusions were not found to be an independent risk factor for severe sepsis, this is somewhat surprising considering the current literature. Blood transfusions have been suggested to induce immunosuppression and shown to be a significant risk factor for post-injury infections.<sup>103,115,117</sup> One explanation could be the limited number of patients, which makes the study too small to detect massive transfusion as an independent risk.

## *Pneumonia*

In *study I* approximately one quarter of the patients developed pneumonia during their ICU stay. The incidence of pneumonia seems to increase with severity of injury but diverging results regarding the influence of severity of injury may suggest that other factors than the extent of tissue injury *per se* may be involved in the development of post-injury pneumonia.<sup>34,60,61,118</sup> Necrotic tissues and ischemia-reperfusion injury, both common in trauma patients, affect the immune system and contribute to systemic inflammation through DAMPs and other mediators. These changes may predispose seriously injured patients to development of pneumonia.<sup>42-44,119,120</sup>

Previous studies have demonstrated an association between blood transfusions *per se* and post-injury pneumonia.<sup>121,122</sup> The age of blood has also been correlated to pneumonia in a recent study blood units older than 14 days was independently associated with post-injury pneumonia, whereas transfusion with fresh units was not.<sup>123</sup> Blood units transfused in *study III* were generally stored for less than a week. This may explain why massive transfusion was not identified as an independent risk factor for pneumonia. Definitions of pneumonia vary in this field of research and make it difficult to compare cohorts.<sup>124,125</sup> In this study we chose to include all patients fulfilling the pneumonia criteria used by the Swedish intensive care registry.<sup>50</sup>

We identified a GCS of 3-8 to be an independent predictor of pneumonia. Low GCS has previously been shown to predispose to pneumonia.<sup>61</sup> Immobilisation, aspiration, and potential subsequent atelectasis formation, rather than the decreased consciousness *per se* may contribute to the development of post-injury pneumonia. Early intubation would theoretically protect against aspiration, but has also been suggested as a risk factor in the literature. It is likely that intubation in the field reflects the state of the patient rather than being a cause of subsequent pneumonia.<sup>60,61,126</sup> In *study III*, *Staphylococcus aureus* and *Enterobacteriaceae* were the most common pathogens isolated in the lower respiratory tract. These and other pathogens identified in this study and their variation over time are in line with the results of a previous study not restricted to trauma patients.<sup>127</sup>

## Mortality

### *Study I and III*

In these studies the ICU mortalities were less than 10% in the cohorts of trauma patients with a fairly high degree of illness. These findings are well in line with other authors such as Ulvik *et al* reporting 14%<sup>46</sup> and Antonelli *et al* who reported 19% ICU mortality in a European trauma cohort.<sup>97</sup> We used 30-day post-injury mortality as an outcome parameter in *study I* in order to reduce the effects of differences in patient management between units where ICU mortality may be affected by the discharge routines. Thirty-day mortality in *study I* was consistent with several other reports of post-injury death. A recent Norwegian study showed a 30-day mortality of 17% in a trauma patient cohort with a median ISS of 25.<sup>91</sup> A large American study reported a hospital mortality of 7% with a mean ISS of 14<sup>128</sup> whereas Frink *et al* noted a 14% hospital mortality with a mean ISS of 25.<sup>101</sup>

Pre-hospital time seems to be of importance. In *study I* a rescue time over one hour proved to be an independent risk factor for mortality. Prolonged on-scene time has previously been shown to be an important factor for post-injury death. Liberman *et al* showed that despite the use of advanced life support teams yielding a longer on-scene time, mortality was higher than for basic life support teams with a shorter on-scene time.<sup>129</sup>

As expected high age and significant head injury were common among non survivors and independent risk factors for mortality. In line with a recent Scandinavian study<sup>91</sup> but in contrast to several previous studies high ISS was not an independent risk factor for death in *study I*.<sup>128 130 131</sup>

### *Study II*

The optimal follow up time of trauma victims has been subjected to debate. The commonly used outcome definition of mortality before end of care or hospital death has been criticised as a notable number of deaths may occur after discharge from hospital.<sup>12,15,93,94,132,133</sup> Moreover, discharge routines differ significantly between nations and institutions.<sup>134</sup> Thirty-day mortality, currently used by the UK trauma audit and research network (TARN)<sup>135</sup> has been advocated as an appropriate follow up time by Skaga *et al*<sup>12</sup> who noted that only 4.6% (15 of 323 death during study period) of the trauma patients in their study died between 30 and 100 days. In line with *study II* where mortality was relatively low increasing from 5.2% at 30 days to 9.3% at 360 days post injury.

