# Fracture of the Tibial Diaphysis: Epidemiology, Management and Outcomes

Ritchie Greer Strain

Submitted in accordance with the requirements for the degree of
Masters by Research

The University of Leeds

October 2022

I, Ritchie Greer Strain, confirm that the work submitted is my own and that appropriate credit has been given where reference has been made to the work of others.

## Acknowledgments

I have huge respect and gratitude to my supervisors Professor Peter Giannoudis and Mr Nikolaos Kanakaris. The support, encouragement and patience they have provided has been both motivating and inspiring.

A special thank you is reserved for Mr James Vun. A colleague, supporter and now a good friend.

# Abstract

## Introduction

Tibial shaft fractures represent 2% of all fractures. A high percentage of them present as open fractures possessing a higher incidence of local complications. An accurate description of the epidemiology and outcomes of these injuries is lacking and often based on small or outdated studies.

## Aims

This work aims to provide an accurate description of the epidemiology and demographics of tibial shaft fractures in the city of Leeds over a 12-year period from 2008 to 2019. It will also describe the modern orthopaedic management of these injuries and provide accurate rates of major complications including infection, delayed union and non-union.

## Methods

A retrospective cross-sectional study of all adults (18 years and older) who presented to a Major Trauma Centre (MTC) with tibial shaft fractures in the city of Leeds from January 2008 to December 2019. Descriptive statistics were employed to report on empirical rates of major complications and basic inferential statistics were used to compare treatment modalities against these outcomes.

## Results

A total of 1220 tibial shaft fractures were recorded over 12 years. The incidence has risen from 8.08 per 100,000 and year in 2008 to 13.1 per 100,000 and year, a 60% increase. The proportion of elderly patients was found to be increasing more steeply than other age groups and these patients are largely female. Non-unions rates have been slowly reducing over time with an overall rate of 6.6% (4.2% in closed fractures and 11.7% in open fractures). The rate of other major complications was noted to be static. Plate osteosynthesis confers the highest rate of non-union, deep infection and osteomyelitis in both open and closed injuries.

## Conclusion

Over the past decade, tibial fractures are increasing in both number and complexity, more so in the older population. Plate osteosynthesis confers higher major complication rates compared to other treatment modalities.

# Table of Contents

# 1. List of Tables

# 2. List of illustrations

# 3. Introduction

## 3.1 Background information

Diaphyseal tibia fractures are among the most commonly fractured bones in the human body representing about 2% of all fractures (1). They range from simple closed injuries with predictable outcomes to multifragmented, open fractures that may result in complications. Despite the frequency with which they occur and the advancing care of the modern trauma patient, they persistently remain a challenge even in the hands of experienced trauma surgeons.

Tibial shaft fractures are not a single entity, but instead represent a spectrum of injuries. They can be the result of low or moderate energy mechanisms with simple isolated injuries and can progress to high energy, limb threatening injuries as part of a multiply injured patient. The unique anatomical location of the tibia within the body is implicated in its potential for poor outcomes and notorious complication rates. Its subcutaneous antero-medial border leaves comparatively little soft tissue envelope to house the vascular supply and little room for displacement of the fractured ends before the skin is breached and an open fracture is sustained. This is an orthopaedic emergency requiring urgent management and soft tissue resuscitation.

The bulk of injuries occur in the younger age group. However, there is also a small but significant group of low energy fragility fractures in elderly patients, the so called 'silver trauma', which is gaining increasing interest. Injuries in this age group are complicated by poor patient physiology, underlying comorbidities and complex fracture patterns. In this age group, injury is likely the result of low bone mass density, or osteoporosis, rather than high energy transfer during injury. With a rising elderly population in the UK(2), this may become an increasing problem.

