OPEN TIBIAL FRACTURES IN SWEDEN

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OPEN TIBIAL FRACTURES IN SWEDEN
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By

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Imagine that you are crossing the street on your daily walk to work. A car comes towards you with high speed. Suddenly you find yourself lying on the street with a sharp pain in your leg. You look down and find it’s looking odd, turned the wrong way and blood is dripping...

In the ambulance on your way to the emergency department, many thoughts pop up in your mind. Will you survive? And if you survive, will life ever be the same?

In fact, fractures of the lower leg, especially those where bone is sticking out, are awful injuries. Long hospital stay, multiple surgeries, infections and wound problems are to be expected. Patients may have poor function and pain. The pain sometimes necessitates powerful drugs, like opioids, which could lead to addiction. People with a history of psychiatric problems are especially at risk for overuse. If there are such problems, an open fracture of the leg will just add more and more problems...

Healing time is long, from six months to one year. There is even a small risk that leg leg will be amputated, although we know that if we compare two people with this injury, the one that was amputated has the same quality of life as the one with the leg still there.
If we want to prevent some of the complications and improve the outcome, it is important to know more about the patients and their injuries. There is a lot of information stored about this in our healthcare registries. Every time when you are admitted to a hospital, some of the information about you and your injury will be registered. We know from our research, due to our system of national registration numbers, that the information is most often correct. In fact, around 90% of lower leg injuries with open wounds are registered correctly.
What do we know about the people who suffer from awful lower leg injuries, based on knowledge from our registries?

We know that certain people are more at risk than others. One such group is young men. They might take more risks and they are more often involved in accidents, like traffic accidents and falls from height. Maybe they are not so careful about themselves and maybe they have psychiatric problems, as they are also more involved in suicidal attempts.

Another group at risk are elderly women. They are not so often involved in high energy accidents, but they tend to get injured just by falling on the ground. Probably because they are old and frail and have lots of other problems with their health.

We also know about these groups that they do not just get severe lower leg injuries. In addition, they have an increased risk of dying compared to an average person in Sweden, at the same age. Not much, but still the risk of dying after a severe injury of your lower leg within 90 days is about 0.5% for a person younger than 65 years of age, and about 6.5% after the age of 65 years.

Now you probably wonder, what is there to do about it? How can we help these people?

In fact, there is a lot we can do!

The first thing is prevention. We can try to prevent accidents, for example by traffic safety measures and by preventing falls. And when the injury is a fact, we can identify the people at risk, e.g. the younger men, and try to take better care of them and to pay more attention to their psychosocial situation.

We can be more careful when elderly people are injured. Often they can´t speak for themselves and tend to stand back in the line for treatment. We simply have to prioritize them!
So the answers to the questions in the beginning are:

Yes, you will most certainly survive this accident.
And no, your life will not be exactly the same.

So, be careful and watch out when you are out on the streets!
And if you are old and your sense of balance is not so good anymore, wear proper shoes in winter-time and avoid things that you can slip on in your home!

Take care of each other out there!
background

Open tibial fractures are serious injuries, challenging both for patients and doctors. For the patients, personal, psychological and physical costs are enormous. For healthcare and society, open tibial fractures are injuries that require resources at a high cost. The literature on Swedish patients with open tibial fractures is sparse. Fortunately, we have our national patient registers that represent an invaluable source of information.

The aim of this thesis was to map the population of Swedish patients with open tibial fractures, with specific attention to serious complications, mortality and opioid consumption. Furthermore, we aimed to identify fields with room for improvement and possibilities of prevention.

**Study 1** is a nationwide study on amputation rate and reconstructive surgery after open tibial fractures, based on all 3,777 Swedish patients admitted during 1998-2010. Amputation rate over-all was low, 3.6 % during the study period. Reconstruction surgery was performed in 9 % of the patients. Main risk factors for amputation were age above 70 years and reconstructive surgery, the latter as an indicator of severe soft tissue injury. The amputation rate after attempted limb salvage with either a pedicled or free flap was 9 %. We also evaluated timing of reconstructive surgery and found results consistent with gold standard according to Godina’s earlier work: flap surgery should be performed within 72 hours whenever possible.

**Study 2** is a study on mortality and causes of death based on the same study population as in study 1. We found an increased standard mortality ratio for all age- and gender groups during 2 years after injury. External causes of death were over-represented in all age-groups, and dominating among the younger patients 15-39 years (accidents, suicide and poisoning). Risk factors for premature death were increasing age, length of hospital stay, limb amputation and cause of injury. Two main populations especially at risk were identified: the elderly population and younger/middle-aged men.

**Study 3** is based on data from both the Swedish National Patient Register and the Swedish Register of Prescribed Drugs, during the study period 2007-2019. We found that patients with consumption of pharmaceuticals for psychiatric disorders (depression, anxiety and drug dependency) were at risk for prolonged use of opioids after an open tibial fracture. We conclude that patients with prescribed pharmaceuticals at admission should be identified and may need extra support during de-escalation of their opioid consumption.

**Study 4** is a validation study of the diagnosis open tibial fracture in the Swedish National Patient Register. Positive predictive values (PPV) were calculated through review of a randomized sample of patient records. We found PPV to be high, 87 %. We calculated the PPV for two sub-groups, moderate and severe injury (defined as having procedure codes for amputation and/or reconstructive surgery). Severe injury had a higher PPV (96 %) compared
with moderate injury (86%). In conclusion, the Swedish National Patient Register is well suited for research purposes regarding trauma diagnoses.


II. Mortality, risk factors and causes of death in Swedish patients with open tibial fractures - a nationwide study of 3,777 patients.