A large Finnish study showed that survival of trauma patients requiring intensive care was comparable to the general population after three months post-trauma.<sup>136</sup> In contrast, other studies<sup>91,93,133</sup> highlighted an excess mortality for more than two years after the trauma data much in line with the results of *study II* suggesting that longer follow up times may be appropriate in trauma patients.

As expected, SMR was markedly elevated at 30-days in *study II*. Interestingly, SMR was also elevated at 360 days post-injury among men one year after trauma, a finding in line with other studies<sup>132,133</sup> showing increased post-discharge mortality for trauma patients in relation to the general population. Shafi *et al* found that the survival of trauma patients with major injuries was significantly lower than for minor trauma patients and the general population for several months post discharge.<sup>15</sup>

Thorough examination of causes of death after discharge from hospital is necessary in order to elucidate the contributing explanations. Few studies have addressed this topic. Mullins *et al*<sup>132</sup> investigated causes of death for a large United State trauma cohort and found that late death up to one year was to a large extent designated as “nontrauma death”. Claridge *et al* could demonstrate that mortality after hospital discharge was to a high degree associated to trauma, particularly in younger patients. They also report differences in risk factors for inpatient mortality and mortality after discharge.<sup>137</sup> In a German study, Probst *et al* found differences in cause of deaths between trauma patients and a matched German general population after discharge from hospital.<sup>138</sup>

It could be questioned whether late deaths are trauma-related, connected to pre-existing medical conditions or if the patients who become trauma victims are a selected group with an increased risk of being involved in fatal accidents.<sup>15,138,139</sup>

## HOST FACTORS AND SOCIOECONOMY

### *Comorbidity*

Assessing the impact of pre-existing medical conditions on post-injury outcome is associated with difficulties due to methodological differences concerning grading of disease and outcome measures. Previous research has indicated that comorbidity is related to excess mortality and that this effect cannot be explained by age.<sup>66</sup> Hollis *et al*<sup>65</sup> demonstrated that this effect was predominantly seen in less injured patients. In a study from Norway, pre-injury ASA-PS score<sup>140</sup> was an independent predictor of 30-day post-injury mortality after trauma, even after adjusting for the variables in the traditional TRISS.<sup>95</sup> Moreover, particular pre-existing medical conditions, such as liver cirrhosis, end stage renal disease and diabetes have been advocated as strong risk factors for trauma-related death.<sup>141,142</sup> The overall prevalence of comorbidity was about 40% in *study I and II*, a proportion in agreement with several other studies.<sup>65,66,93</sup>



The presence of comorbidity did not influence 30-day mortality in *study II*, but proved to be an independent risk factor for death during the first year for patients surviving beyond 30 days. In *study II* we also performed an additional analysis using weighted comorbidity according to the Charlson index in the regression model. The results of this analysis showed no difference from the analysis using the unweighted index. It could be questioned whether late deaths are trauma related and associated to a risk behaviour or caused by pre-existing medical conditions *per se*.

Clinical experience and previous studies suggest that a significant proportion of patients taken care of after trauma are suffering from psychiatric disorders and/or substance abuse problems.<sup>143-145</sup> In *study IV* we categorised pre-existing medical condition into three groups; somatic, psychiatric and substance abuse diagnoses.

We could show that comorbidity is a strong independent risk factor in a time-dependent manner, where the risk of trauma is greatly increased if you have been treated for a substance abuse-related disorder within six months before the trauma. This suggests a strong impact of active drug use. Notably, recent treatment for a somatic disorder significantly increased the risk of severe trauma. This may reflect that patients with a new or active somatic disease are more prone to injury. Psychiatric diagnoses were a strong independent risk factor without a time-dependent manner. Multiple causes may contribute, such as medication side effects, increased risk behaviour or symptoms correlated to psychiatric disorders.<sup>144,145</sup>

Few studies have addressed this temporal relationship before. Preventive measures are generally difficult to provide but our study emphasises the need of vigilance in specific groups with a marked risk of becoming trauma victims. Recently, a European cooperation among experts from major trauma organisations agreed on a core data set where comorbidity was recommended to be measured with ASA-PS. Maybe this could help us to find a standard for assessment of somatic comorbidity in a trauma population.<sup>27</sup> *Study III* also shows that it is necessary to take into account psychiatric and substance abuse disorders in trauma research.