Historically, the corner stone of tibial shaft fractures was non-operative management in plaster cast. Good outcomes were reported with this method in the 1970s by Sarmiento(3). Unfortunately, these results could never quite be reproduced in subsequent studies. Since then, there has been a sea-change with the advent of intra-medullary devices and now operative management is the preferred strategy for these injuries. In recent years there is an increasing array of fixation strategies for tibial shaft fractures, including plate fixation, reamed and unreamed intramedullary devices and external fixation using fine wire frames. All of these methods differ in their approach and methodology. Several studies have attempted to compare these methods, but often rely on direct comparisons or small number studies(4–7). One of the largest randomised controlled trials conducted in the fixation of tibial shaft fractures, the SPRINT trial(8), evaluated the use of reamed versus un-reamed intramedullary nails only. However, with an increasing and diverse array of options available to surgeons, it is important to compare and evaluate the association of various treatment strategies with eventual outcome and complication rates.

Complications rates following tibial shaft fractures are often quoted, but stem from small scale and historic studies and with little differentiation between the varied sub-categories of injuries or fixation methods. One complication which has almost become synonymous with tibial shaft fractures is non-union, where there is a failure of the fracture healing process. It is a particularly devastating complication for both patients and health care systems. At least 25 studies quote tibial non-union rates of 2 – 10% and all make reference to a US textbook published in the 1990s(9) which may be unreliable. The most widely held definition is held by the U.S. Food and Drug Administration (FDA) which defines a non-union as a fracture that is at least 9 months old and has not shown any signs of healing for 3 consecutive months(10). Following this definition, a significant amount of time will have elapsed just to achieve a diagnosis and before any form of management or treatment has been instigated. This can result in escalating healthcare costs(11) of up £26,000(11,12), multiple further operations and reduced quality of life for patients(13,14). It becomes apparent that prediction and prevention of non-union is superior to managing established disease. To that end several predictive tools have been proposed(15,16) but their exact utility and accuracy has not been substantially tested in large numbers of external cases.

## 3.2 Why is this body of work required

As stated previously, tibial shaft fractures represent a spectrum of injuries from simple to complex. Therefore, they cannot be grouped and studied as a single entity. For example, segmental fractures may have different outcomes to simple spiral fractures and this distinction should be made for an accurate and complete description of tibial shaft fractures. Several studies have attempted to compare small elements, for example fixation methods, with each other, but often comprise small studies with low patient numbers. Other larger studies group vast numbers of patients together through national database enquires to make general counts and descriptions without specific details or further breakdown of injuries into component parts for evaluation. Furthermore, many of these large epidemiological surveys of tibial fractures are now several decades old. As modern orthopaedic methodologies and population demographics have progressed, these results warrant updating. Although epidemiological data may not necessarily inform management strategies and progress treatment modalities, it is important to quantify the problem so that healthcare systems can plan and proportion resources appropriately.

## 3.3 Aims

As described in the introductory chapter, the burden, complications and modern day management strategies for tibial shaft fractures requires further accuracy in its reporting and updating. In reference to this, the aim of this body of work is to address these. Therefore, the following objectives are proposed:

- Explore and report on the incidence of diaphyseal tibial fractures within the city of Leeds and the surrounding catchment area between 2008 and 2019.
- Report the patient demographics, mechanism of injury, management and classification of diaphyseal tibial fractures between 2008 and 2019.
- Report the outcomes of diaphyseal tibia fractures in terms of complications, re-operations and union.

- Evaluate and compare known scoring systems for predicting non-union using the patients included in this study.

## 3.4 Structure of work

This body of work will attempt to provide a narrative on addressing these aims. A comprehensive literature review will be undertaken to identify, describe and evaluate the current literature surround the epidemiology, management and outcomes of tibial shaft fractures. The studies described will be evaluated in their scope, strengths and deficiencies in addition to what may be remedied and addressed by this work.

Chapter 5 will describe in detail the methodological approach and the reasons for adopting this method. A discussion on the limitations of these decisions will also be detailed.

Chapter 6 will describe the results of the work and itself comprise several sections. First, a broad reporting of the incidence of injuries and demographics will be described. Second, a description of the fixation strategies utilised, complication rates and the association between the two. Third, a focus on non-united fractures and the methods of addressing these will be presented with a comparison of previously reported non-union risk scores and how they perform on data gathered from this study.