III. Risk factors for long-term opioid consumption after open tibial fracture

Ulrika Tampe, Rüdiger J Weiss, Carl-Olav Stiller, Karl-Åke Jansson

*Manuscript*

IV. Diagnosis of open tibial fracture showed high positive predictive value in the Swedish National Patient Register

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<th>Description</th>
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<tr>
<td>ASA</td>
<td>American Society of Anaesthesiologists</td>
</tr>
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<td>BOA</td>
<td>British Orthopaedic Association</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>E-code</td>
<td>External cause of injury code</td>
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<td>GHOISS</td>
<td>Ganga Hospital Open Injury Score</td>
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<tr>
<td>HR</td>
<td>Hazard Ratio</td>
</tr>
<tr>
<td>ICD</td>
<td>International Classification of Disease</td>
</tr>
<tr>
<td>ISS</td>
<td>Injury Severity Score</td>
</tr>
<tr>
<td>LEAP</td>
<td>Lower Extremity Assessment Project</td>
</tr>
<tr>
<td>LOS</td>
<td>Length Of Stay</td>
</tr>
<tr>
<td>MVA</td>
<td>Motor Vehicle Accident</td>
</tr>
<tr>
<td>NPWT</td>
<td>Negative Pressure Wound Therapy</td>
</tr>
<tr>
<td>OR</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>PPV</td>
<td>Positive Predictive Value</td>
</tr>
<tr>
<td>RTA</td>
<td>Road Traffic Accident</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SMR</td>
<td>Standard Mortality Ratio</td>
</tr>
<tr>
<td>SNPR</td>
<td>Swedish National Patient Register</td>
</tr>
<tr>
<td>STRADA</td>
<td>Swedish Traffic Accident Data Acquisition</td>
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</table>
1 INTRODUCTION

The tibial shaft is a common location for fractures and the most frequent open fractured long bone in adults (1). Due to the closeness to the skin up to 18% of all tibial shaft fractures are open with a majority being severe (2, 3). Open tibial fractures are associated with serious complications such as osteomyelitis, non-union, mal-union, and amputation (4, 5). Strategies for soft-tissue management are as important as fracture stabilization. High-energy open fractures are usually classified as Gustilo type III injuries (fig 1) (6). In Gustilo IIIb injuries there is not enough soft tissue to cover the bone and reconstructive surgery is necessary to save the limb. In severe cases, the choice is between attempted limb salvage and amputation. These injuries are extremely demanding for both patients and doctors. Extended length of stay, multiple surgeries and complications cause great suffering. The number of patients with severe injuries is limited but the costs are considerable for each case. Complicated cases are usually recommended to be centralized to units where a multidisciplinary (orthopaedic and reconstructive surgery) approach is available. The epidemiology and treatment have been mostly studied in trauma centers. However, no longitudinal national data exist. Therefore, this field is of importance for further research and investigation. National guidelines, as present in Great Britain, would be useful also in Sweden (7, 8).


2 LITERATURE REVIEW

Epidemiology and mechanism of injury

Open fractures occur with an incidence of 31 per 100,000 people per year in the United Kingdom (1) with the tibia and/or fibula being the most frequent fractured long bones. Tibial shaft fractures decrease in occurrence, especially through a reduction in males (3). The incidence of open tibial diaphyseal fractures is reported 2.3 to 3.4 per 100,000 people per year in north European countries (1,3). Males in their twenties and females around sixty years of age are most common victims (9). Motor vehicle accidents and falls cause the majority of injuries. Among open fractures of the tibia and fibula, 72 % are isolated fractures, and accompanied by an average injury severity score of 14, which represents a moderate injury pattern (1,10).

History

Historically as well as now, open fractures of the lower leg have been injuries to fear-sometimes fatal.

Even the ancient Egyptians knew the need of soft tissue coverage for open fractures:

"Whenever there is a gaping wound, such as that inflicted by the mouth of a crocodile it should be covered with meat", was written already in 1800 BC (Edwin Smith Papyrus, Egypt).

The citation from Hippocrates (400 B.C.) illustrates the difficulties and poor prognosis at that time: "...not to reduce it is to incur the reproach of ignorance; to reduce it is to increase the chance of death."

The importance of proper wound treatment was recognized and different strategies were suggested.

In ancient China, according to the Taoist priest Lin (846 A.D.), wounds should be enlarged with a sharp knife and washed with boiled water. After that, the fracture could be reduced and the wound sutured or not.
Historically, the wound was mostly left open for drainage and the importance of cleaning and wound revision and lavage with different solutions was described. For centuries, several treatments have been proposed, more or less successful. Much of this development has been achieved during war and on the battlefield.

The term "debridement" was coined during wars of Napoleon (1803-1815), where the wounded were transported to field hospitals for treatment.

During the American Civil War (1861-1865) severe open fractures due to gunshot wounds were frequent, and amputation was the choice of treatment for 50% of the cases, with a mortality of 26%.

During World War I (1914-1918), the orthopaedic surgeon Baer found out by accident that wound treatment with maggots was very successful for acute open fractures, but also for chronic infection and osteomyelitis. He even started a maggot farm. Unfortunately, this treatment was not acceptable for many patients.

During the Spanish Civil War (1936-1939), debridement, gauze and prolonged plaster treatment was successfully used in over 1000 cases. The plaster was changed every 15-30 days.

References: 11, 12.

Development of modern treatment

Among further advances, the introduction of penicillin during World War II was crucial for the treatment and prophylaxis of infections (13).

Modern external fixators were introduced by Hoffman in 1938, providing stability to the fracture and facilitating wound care (14). Today, traditional external fixators are used as temporary fixation for severe cases of open tibial fracture.

The Ilizarov frame was presented in 1951 (15), a circular frame that could be used as definitive treatment. Acute shortening was used to overcome the problem with lacking soft tissue.
The Taylor Spatial Frame (TSF, 1994) was developed as a modern alternative facilitated by computer software.

New internal fixation devices were introduced. Modern reamed intramedullary nails are used for open tibial shaft fractures since the 1990’s. The concept of angular stability and locking plates like LISS (Less Invasive Stabilization System, 2001) and LCP (Locking Compression Plate, 2003) was introduced (16).

Earlier, for many cases with deficient soft tissue, amputation was the only alternative. During the 1970’s, the amputation rate was 15% (11). Modern reconstructive surgery was presented in Godina’s seminal work 1986 (17). He introduced the concept of early coverage with free flaps for open tibial fractures, which showed to be more successful than late reconstruction.

Additionally, artificial skin products and vacuum assisted closure therapy were developed during the last decades. Nowadays, negative pressure wound therapy (NPWT) is recognized as temporary wound treatment before definitive coverage (18).
<table>
<thead>
<tr>
<th>Anatomy</th>
<th>ICD code</th>
<th>Description</th>
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<tbody>
<tr>
<td>S82.11</td>
<td>Open fracture of the proximal tibia</td>
<td></td>
</tr>
<tr>
<td>S82.21</td>
<td>Open fracture of the tibial shaft</td>
<td></td>
</tr>
<tr>
<td>S82.31</td>
<td>Open fracture of the distal tibia</td>
<td></td>
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</tbody>
</table>

Figure 1. Tibial bone. ICD codes for open fracture, proximal part, tibial shaft and distal part.