## Gender

The impact of gender on survival after trauma has been studied both in experimental and clinical settings. Whilst experimental studies indicate superior survival for female subjects, an effect suggested to be linked to sex steroids,<sup>74-76</sup> clinical studies have shown inconsistent results.<sup>146</sup> Even though several studies have reported that male gender constitutes an independent risk factor for trauma-related mortality other studies have been unable to show this relationship.<sup>69-72</sup> The hypothesis that female sex hormones may be protective has led to the suggestion by some authors that exogenous estradiol could be considered as a therapeutic agent in the trauma room.<sup>147,148</sup> This approach might be questioned considering the literature where some studies show that the protective effect is seen only in elderly women.<sup>149</sup> This was also the finding in *study II* when we stratified the cohort into two age groups. The protective effect of female gender was limited to the older group. The age limit was chosen on the assumption that a majority of women will have undergone menopausal changes by the age of 55 in order to minimize the potential confounding association of sex hormones and outcome. A gender difference was also apparent in the SMR analysis; male patients had a significantly increased SMR during the first year after trauma, whereas female patients were comparable with the general population already after 90 days.

## Socioeconomy

The effects of socioeconomic differences on the risk of trauma as well as morbidity and mortality have been studied previously.<sup>138,150-152</sup> The relationship is well documented but the causality is far from clear. A recent WHO report describes that previous studies have usually been focused on a specific injury mechanism e.g. falls or traffic accidents and have not had the opportunity to include injury severity as a variable.<sup>153</sup> In *study IV*, we included severity of injury and did not limit the analysis to a certain mechanisms of injury.

Definitions of SES differ in previously published literature and this can lead to difficulties when comparing studies. Two of the most common ways to describe SES on individual level are education and income.<sup>153</sup> Other authors have shown that SES is a risk factor for injury,<sup>151,154</sup> but few have taken into account the impact of comorbidity and <sup>154</sup> SES in the same analysis.

We could demonstrate that low levels of education and income were significant risk factors for trauma, even after adjustment for somatic, psychiatric and substance abuse diagnoses.

Different factors may explain the association between SES and the risk of trauma. One is that SES are exposed to increased risks in life e.g. hazards at home and in the neighbourhood. Another theory is that socioeconomy affects the vulnerability,

which can be described as the ability to prevent health problems and take various precautionary measures. This could explain the distribution of mechanisms of injury in different SES seen in *study IV* where assault and self-inflicted injury were uncommon in high SES. A third explanation is that the consequences of illness or injury differ according to SES, e.g. adherence and access to medical treatment and technology.<sup>150,155-157</sup>

## **FUTURE PERSPECTIVES AND CLINICAL IMPLICATIONS.**

There is a significant proportion of patients who die and/or develop complications early after injury. We could also demonstrate that there is an increased, still unexplained, mortality after hospital discharge among patients treated for injury.

Great efforts have been made to develop the care for the severely injured patient. The mortality and morbidity rate among severely injured patients treated in mature trauma centres have declined over the last decades. Despite this, there are still questions to be answered that can lead to improved care. One important challenge is the assessment and studying of long-term effects of trauma. The burden of traumatic injury is multidimensional and there has been limited development of measures for assessment of post-discharge follow-up.

We have to improve our ability to follow up and study long-term effects of trauma such as quality of life, return to work and related risk factors, functional outcome and psychological sequeale. It is my belief that the results of this thesis will help us to identify trauma patients with an increased risk of long-term morbidity and mortality. This patient group is in need of increased attention and improved follow-up after discharge from acute care.



## CONCLUSIONS

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- We found a high incidence of multiple organ failure, acute lung injury and severe sepsis among ICU-treated trauma patients whereas 30 and 90-day post-injury mortalities were relatively low.
- ICU-complications and death were not uniformly affected by the different risk factors.
- The influence of host factors on outcome after trauma differs over time. Male gender was an independent risk factor for mortality at one year but not at 30-days post injury. The effect of gender seems to be restricted to elderly patients.
- The presence of comorbidity became a significant risk factor beyond 30 days after trauma.
- A persistent excess mortality in comparison to the general population was seen among men one year after trauma.
- There was a high incidence of pneumonia among ICU-treated trauma patients. Reduced consciousness was an independent risk factor for development of pneumonia after severe injury
- Level of education and income as well as psychiatric, substance abuse and somatic comorbidity were all independent risk factors for trauma. Active substance abuse strongly influenced the risk for trauma and had a time dependent pattern.

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