Finally, a discussion summarising the findings and the lessons to be drawn from the work will be considered and summarised including a reflection on the strengths and limitation of the work.

# 4. Literature Review

Herein a detailed literature review will be presented. Multiple sources were consulted in order to obtain relevant literature. These sources include Medline, Embase and Emcare and was conducted in October 2020. Publications from all time periods were included if they were available in the English language and focussed on an adult population. In addition, the references and citation analysis of relevant publications were also scrutinised in order to identify further relevant literature. The full search strategy can be found in Appendix A.

## 4.1 Epidemiology

There are several published studies regarding epidemiology of tibial fractures from the Swedish Fracture Registry (SFR) and although both Sweden and the UK represent developed western healthcare systems, it is no guarantee that results are interchangeable. There is comparatively little published data relating to a UK population. Those that have been reported date back to the 1990s and perhaps have become outdated in terms of population estimates, demographics and treatment modalities.

Court-Brown et al reviewed the epidemiology of all diaphyseal tibia fractures presenting to their institution from 1988 to 1990. A total of 523 diaphyseal fractures were identified. The aimed to study tibial diaphyseal fractures in isolation. More than half of these injuries (54%) were simple type A fractures, with the rate of multifragmented fracture increasing with patient age. Although Soccer injuries were the one of the most common mechanisms of injury, these tended to follow a benign course with simple fracture patterns with few open injuries. The authors reported a high rate of open injuries (23.5%) which tended to occur in an older age group with more complex fracture patterns. Of note, the average age of patients sustaining open fractures after a simple fall was 71.3 years. This subgroup of patients may pose challenges to orthopaedic and plastic surgeons alike (17). According to the authors, this was the first review of tibial fractures using modern classifications. Unfortunately, due to the lack of a denominator, it is not possible to ascertain the incidence of tibial shaft fractures in the population for comparison. In addition, adolescent patients aged 12-years and older were included who have yet to achieve skeletal maturity and where non-operative management is still the preferred treatment modality(18).

Singer et al prospectively reviewed all fractures managed within the city of Edinburgh and surrounding areas in 1992(19). They presented a detailed breakdown of the incidence of tibial shaft fractures according to age. Injuries with a soft tissue component, tertiary referrals and patients aged 95 and over were excluded leaving this incomplete. It is unclear what the authors classed as ‘injuries with a soft tissue component’ and whether this included open fractures as there was no mention or analysis of open fractures. This is important given that open injuries are of particular interest and as Court-Brown et al had alluded to, a reasonable proportion of elderly patients sustain low-energy, open injuries (17). The authors report a bimodal distribution of femoral and tibial diaphyseal fractures occurring in young men (15 to 34-years-old) and elderly men and women (70+ years). The study period only spanned one year in 1992. Again, this study is now several decades old, and the figures quoted may be outdated and not applicable in today’s context and population.

The National Centre for Health Statistics recorded 492,000 tibia, fibula and ankle fractures in the United States in 1992(20). According to census data, the population of the United States was 255,414,000(21) giving an incidence of 192 cases per 100,000 and year. The inclusion of both ankle and fibula fractures may account for the elevated rate when compared to other studies. Again, the study period was only one year in duration and so inferences on trends cannot be made and may not be applicable in the context of the modern healthcare environment and orthopaedic management.

There have been several more up to date accounts of tibia fractures. In 2001, Van Staa et al. reported on the incidence of all tibia fracture within England and Wales between the years 1988 to 1998(22). They reported that the rate of tibia, fibula and ankle fractures combined was 14.8 per 100,000 population and year. This suffers from similar limitations to the previous studies. Tibia fractures could not be discerned from fibula or ankle fractures. In addition, comments on the trend or change in incidence during the study period were not made. Cases were derived from the General Practice Research Database, and although found to be representative of the population, only 6% of patients are included(23).