Figure 2. Cross section of the lower leg, illustrating the deficiency of soft tissue over the anterior tibial bone.
### Classification

<table>
<thead>
<tr>
<th>Gustilo Anderson</th>
<th>Description</th>
<th>Illustration</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Low energy Wound &lt; 1cm</td>
<td><img src="image1.png" alt="Image" /></td>
</tr>
<tr>
<td>II</td>
<td>Low energy Wound 1-10cm</td>
<td><img src="image2.png" alt="Image" /></td>
</tr>
<tr>
<td>III A</td>
<td>High energy Adequate soft tissue coverage</td>
<td><img src="image3.png" alt="Image" /></td>
</tr>
<tr>
<td>III B</td>
<td>High energy Inadequate soft tissue coverage</td>
<td><img src="image4.png" alt="Image" /></td>
</tr>
<tr>
<td>III C</td>
<td>Any open fracture with vascular injury requiring repair</td>
<td><img src="image5.png" alt="Image" /></td>
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</table>

Fig 3. Summary of the Gustilo Anderson classification.

The fracture pattern is described using the classification established by a collaboration between Arbeitsgemeinschaft für Osteosynthesefragen (AO) and Orthopaedic Trauma Association (OTA) (19). Assessment of location, fracture pattern and articular involvement permit a reliable classification of long bone injuries (20).

Open fractures of the tibia are often classified according to the Gustilo Anderson classification, which was first described in 1976. The classification was further specified in 1984, when Gustilo III injuries were defined as high energy and subdivided into A, B or C. In this form, it is still in use today (6). The injury is classified according to the wound size, the soft-tissue damage, bone exposure and arterial injury (Fig 3). Although widely used the inter-observer agreement has been reported to be only 60% (21, 22). Advantages are that the
classification is easy to remember and to communicate. There are other classification systems for open fractures as the one proposed by the Orthopaedic Trauma Association (OTA) in 2010 (23). It seems to have advantages in determining treatment over the Gustilo Anderson classification (21).

The open fracture study group from the OTA recommends to use their classification after the initial debridement (24).

The Ganga Hospital Open Injury Score (GHOISS) was presented in 2006 (25). There are several advantages including high inter-observer agreement and high sensitivity as well as specificity for amputation or limb salvage. Components in the score are covering tissues, skeletal structures, functional tissue and co-morbid factors.

Clinical presentation

The population with open tibial fractures is heterogeneous. There are complicated high energy injuries mostly affecting younger men, due to transport accidents and falls from heights. The other dominating sub-group consists of women with low energy injuries caused by simple falls (1, 9), (Fig. 4, Fig 5). Penetrating injuries like gun-shot wound are increasing in Sweden, also presenting as open tibial fractures (26).
Fig 4. High energy fracture Gustilo III.

Fig. 5. Low energy open fracture Gustilo II.
**Imaging**

The fracture is usually examined with standard x-ray as well as computed tomography. In cases where an arterial injury is suspected, angiography should be performed. When possible, photos of the injury should be saved digitally in patients records.

**Initial management**

Standard for initial management is debridement, cleaning and irrigation of the soft tissue and temporary or definitive stabilisation of the fracture (27). Classification of the open fractures should be performed, preferably during surgical debridement. Intravenous antibiotics should be administered as soon as possible, preferably within 3 hours (28, 29). In a recent study they showed that antibiotic prophylaxis should be administered within 66 min for maximum success (30). Administration of antibiotics in the prehospital setting has been discussed, especially during long distance transportation.

In Sweden, according to recent guidelines, cloxacillin is recommended for Gustilo 1-2 injuries. For Gustilo 3 injuries, antibiotics with a broader spectrum is recommended (cefotaxim or piperacillin/tazobactam) (31).

Ankle Brachial Index (ABI) should be measured and if <0.9, further investigation of vascular status should be performed.

**Timing**

The timing of this first surgical debridement has been a topic of discussion. Historically, a time limit of 6 hours was recommended. Nowadays an orthoplastic team under optimal conditions at the earliest opportunity during daytime surgery is recommended, since a time-limit of 6 hours has not been shown to improve results (32, 33, 34, 35). Only when there are grossly contaminated wounds or other injuries that require immediate surgery, the surgery should be undertaken in sub-optimal conditions. The British Orthopaedic Association have updated their guidelines in 2017 accordingly (36). Hull and colleagues analysed deep infection rates in open fractures with time as a continuous variable and found a 3 % increase
of deep infection rate per hour of delay (37). Infection rates were significantly increased in Gustilo Anderson Type IIIB and IIIC compared to Type II and IIIA as well as in tibial compared to non-tibial fractures.

Type of irrigation has been studied by the FLOW investigators in a multicenter blinded study comparing different solutions and irrigation pressures (38). It was concluded that low pressure irrigation may reduce re-operation rate for infection and wound healing problems.

Negative Pressure Wound Therapy (NPWT) is a method to temporarily cover open wounds. It seems to be a good way to temporarily protect open fractures from infection but does not replace the need for soft tissue reconstruction and should not be allowed to postpone definitive coverage (11, 18, 39).

**Surgical treatment**

In low energy injuries, the fracture could be stabilized by a plaster cast, pending definitive surgical treatment. Immediate stabilization by external fixation of the fracture is mostly done for severe cases. This temporary fixation is later changed to a definitive method, such as intramedullary nailing, plating or in some cases as definitive treatment an external frame, for example the Taylor Spatial Frame (TSF).

Primary stabilization with intramedullary nailing along with soft tissue reconstruction at first surgery has been studied and is a preferable alternative when possible, though difficult to implement in Sweden due to the advanced resources that are required (40, 41). Soft tissue coverage should, when possible, be undertaken within 72 hour to prevent deep infection. This concept was introduced by Godina already in 1986 (17), and seems to be applicable on Swedish patients (9).

**Reconstruction or amputation**

Amputation rate after open tibia fractures is low and found to be 3.6% in our Swedish registry study (9). Several scores are described to decide whether to go for salvation or amputation in lower-leg injuries. A prospective study evaluated five of them and reported high specificity and low sensitivity. They conclude that the decision of limb salvage or amputation should not solely be based on a score (42).
There is no clear evidence to support either limb salvage or primary amputation (5). No significant differences in quality of life were seen after two years (43).

“Clinical practice guideline for limb salvage or early amputation” was adopted by the AAOS in 2019 (44). Recommendations with associated level of evidence are presented. It is stated that: “Physicians should not utilize extremity specific scores to select limb salvage vs. amputation, or to predict outcomes for patients with high energy lower extremity trauma” (moderate evidence for statement). Regarding choice of treatment, there is moderate evidence for considering the burden of injury and prioritizing patient survival. Most important, there is strong evidence for the statement “Clinicians should screen all patients with high energy lower extremity trauma for psychosocial risk factors (e.g. depression, PTSD, anxiety, low self-efficacy, poor social support) affecting patient outcomes”.

**Reconstructive surgery**

An open fracture could be described as a soft tissue injury with a broken bone within.

Reconstructive surgery for coverage of the bone is often illustrated with the reconstructive ladder, with steps from simple to highly advanced measures.

![Reconstructive ladder](image)

Fig 6. Traditional reconstructive ladder.
Today, primary closure is recommended when possible, that means not vastly contaminated wound and closure without tension.

NPWT could be used temporarily, awaiting definitive coverage. Split skin graft is used when no bone is exposed, for coverage of muscle or in combination with muscle flaps. For open tibial fractures Gustilo IIIB, first choice can be a free flap, since soft tissue transferred from outside the zone of injury is sometimes preferable.

**Pain**

Pain after lower leg surgery/injury is a considerable problem. One half of the patients report persistent pain after 3 months (45). According to statistics from the National Board of Health and Welfare for the year 2015, 9 % of the Swedish population had an opioid drug dispatched during the whole year (46). The literature is sparse and this field is in need of further research.

**Mortality**

There are few studies concerning mortality after tibial fractures. There are studies on smaller series of elderly patients that show a relatively high mortality, comparable to the population of hip fracture patients (47, 48, 49). Open fractures showed a higher mortality, and standard mortality ratio was increased (47).

**CHALLENGES TODAY**

There are many challenges associated with assessment and treatment of patients with open tibial fractures in Sweden. One is the co-operation between smaller emergency hospitals and trauma centers, where especially high energy fractures may need multi-professional ”orthoplastic” assessment. There are large sparsely populated areas in Sweden, and transportation could be demanding. Lack of resources (operating theatres, staff, overcrowded hospitals) affects logistics and timing of surgery.
The choice of amputation or limb salvage will probably remain a topic of discussion. Important improvements for all patients are avoiding short-term and long-term complications, reducing mortality, choosing the right treatment individually, proper prescription of and termination of pain medication. Other areas of improvement are psychosocial support for patients as well as primary and secondary prevention.
3 RESEARCH AIMS

Study 1

To study amputation rate and reconstruction rate, types and timing of reconstruction, with data from the Swedish National Patient Register.

Study 2

To study mortality after open tibial fracture, causes of death and associated risk factors, with data from the Swedish National Patient Register.

Study 3

To study opioid consumption among patients with open tibial fractures and risk factors for prolonged use. The study is based on data from the Swedish National Patient Register and the Swedish Register of Prescribed Drugs.

Study 4

To validate the diagnosis open tibial fracture and associated E-codes in the Swedish National Patient Register.
4 MATERIALS AND METHODS

Data sources

This thesis is based on National Registers, held by the Board of Health and Welfare. These registers are regarded as having high quality (National Board of Health and Welfare, 2014).

Coverage, means rate of participation among treating units/hospitals.

Completeness means rate of registered individuals related to the actual population.

Both coverage and completeness are regarded as high for these registers, also related to our study population. Patients with open tibial fractures are exclusively treated as inpatients.

Our validation study aimed to quantify the number of patients that were wrongly diagnosed as having an open tibial fracture, resulting in a positive predictive value for the diagnosis.

What we do not know, is the number of open tibial fractures that were incorrectly classified as closed fractures.

The Swedish National Patient Register (SNPR)

This register covers more than 98 % of all hospital admissions in Sweden (50). Coverage and content expanded since 1964, when the register was founded. In 1998, all regions in Sweden were reporting admissions. A 10-digit national registration number for each individual in Sweden allows epidemiological studies on a nationwide basis. The Register includes e.g. data on diagnosis, surgical procedure codes, and demographic data for each hospital admission in Sweden

The Swedish Causes of Death Register

The register was started in 1961 and covers more than 98 % of all deaths in Sweden (51) and comprises dates of death and causes of death for the Swedish population. Causes of death are coded according to the International Classification of Diseases (ICD 10). The reliability of the underlying cause of death was 77 % according to a study from 1995 (52). Younger age, malignancies and acute diseases were associated with higher reliability.
Swedish Prescribed Drug Register

The register was started in 2005 and covers all prescribed drugs in Sweden including dates and amounts that are prescribed and dispatched.

The thesis *Open tibial fractures in Sweden* is based on:

Swedish National Patient Register: Study 1, 2, 3, 4.
Swedish Prescribed Drug Register: Study 3.
Swedish Causes of Death Register: Study 2, 3.

Population

We identified patients with open tibial fractures in Sweden from ICD codes. The codes used were S82.11 (open fracture of the proximal tibia), S82.21 (open fracture of the tibial shaft) and S82.31 (open fracture of the distal tibia). For study 1, 2 and 3 we chose the adult population ≥15 years.

Children, defined as growing individuals, differ from adults regarding treatment, prognosis and results. We do not know if the results would have been different with children included. More valuable for this sub-population would be separate studies focused on children.

In the validation study all ages were included.

Children under age 15 represented approximately 7% of the study population.

In most emergency hospitals in Sweden, children are treated by general trauma orthopedic surgeons. Only in a few hospitals in Sweden, injured children are treated separately from adults.
We applied for data from the National Patient Register several times and we updated the time period accordingly. For study 1 and 2 the study period was 1998-2010. For study 3 the study period was 2007-2019, and for study 4 2007-2016.

Hence, our population was not identical, but we prioritized to get recent data. Especially regarding opioid drugs, the prescription pattern has changed significantly during recent years (53).