In 2006, Court-Brown(1) again reported on the incidence of all fractures in the adult population of Edinburgh in the year 2000. They found an incidence of 21.5 per 100,000 and year. There was a 61:39 male to female ratio and demonstrated a unimodal distribution of young men and older woman. The study lacked further detail in terms of mechanism of injury, fracture patterns and the proportion of open injuries.

Larsen and colleagues(24) attempted to record a the incidence of tibial shaft fractures using complete population data from northern Denmark during 2009 and 2010. They reported an incidence of 16.9 per 100,000 and year for all patients including the paediatric population. They demonstrated a trend towards higher energy mechanisms in males and lower energy mechanisms in females. A total of 196 patients were included and appears to be an accurate report, but there was no discrimination between open and closed injuries or patient demographics beyond gender and age.

In 2018, Wennergren et al conducted an epidemiological survey of all tibial fractures using the Swedish Fracture registry(25). They showed an overall incidence of tibial fractures of 51.7 cases per 100,000 and year. Tibial shaft fractures had an incidence of 15.7 cases per 100,000 and year with a male dominance of 59% and mean age 47 years. They also reported a high rate of open fractures at 17.7%, similar to previous studies. This data was prospectively collected, and the accuracy of the Swedish Fracture registry is well documented(26). The study period was five-years and included 417 diaphyseal tibia fractures.

Many of these studies are based on registry databases with large cohorts. However, the accuracy of registry-based databases has been questioned(27,28). In addition, some of these studies lack specific details regarding fracture patterns, injury management and trends over time. The UK based studies performed by Court-Brown and Singer are now 30+ years old within which time there has been progression in understanding of trauma management in addition to implant design and technological advancement. These assessments need updating in order to continue to inform modern healthcare decisions.

## 4.2 Comparison of Treatment Modalities

Several fixation strategies have been adopted to manage diaphyseal tibia fractures. These include plate osteosynthesis with both bridging and compression goals, minimally invasive techniques (MIPO) and open extensile approaches, external fixation including circular frames and intramedullary (IM) devices. Despite a wealth of published material comparing these treatment options, there still remains ongoing controversy regarding superiority of one method over another(5). Several studies aim to compare a combination of these in terms of outcomes and complications. This has not proven to be an easy task as there is a wide spectrum of diaphyseal tibial fractures. Multiple different fracture patterns, high and low energy injuries with significantly different complication profiles and open fractures where the soft tissue injury adds additional complexity all compound each other. In addition, there now exists a wide variety of fixation methods including non-operative, internal, external and intramedullary fixation methods available.  It has become quite difficult to control all these different variables in order to compare certain aspects of management. Furthermore, the approach to tibial shaft fractures has changed over the past several decades. With non-operative management dominating the end of the last century, orthopaedic surgeons now prefer operative fixation, largely in part due to the invention and popularisation of intramedullary devices.

### 4.2.1 Non-operative management

Traditionally, management of tibial shaft fractures followed non-operative principles. In 1970, Sarmiento popularised the concept of functional bracing for tibial shaft fractures. Subsequently, the authors reported on 1,000 tibial shaft fractures treated by this method(29). They reported a low rate of non-union (1.1%) and malunion. Sarmiento et al has since published several prospective series of tibial shaft fractures treated effectively by non-operative measures(3,30–32). It is worth noting that these fractures were treated at a specialised clinic where the application of non-operative management of tibial fractures is well established. The outcomes measured included time to union, angular deformity and shortening. Sarmiento concluded that bracing is an acceptable method for treating tibial shaft fractures if acceptable length can be restored in an axial stable fracture, or if the initial shortening is acceptable in an axial unstable fracture given that final shortening does not exceed initial shortening. Therefore, for axially unstable injuries with unacceptable shortening will not be amenable to non-operative bracing. This caveat may account for the discrepancies in results with other studies evaluating functional bracing for tibial shaft fractures. Unfortunately, the number of patients who failed non-operative management was not reported on in the study, so the success of non-operative measures was not apparent.