**Sub-groups and variables, definitions**

For the individuals of our population, we extracted demographic data, diagnosis, E-codes and procedures related to our research aims. Regarding reconstructive surgery and amputations we consistently searched for the same codes:

Amputations: above-knee amputation (NFQ19), knee disarticulation (NGQ09), and below-knee amputation (NGQ19).

Reconstructive surgery: free flaps (ZZQ), pedicled flaps (ZZS), and skin graft only (ZZA00).

**Fixation methods**

In study 1, we searched for fixation methods as procedures: intramedullary nail, plate and screws, closed reduction, external fixation, combinations and miscellaneous. It would certainly be of interest to validate the procedure codes.

**Early and late amputations, etiology of amputation**

For study 1, amputations were grouped into early or late. Early amputation was defined as within 3 months, and late amputations after 3 months. We considered that amputations within 3 months were most likely linked to the acute injury, whereas late amputations were associated with chronic complications or other causes.
The cause of amputation was registered as severe acute injury, infection/osteomyelitis, pseudarthrosis, high age and other/unknown. We chose these variables from associated diagnoses at the admission and time of amputation. High age was considered to be associated with co-morbidities that could lead to amputation. Of course a more valuable source would have been patient records.

*Timing of flaps*

Reconstruction with free or pedicled flaps was categorized in three groups for evaluating timing of the procedure: within 72 hours (3 days), reconstruction within 4 to 90 days and reconstruction after 90 days. We chose these ranges as a comparison to Godina’s work (17).

*Moderate and severe injuries*

For study 4, we defined the two sub-groups: ”moderate” and ”severe” injury. These definitions were based on the assumption that injuries connected to surgical procedure codes for either amputations or reconstructive surgery represented more severe injuries. All patients having one or more of these codes were regarded as ”severe” and the rest as ”moderate”. As register studies are built on retrospective data and classification is not a variable in the register, we found this to be the best option. We continued to use this definition in study 3, that was conducted after study 4.

During review of patient records for study 4, we could classify the injuries retrospectively according to Gustilo Anderson. In the group of severe injuries, 80% were Gustilo 3B or 3C. Among moderate injuries, only 4% were Gustilo 3B or 3C.

Therefore, through reviewing almost 150 records from each sub-group we concluded that our definition was valid for the purpose.

*Mechanism of injury*

Mechanism of injury was defined from the E-codes. For study 1 we had the following groups: fall on the same level, un- specified fall, fall from height, motor vehicle accident (MVA), and miscellaneous. Fall from height and MVA were considered as high energy mechanisms for the risk factor analysis. For study 2, we chose a further division into sub-groups, as we
thought that our first analysis was too un-specified to get conclusive results, above all the group of MVA. We used the broader definition transport accidents which is more correct, as not all of these include motor vehicles. We selected and defined the term unprotected road users as we consider them especially at risk for severe injuries.

The following groups were used in study 2:

Fall from standing height (equivalent to fall on the same level), fall from height, car accidents, transport accidents with unprotected road users (bicycle accidents, motor bike accidents, horse riders, and pedestrians hit by motor vehicles), self-destructive injuries and miscellaneous.

*High or low energy injury*

To our knowledge, there is no validated definition of high or low energy related to these injuries. During review of patient records for study 4, we chose to group the following as low energy: fall from standing height or lower height, sports injuries or low energy vehicle accidents (i.e. un-tripped bicycle rollover). High energy was defined as falls from height, crush injuries, gunshot injuries and high-energy road traffic accidents (i.e frontal crash). It would be interesting to look further on these data, although we conclude that in many cases the distinction between low and high energy is difficult to make without detailed knowledge of the accident.

*Causes of death and death date*

For study 2 we searched for underlying cause of death and death date from register data. The aim of study 2 was to look at mortality and causes of death. We grouped the causes according to the European shortlist for causes of death (54):

Diseases of the respiratory, circulatory, digestive, nervous and musculoskeletal system, malignant neoplasms, mental and behavioural disorders, endocrine and metabolic diseases, external, unknown and unspecified causes, and miscellaneous. External causes were further divided into transport accidents, accidental falls, accidental poisoning, suicide and intentional self-harm, homicide and assault, drowning accidents and events of undetermined intent.
For study 3, we used the death date to exclude patients deceased during the study period, as otherwise there would have been a statistic error when deceased patients were counted as having no dispatched drugs.

**Early and late mortality**

The primary outcome variable in study 2 was early mortality, defined as death within 90 days after injury. We assumed that these deaths were most often correlated to the accident, as an early or late complication. Late mortality, defined as death between 90 days and 2 years. We chose 2 years as a reasonable time limit within the study period of 13 years, and we assumed that these were mostly not correlated to the accident. Hence, we analysed the two groups separately regarding Standard Mortality Ratio (SMR) and risk factors.

**Standard Mortality Ratio**

Standard Mortality Ratio (SMR) is used to quantify excess mortality. SMR is a ratio of number of deaths in the study population and expected number of deaths in the general population, stratified by gender and age.

To illustrate and quantify death rate compared to the total population we calculated expected deaths in each age group and compared to the excess deaths, also expressed as excess death rate.

**Opioid consumption and risk factors for prolonged use**

For study 3 we evaluated the use of opioids from 6 to 24 months after the injury. As risk factors we included the use of pharmaceuticals for psychiatric disorders before the injury. We chose to group them as opioids, antidepressants and benzodiazepines. In other words, we used the consumption of pharmaceuticals as a marker of psychiatric disorders: opioid dependency, depression and anxiety.

From the register of prescribed drugs, we collected dispatched drugs with defined ATC codes representing the above pharmaceutical groups. As a marker of on-going use, we considered a dispatched drug from 3 months before the injury until the injury as reasonable. Then, we evaluated the consumption of any type of opioid drug at 6, 12, 18 and 24 months after injury.
Risk factors for prolonged use were analysed in regression analysis. As potential risk factors we chose age, gender, moderate or severe injury and dispatched drugs from the above ATC codes during three months before the injury.

**Review of patient records**

Our validation study is based on a random sample of 300 cases, that were decoded and identified by the Board of Health and Welfare, as ethical consent was given for review of records. We collected the records by letter of application to the chief of department and thereafter the administration of the department. When no answer was sent, we reminded by letter, telephone or e-mail and eventually, almost all hospital gave consent and provided the necessary documents. We were sent records that were different in their extent, from complete charts from all health care professions, to a few pages of surgical reports. We concentrated on doctors’ notes of admission, surgical reports, radiology reports and notes of discharge. In total, records for 282 patients were reviewed.

While reviewing, we also classified the injuries according to the Gustilo classification, retrospectively (not published).

**STATISTICS**

**Register based research**

This thesis is based on Swedish national healthcare registers, where both coverage and completeness is high. There are some principles when dealing with a total population that differ from sample studies. Power calculations are not necessary. According to modern epidemiology, presentation of frequency is sufficient when presenting and comparing observed cases in a population. The relevance of traditional testing and p-values is debatable, as the numbers are from the total population.

Study 1 and 2 are published in papers with readers from the field of orthopaedics and traumatology, and the results are presented the traditional way showing data on odds ratios and p-values.
Study 4 is published in and adjusted to an epidemiological paper, where p-values and odds ratios were not shown in tables.

Throughout our studies, we had several small size groups, i.e., types of reconstructive surgery and causes of injury. Therefore, we used Fisher’s exact test (non-parametric) to compare small size sub-groups. It is designed for small samples (<25) or samples without normal distribution.

Logistic regression analysis was used for risk factor analysis in study 1, 2 and 3. With regression analysis, it is possible to adjust for confounding factors, to find possible risk factors/associated factors.

Bon Ferroni correction is recommended when performing several comparisons, which means that the level of the p-value needs to be corrected (in this case from p<0.05 to 0.005). The more comparisons, the greater the risk for a ”type 1 error”, a result that is significant by chance.

Cox regression is a time-to-event analysis that is used especially for mortality. Cox regression was used in study 2, when analysing mortality from 2 years and beyond.

PPV (positive predictive value) was used to validate to what extent the diagnosis open tibial fracture was correct in the register, which was the topic of study 4. PPV is the number of correct diagnosis divided by the sum of incorrect and correct diagnoses, expressed as a percentage. The standard method in this case is review of patient records. We used a random sample, as it is practically impossible to review thousands of records.

We reviewed 300 records. We chose to take our random sample from two sub-populations, moderate and severe injuries (see above). The reason for this was to review enough of severe injuries. Those were a smaller part of the total population (12 %), though a significant problem for both patients and health care. We chose the sample size with regard to study 1 as we knew the rate of amputations (2 %) and reconstructions (9 %). We managed to access and review 92 % of the sample. When comparing the sub-groups we used Fishers exact test and calculated odds ratios.
ETHICAL CONSIDERATIONS

The thesis is based on Register data from Swedish National healthcare registers, held by the Board of Health and Welfare. Register research is analysed and presented on a group level, considered not to have negative effects on patients. The strength of this thesis is that it is based on the entire Swedish population. For study 4, review of records was performed based on a random sample. To acquire data from all hospitals, we wrote a letter to the chief of department for consent. Thereafter, we could collect patient files from the department administration. Ethical consent for this study was acquired before the General Data Protection Regulation (GDPR) was implemented, but we collected the records thereafter. Some hospitals had their own internal ethical boards, that had to give a second consent. It was a time-consuming work, many reminders, e-mails and telephone calls to some departments. Eventually there were only two hospitals of significance that refused to disclose the patient files. Still, “their” patients could not be part of the study. Possibly, this kind of research based on direct data from patient records will be impeded by the new law, and in the future, be more unusual.

Review of patient records calls for great integrity by the reviewers. No information that could identify individuals was published.

For summary of ethics applications, see Fig 7.
Fig 7. Summary of Ethics applications.
5 RESULTS

Characteristics of the study population

Study 1 and 2 evaluated the same population, 3,777 Swedish patients during a 13 years study period, 1998-2010. The majority of patients were male (67%). Among fractures, 60% were located in the tibial shaft (60%), 14% were located in the proximal part and 26% in the distal part of tibia. Mean age of the patients at admission was 47 (SD 20) years (males 42 [SD 20] and females 55 [SD 22]). Among fixation methods, an intramedullary nail was the most common method (32%).

Regarding causes of accident, motor vehicle accidents accounted for 43% of the injuries followed by falls from standing height (21%).

Amputations and reconstructive surgery

In study 1 we focused on patients with severe injuries, affected by either amputation or reconstruction. In the total population, amputation rate was 3.6% and 9% of the patients had reconstructive surgery. For patients that had reconstructive surgery, amputation rate was higher: 7% for patients with skin graft, 10% for pedicled flaps and 9% for free flaps.

We evaluated timing of reconstructive surgery and found that reconstruction within 72 hours was more successful than within 4-90 days (p=0.04). All 27 reconstructions performed within 72 hours were successful.

In logistic regression analysis we assessed factors associated with amputation. We found that age above 70 years (OR 2.7, 95% CI 1.1-6) and reconstructive surgery (OR 3.1, 95% CI = 1.6-5.8) were associated with higher risk for amputation.

Additionally, we analyzed fixation methods and found that other methods than intramedullary nailing as single stage treatment were associated with a higher risk for complication.

From the review of patient records, we ascertained that high-grade Gustilo class injuries were more at risk for severe complications. 12% out of the total population were affected by so severe injuries, that they had either amputation or reconstructive surgery. In the random sample sub-group of Gustilo 3B and C patients, 80% had such severe injuries.

Among severe injuries, 12% were Gustilo 1 or 2, thus low energy injuries.

Mortality

In study 2, we focused on mortality in the Swedish population of patients with open tibial fractures. We studied a population of 3 777 patients for 13 years, and found an overall mortality rate of 11%.

Our primary aim was to study early mortality within 90 days. In the age group 65 years and above, we found the highest mortality rate, 11%.

Causes of death were grouped as cardiovascular, malignancy, external causes or other. External causes were over-represented in all age groups, especially among the youngest (15-39 years), where they constituted 79%. In contrast, among the oldest (65-101 years) external causes accounted for 12% (Fig 9). External causes were dominated by transport accidents, followed by poisoning, suicides and falls (Fig 10).
Fig 9. Causes of death in different age groups (Tampe et al 2018).

Fig 10. Types of external causes.
SMR was overall higher for patients with open tibial fractures, though in some age and gender groups, there were very few individuals.