Oni et al(33) reported on 100 tibial shaft fractures managed by non-operative bracing. The treatment protocol was described and standardised for all patients using a patellar-tendon bearing cast. 81% of fractures were clinically united by 20 weeks and with continued non-operative managed, 96% were united by 30 weeks. Only 4 patients required non-operative intervention for non-union. Of note, only closed adult fractures were included. Fracture morphology was described but not using modern classification systems.

However, further study into the non-operative management of tibial shaft fractures have not yielded similar results. Coles et al(5) conducted a literature review of tibial fracture management. Five randomised trials and eight prospective studies were eventually included. When pooled together, the studies yielded 145 fractures treated non-operatively. These patients had a combined non-union and delayed union rate of 17.1%, higher than any other treatment modality.

Swart et al(4) reported on their standardised non-operative treatment of diaphyseal tibial fractures over a 10-year-period. At their institution, all closed, isolated, extra-articular tibial fractures are initially trialled with non-operative management in a functional brace. A total of

332 fractures were included for non-operative measures. There was a high rate of failure with 70.2% of patients being converted to operative intervention, including 10 patients (3.01%) for non-union. The authors conclude that, non-operative management is challenging but still feasible for a subset of patient with low energy injuries.

### 4.2.2 Intramedullary Devices

The Study to Prospectively evaluate Reamed Intramedullary Nails (SPRINT) trial is a large multicentre, randomised control trial assessing the difference in outcomes between reamed and un-reamed intra-medullary fixation of tibial shaft fractures. A total of 1339 open and closed tibial shaft fractures across sites in the United States, Canada and the Netherlands were included. The primary outcome was a measure of re-operation rates due to various causes. The Authors found a possible benefit for reamed nails in closed fractures only (relative risk, 0.67; 95% Confidence Interval 0.47 to 0.96; P = .03). However, this difference was largely due to auto-dynamisation (spontaneous locking bolt breakage leading to dynamisation) and not due to a conscious or planned procedure to address non-union or otherwise. Furthermore, follow up was conducted for one year which may not provide sufficient time for complications such as osteomyelitis or metalwork prominence to occur as these can take several years to present. This trial is the largest prospective randomised trail conducted on tibial shaft fractures over multiple geographical sites.

Similarly, a large Cochrane review(34) and subsequent update(35) which included 2123 tibial fractures across nine randomised and 2 quasi-randomised trials failed to show superiority between various intra-medullary devices. In particular, there was no statistical difference in the major re-operation rate, or any complication between reamed and un-reamed nails. Only after sub-group analysis, did the authors find a trend towards reduced rates of non-union with reamed nails as opposed to un-reamed nails for closed fractures only.

The American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) is a national database in the United States whose aim is to collect data on post-operative complications rates. Several authors have used this database to evaluate the post-operative rate of tibial fractures. Dodd et al(36) compared intramedullary nails (IMN) with open reduction internal fixation (ORIF) with a plate for femoral and tibial shaft fractures. A total of 1429 operatively treated tibial fractures (450 ORIF, 979 IMN) were extracted from the ACS-NSQIP. The authors showed that ORIF resulted in a statistically significant increase in the rate of major and minor complications of any kind. In a similar study by Upfill-Brown et al(37), 4963 tibial shaft fractures undergoing ORIF or IMN were extracted from ACS-NSQIP. Patients undergoing ORIF were more likely to suffer surgical site complications, including wound dehiscence and superficial and deep infection (OR 2.04, P = 0.03). These studies include large numbers of cases, but patients were only followed up for 30-days postoperatively and as a result complications such as non-union, osteomyelitis, metalwork removal or complications beyond this time period will not be included. One could argue these are perhaps the most important complications to record, particularly non-union and chronic infection which can result in several repeat operations at substantial cost.

Foote et al(38) conducted a multiple-treatment comparison meta-analysis of six different fixation methods in open tibial shaft fractures from 13 randomised studies. They compared treatment with reamed and un-reamed IMN, Ender nail, Plate osteosynthesis, AO external fixation and circular frames using the Ilizarov technique. The authors concluded the that un-reamed IMN may be the superior option for open fractures regarding re-operation rates. Unfortunately, no conclusion regarding secondary outcomes such as deep infection and malunion could be made owing to small numbers of reported events. In addition, circular frames were not included in the final ranking of surgical methods due to very low quality of evidence.