We assessed factors that were associated with early (within 3 months) or late (3 months to 2 years). For the early deaths, associated factors were age 65 and above, and limb amputation. For later deaths, associated factors were age 40 and above, limb amputation, increasing length of stay and fall from standing height as cause of accident.

Positive predictive value (PPV) of the diagnosis open tibial fracture

Study 4 showed that PPV of the diagnosis open tibial fracture was high, 87%. Hence, research based on the Swedish National Patient Register for this trauma diagnosis is relevant and serves its purpose. PPV for E-codes was lower, 74%.

Among patients with severe injuries, PPV was higher at 96%. For patients with moderate injuries, PPV was lower at 86%.

PPV was calculated as sum of correct diagnoses divided by the sum of correct and incorrect diagnoses. The gold standard method is review of patient records. Flow chart for the study population is shown in fig 11.
Fig 11. Flowchart. Original study population, sub-groups of moderate and severe and moderate injuries, random sample for review and resulting correct and incorrect codes (Tampe et al 2020).
**Opioids**

In study 3, we focused on opioid consumption after open tibial fractures and risk factors for prolonged use. The study population was patients with open tibial fractures during 2007-2019, totally 3,460 individuals. Out of these, 332 (10%) had a dispatched opioid drug during 3 months before the injury. Corresponding data for antidepressants was 445 (13%), and for benzodiazepines 192 (6%). Combinations of drugs is shown in fig 12.

![Venn diagram](image)

Fig 12. Venn diagram. Number of patients with dispatched pharmaceuticals including combinations of drugs, during 3 months before the injury.

The consumption of opioids increased to 22% of the population after 6 months. By 24 months, the consumption had decreased to 10%, the same as before the injury.

Independent risk factors for prolonged opioid consumption according to regression analysis were consumption pre-injury of all the above drugs, age-group 41-64 years and severe injury.
6 DISCUSSION

Patients with open tibial fractures in Sweden – who are they?

This thesis and the four studies it is built upon will hopefully give some answers and provide new knowledge on these individuals. In essence, we will present and discuss a variety of their characteristics, associated complications and challenges they will face.

Study 1 is focused on the most complicated injuries. We will discuss the importance of timing for reconstructive surgery, and risk factors for major complications in the form of amputations. Also, we will point out the advantage of National Guidelines.

Study 2 presents results on mortality and death causes. We conclude the importance of prioritizing the elderly patients with open tibial fractures. We identify a subgroup of younger men with higher mortality than the normal population.

In study 3, we verify that pharmaceutical treatment of certain psychiatric disorders is a significant risk factor for prolonged use of opioids after injury. We will discuss the need for improvement of psychosocial support after open tibial fractures, when the population includes a higher proportion of individuals with psychiatric disorders than the total Swedish population.

From the results of study 4, we conclude that the Swedish national healthcare registers provide valid information on the study population.

Characteristics of the study population

Results of age and gender data suggests that the Swedish population of patients with open tibial fractures is similar to other North European populations. We could confirm the heterogeneous population with younger males and women around 60 as the major parts. Mean age was 47 years and 67 % were males in the cohort from 1998-2010, and in fact identical in the cohort from 2007-2019 (9, 56).
12 % of tibial shaft fractures in Sweden are open (3), compared with 21 % from Edinburgh (1). Populations from trauma centra show even larger percentages of open fractures, 60 % in a recent study from European trauma centers (57). Most epidemiological studies are from trauma center populations where there is a larger part of younger patients with high energy injuries.

Transport accidents and falls were the predominating causes of injury.

In a cohort from Edinburgh of 1502 patients during 1990-1999, they found 75 % men with a mean age of 32 years (2).

Our study population, the entire Swedish population, is not limited to trauma centers, but to all Swedish emergency hospitals. Probably therefore, our patients are older and with a higher percentage of women. It is also possible, as in many sub-populations of fracture patients, that there is an increasing number of female osteoporotic patients compared with males. In another study from Edinburgh on the changing epidemiology of open fractures, they showed that the number of transport accident was decreasing during 1988-2010 (58).

Reconstructive surgery and timing of flap

We found 93 free flaps and 76 pedicled flaps according to our first study of reconstruction and amputations. We could confirm Godina´s conclusion that timing is important. Reconstructive surgery should be performed early, preferably within 72 hours or maximum one week. There are a limited number of cases in Sweden, but still, all 27 reconstructions performed within 72 hours were successful.

In the study population 1998-2010, 9 % of the patients had a soft tissue reconstruction with either free flap, pedicled flap or skin graft only. Of all reconstructed patients, 7 % had an amputation. Of the patients with free and pedicled flaps, 9 % and 10 % respectively had an amputation. These numbers are comparable to other studies. The rate of amputation after attempted limb salvage varies widely according to the literature, from 4-40 % (5, 59, 60). The rate of reconstruction has increased due to improvement in surgical methods (5). However, in retrospect, many patients prefer early amputation to late amputation (61).

Our recommendation is in line with the British guidelines from British Orthopaedic Association/Bapras (7).
Swedish National Guidelines would be useful as support to the triage of these cases. Advanced resources are required: a multi-professional team with skilled orthopedic and plastic reconstructive surgeons, operating theatres with appropriate staff and well-functioning co-operation between emergency hospitals and trauma centers.

The latest update from BOA 2017 includes recommendations for initial assessment and timing to equalize the treatment of these injuries regardless of location and hospital (36).

Mortality and causes of death

We analyzed mortality for age- and gender-specific age groups through analysing standard mortality ratios. Overall, there was an increased death rate, for early mortality (within 3 months) as well as for late mortality (three months and beyond). For the elderly, fall from standing height is a significant risk factor among causes of injury represented the frailty related to this subgroup.

Further, we could conclude that males aged 15-60 years had an increased death rate during the study period.

For the younger population 15-39 years, cause of death by external causes such as transport accidents, suicide and poisoning were paramount. The elderly population 65 years and above were most likely to die from cardiovascular disease, though external causes were over-represented compared with the general population.

Validity of diagnosis- register

There are few studies presenting PPV:s for trauma diagnoses in the Swedish National Patient Register. We found no publication on validation of E-codes. The register is widely used for research based on populations that are identified and chosen from the diagnosis.

With a gold standard method, review of patient records, we showed that PPV for the diagnosis open tibial fracture is high, at 87 % overall. This is comparable with results from other national registers in Scandinavia, regarding hip fractures (62, 63). It might have been appropriate to start with study 4. But, we think that the high PPV strengthens the results from
study 1, 2 and 3. Probably, the SNPR could be used for research on other groups of trauma patients as well.

We chose to present PPV:s for two subgroups, moderate and severe injuries. We introduced and defined these terms as severe injuries are only 12 % of the study population. We wanted to review a larger part records for severe injuries. We could validate ”moderate” and ”severe” during the study by retrospective classification of all reviewed injuries (not published). Among severe injuries, 80 % were classified as Gustilo IIIB-C whereas among moderate injuries, Gustilo III B-C were only 4 %.

We conclude that our definition could be used to search for complicated injuries Gustilo B-C.

During analysis, we found that PPV was higher among severe injuries, and we saw a tendency towards more use of classification systems regarding severe injuries. We also to chose to define high or low energy from review. 78 % of severe injuries were high energy and 58 % of moderate injuries were high energy injuries. It would be interesting to analyse further and produce acceptable definitions of ”high” and ”low”.

_Pain – prolonged consumption of opioids_

At present, opioids is a topic of interest in the light of the opioid epidemic. We have studied the long-term consumption of opioids after open tibial fractures related to the previous consumption of certain pharmaceuticals for psychiatric disorders.

As in some previous studies, we could confirm that consumption of antidepressants, benzodiazepines or opioids before injury represented a major risk factor for prolonged use of opioids thereafter (64,65). To put it differently, consumption of these pharmaceuticals should be seen as sign of psychiatric illness with an increased vulnerability for addictions. We conclude that patients that are prescribed these drugs pre-injury need support and follow-up during de-escalation, to avoid negative consequences related to overuse.

Prevention measures have been proposed by Devin et al, such as specific choices of analgesics and inpatient drug addiction units (66). Further prevention studies would be highly useful.
**Sub-groups of importance**

For the elderly people, just as for patients with hip fractures, open tibial fractures are serious injuries. Mortality is higher, comparable to that of hip fracture patients. Amputations are more frequent, probably due to the patients’ general health and present co-morbidities, i.e. diabetes, cardio-vascular disease or rheumatic diseases.

This highlights the importance of prioritizing these patients and to assess their health condition thoroughly on admission. Additionally, elderly patients should acquire multi-professional care including geriatric competence.

Another population is – mostly – males with self-destructive behaviour like high risk activities, suicide attempts and associated psychiatric disorders. These individuals require psychosocial support from admission to hospital and during follow-up after discharge. They could be helped with drug dependency, their social situation, pain management and coping skills. In our opinion, there is need for improvement.

**LIMITATIONS**

For the validation of diagnosis, almost 300 patient records were reviewed by one orthopedic surgeon. The results might have been more valid with multiple reviewers. A large part of the records was also reviewed by a medical student with similar results.

Register research is associated with limitations as we have to rely on the validity of the data. There can be systematic errors or random errors (67).

One error was studied in our paper on validity of the diagnosis. PPV was high for open tibial fracture.

Other errors could be linked to input of wrong data. We may have missed some cases from the actual population, such as individuals that were misclassified as having a closed fracture when they correctly had an open fracture. We have not quantified this error by review of records for patients with closed fractures. We assume that the number would be low.

For review we were dependent on the files that were provided from the hospitals. They provided various amounts of information. There could be systematic errors if larger hospitals/regions provided more or less information. Two major hospitals in Sweden did not
provide any information at all. Different healthcare registers are not automatically cross-linked.

The procedure of getting data from the registers was more demanding during our last application in 2020. By then, all variables, diagnoses and admissions were not automatically obtained from the register. There is a risk that some patients from our selection could have been missed.

The limitation of register data is significant for study 1. Gustilo class is not a variable in the register.

Although this is a national population, the subgroups of patients with reconstruction are small. It is difficult to detect associations statistically. Too many comparisons in regression analysis increases the risk for type 1 error, that significant results are produced by chance. For this reason, we performed the Bonferroni correction.

The same problem occurred during analysis of standard mortality ratios, some age- and gender groups were very small. As a result, we could not draw any conclusions from those groups.

Regarding risk factor analysis, we did not include co-morbidity index, ASA-class or ISS or other. Hence, some risk factors of importance were not evaluated.

The registration of co-morbidities has lower validity than diagnoses (50). Still, it might have been appropriate to include them.

The Swedish Fracture Register (SFR) in Sweden is now gaining coverage and completeness and has been compared with the Swedish National Patient Register since 2017 (68). Registration in SFR was started in 2011, data are registered by orthopedic surgeons and include a wider range of fracture-specific data and treatments. Wennergren et al found a high reliability in classification of tibial fractures according to AO/OTA, in a study of 114 cases (69).

Today, coverage and completeness has reached 70-80%. We have not compared our data with the SFR. Probably, the SFR will develop into the primary source of data on fractures in Sweden.
7 CONCLUSIONS

The Swedish National Patient Register is appropriate for research on patients with open tibial fractures, as PPV of the diagnosis is high. Collected data on the rate of serious complications are correct.

Amputation rate is generally low. Reconstruction rate is comparable to other populations. One in ten reconstructed patients will need an amputation.

Gold standard for timing of reconstructive surgery, within 72 hours, could be affirmed.

Risk of death after open tibial fractures is increased for all age and gender groups and external causes are over-represented. Elderly patients are a vulnerable sub-group that should be prioritized.

Consumption of pharmaceuticals for psychiatric disorders including depression and anxiety before the occurrence of an open tibial fracture represent a major risk factor for prolonged use of opioids.

In Sweden, there is need for improvement regarding psychosocial support for patients with open tibial fractures.
8 POINTS OF PERSPECTIVE

To improve treatment of patients with open tibial fractures in Sweden, national guidelines for best practice are necessary. We suggest a multi-professional approach through co-operation, with orthopaedic surgeons and reconstructive plastic surgeons in front, for the development of such documents. This could be accomplished via a national working group (NAG) under “Diseases of the musculoskeletal system”, National Board of Health and Welfare and Swedish Association of Local Authorities and Regions.

Psychosocial support and rehabilitation is an area of improvement. Further research and guidelines for follow-up, as has been developed for some other diagnoses would be a huge advancement.
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10 REFERENCES