### 4.2.3 Circular frame and external fixation methods

Fine wire circular frames employ the Ilizarov method of indirect fracture reduction and multiplanar stability. It benefits from minimal soft tissue injury, early weight bearing and no retained metalwork upon completion of treatment. Although it has been described as an available alternative in the treatment of tibial fractures as early as 1992(39), there are comparatively fewer studies evaluating the outcomes and success of this method on the management of diaphyseal tibial fractures. Those that do tend to concentrate on complex or segmental fractures or those with significant soft tissue injury given the above advantages.

Ramos et al(40) conducted a randomised comparative study comparing IMN to Ilizarov frames for tibial shaft fractures between 2003 and 2010. Fifty-eight patients sustaining open and closed tibial shaft fractures were included (31 frames and 27 IMN). Although not statistically significant, there were fewer major complications including compartment syndrome, deep infection, hardware failure, delayed union, pseudarthrosis and malunion with Ilizarov frames when compared with IMN (12.9% vs 29.6%, p = 0.107). A sample size of 30 patients in each arm gave a power of 80%. The power calculation was based on the combined retrospective rate of deep infection and compartment syndrome in patients treated by IMN only. In addition, open and closed fractures were analysed together. This may confound results as open fractures have been shown to produce higher complication rates. Although sufficiently powered, a larger study may be required to achieve statistical significance in the authors findings, particularly when investigating some of the less common major complications.

A case series of 40 complex tibial shaft fractures managed by the Ilizarov technique was reported by Foster et al in 2012(41). They reported good outcomes in this complex fracture group with 90% progressing to union without the need for additional procedures and good to excellent results reported in several patient reported outcome measures. As stated previously, simple diaphyseal fractures were not included. However, as a case series we do not know how these outcomes compare against similar cases with differing fixation methods.

### 4.2.4 Plate Osteosynthesis (ORIF)

Plate osteosynthesis has long been a standard method for fixation of long bone fractures. Given the tibias subcutaneous anatomy there is a concern over soft tissue stripping, wound complications and infection. Minimally invasive plate osteosynthesis (MIPO) techniques have been developed to try and mitigate this. Plate osteosynthesis can be advantageous in distal shaft fractures where reduction and fixation of the distal fragment can be problematic when employing intramedullary devices.

Littenberg et al(7) performed a meta-analysis of randomised and non-randomised trials comparing the treatment modalities of closed tibial fractures. They showed a reduction in the rates of superficial infection with non-operative treatment (0 – 4% vs 0 – 22%; P =0.05), but a longer time to union (14.7 weeks vs 13 weeks; P = .06) when compared to ORIF. Unfortunately, only one comparative trial included patients managed with IMN therefore only ORIF and non-operative treatments were compared. The authors also acknowledge that the inclusion of non-randomised trials in their meta-analysis may leave the results prone to confounding and bias.

A large, randomised control trial was conducted by M. Costa and colleagues looking at outcomes between plate osteosynthesis and IMN for extra-articular distal tibia fractures(42). A total of 321 patients were randomised to either plate fixation (MIPO or otherwise) or IMN. The primary outcome was Disability Rating Index (DRI) scores at 6 months. There was no statistically significant difference in disability status at 6 months nor was there any difference in complication rate between the two treatment arms.

In 2015, Li et al(43) performed a systematic review of eight eligible RCTs and retrospective studies that compared IMN to plate osteosynthesis with a total number of 487 extra-articular distal tibia fractures. The authors showed an increase in major complications with IMN vs plate. This was largely driven by malunion and anterior knee pain in the IMN group. The plate group showed statistically significant increase in wound problems. Although the authors report an increase in the rate of non-union for IMN, studies assessing non-union as a primary outcome measure were excluded from the systematic review and so this conclusion was made without evaluating all the available evidence and studies whose primary aim was to evaluate the risk of non-union. A more recent meta-analysis by Bleeker et al(6) corroborated this finding with a higher risk of infection with plating (OR: 2.4, 95%CI 1.5 – 3.8) but no statistical difference in the rate non-union, re-operation or functional outcomes.

### 4.2.5 Temporary external fixation

In some instances, tibial fractures are initially stabilised prior to definitive bony fixation. The simplest method of this is via a splint or plaster cast, but in some instances an external fixation device is applied as an intermediate procedure. The use of an external fixator has several perceived benefits. They can provide immediate long bone stabilisation whilst giving access for soft tissue management. This has been well described and has obvious benefits in the context of open fractures. In addition, their use may be mandated in the context of a damage control strategy whereby long bones can be stabilised with minimal surgical insult to try and avoid or alleviate a 'second hit phenomenon'. This has been shown to be safe and effective in this context(44–46). Bhandari et al reviewed the current literature surround the use of temporary fixation of both tibial and femoral shaft fractures in 2005(47). Only one randomised RCT was found comparing temporary stabilisation with cast versus external fixator with the remaining evidence level IV case series. They concluded the technique safe but acknowledge the lack of prospective studies and hypothesised a cohort of 150 to 400 patients would be ideal.

External fixators may produce further physiological benefits in the context of major trauma. Maury et al(48) compared different temporising measures (skeletal traction and external fixation) before definitive management of femoral shaft fractures in severely injured patients. The main outcome measure was on respiratory complications and the need for and duration of mechanical ventilation. This study was retrospective and included 55 patients. Temporising with skeletal traction produced a higher incidence of Adult Respiratory Distress Syndrome (ARDS) than temporising with an external fixator.

Contrary to the perceived benefits, much attention has been given recently to the potential pitfalls and complications associated with the use temporary external fixation. These mostly revolve around possible infective complications. In the previously mentioned literature review, Bhandari et al(47) concluded that external fixators should ideally remain in-situ no longer than 28 days as there is significant increase in the complication rates.

Zelin et al(49) corroborated this finding in a retrospective analysis of 122 open tibial fractures. All patients underwent temporary external fixation of various durations and stratified into one, two- or three-weeks duration. Cases were further subdivided into those who received conversion to internal fixation immediately after removal of external fixation and those who received a 5-to-7-day rest period before final fixation. There was a significant increase in infection rates when temporary external fixation was left in-situ for more than 28 days (23.3% vs 6.3%, p = 0.007). There was no statistical difference in infection rates when definitive management proceeded immediately after external fixation removal or after a period of abstinence.

In contrast, Harwood colleagues(50) compared the rates of superficial and deep infection in femoral shaft fractures that have been temporised to those that proceeded straight to definitive IMN. The infective rates were comparable in both approaches and temporising with an external fixator did not confer any additional infection risk. The authors also measured the contamination of pin-site tracts via bacterial cultures. This revealed that contamination rose substantially when the device was left in-situ longer than 14 days, but this did not result in a clinically apparent infective complication.

Most studies relating to the use of temporary external fixation concentrate on open, high-energy injuries whereby their use is usually necessitated rather than a specific management decision. It may of interest to the trauma surgeon to evaluate their use and safety outside of this context. In addition, the majority are retrospective in nature with few comparisons made to case matched injuries that have proceeded straight to definitive management.

### 4.2.6 Management of open injuries

Optimum management of open tibial injuries is reliant not only on fracture fixation but also on the soft tissue management. Low energy Gustilo-Anderson grade 1 and 2 injuries are appropriate for primary or delayed primary closure or healing by secondary intention. However, high energy grade 3 injuries represent a perilous situation to trauma surgeons. There are a variety of soft tissue reconstructive options including local and pedicled flaps, fascio-cutaneous flaps and free soft tissue transfer. In addition, the timing of these procedures is crucial. The operative management of open fractures begins with the timing of first debridement. The British Orthopaedic Association Standards for Trauma (BOAST)(51) have released guidelines for the timing of this based on the energy of injury and the level of contamination, with all injuries being debrided within 24 hours and soft tissue coverage with 72 hours following injury.

## 4.3 Complications Following Tibial Shaft Fractures

Tibial shaft fractures can be fraught with complications. Waddell et al(52) reported an overall complication rate of 30% in 1983 in a cohort of 38 fractures. Beyond this, complication specific rates are reported often in single centre or small sample studies.

### 4.3.1 Thrombo-embolic disease

The incidence of venous thromboembolism (VTE) in operatively treated tibial shaft fractures varies widely with rate ranging from 1 to 10%(53,54) rising to 45% in patients treated non-operatively in plaster(55). This can rise as high as 77% in polytraumatised patients with the presence of a tibia fracture conferring a five-fold increase in risk(56). However, many of these studies focus on asymptomatic embolic disease that is only diagnosed on venographic studies and not clinically symptomatic disease specifically. The exact significance of these events is unclear.

### 4.3.2 Compartment Syndrome

Compartment syndrome is the presence of elevated pressure within an osteo-fascial compartment such that the capillary network is compromised. This can result in irreversible ischaemic necrosis to nerves and muscles. Management depends upon prompt and emergent diagnosis and decompression in the form of fasciotomy. Tibial fractures have a particular association with acute compartment syndrome with the rate of compartment syndrome ranging from 2 to 10%(57–59) and 36% of all cases of acute compartment syndrome occurring in the context of tibial fractures(60). Furthermore, compartment syndrome has been shown to result in increased average length of stay and health care costs in excess of twice that of patients without compartment syndrome(58,61). The concern over fracture union in patients with compartment syndrome has been highlighted as early as 1987. Court-Brown et al(62) performed a retrospective review of 3,000 tibial fractures treated at their institution. By comparing adult patients who developed a compartment syndrome (n = 17) to a control (n = 25), they concluded that union took an average of 20 weeks longer. Reverte et al conducted a literature review of studies containing tibial fractures that developed compartment syndrome and subsequently underwent fasciotomy. When compared to a control who did not develop compartment syndrome, there was a statistically significant increase in healing time by 4.9 weeks(63).

Stella et al. conducted a systematic review of the literature surrounding the aetiology of compartment syndrome. The authors summarised the risk factors for fracture related compartment syndrome, of which 70% are due to tibia fractures. Young age, Grade 2 open injuries and multi-fragmented and segmental fractures patterns confer risk(64).

### 4.3.3 Non-union

The most agreed upon standard definition of non-union made by the FDA is a fracture that persists for a minimum of nine months or without signs of healing for three consecutive months. All fractures are at risk of this complication, but there is a particular concern regarding tibia fractures with non-union occurring at a rate 3 to 5 times more often than other fractures(65). Many theories have been postulated and most implicate the tibias unique anatomy and subcutaneous border as a major contributing factor. This results in a tenuous soft tissue envelope and hence blood supply. There is a higher risk of open fractures and associated infection risk.

In 2007 Tzoupis and Giannoudis(66) reviewed the literature regarding the prevalence of non-union of diaphyseal tibia fractures. The reported prevalence varied widely according to treatment modality and grade of soft tissue injury reaching 80% in Type 3 injuries managed by unreamed IMN. Although this review was based on a number of small trials with specific fracture patterns and treatment methods, the authors estimated an overall rate of non-union of 6.4% in tibial fractures managed by reamed IMN in both open and closed injuries.

In 2017, Mills et al attempted to report and update the risk of non-union per fracture in the national population of Scotland(67). Data was taken from the national diagnosis coding system in Scotland over a 5-year period. As previously mentioned, the use of coding systems can be imprecise, so the authors cross checked a sample of 100 patients and found the coding data to be 97% accurate. The overall rate of non-union in any fracture was 1.9%. Unfortunately, non-unions of the tibia could not be separated from those of the fibula. After removing fibula fractures from the denominator of their data, a conservative rate of 5.4% and upper limit of 7.5% was concluded based on the previously reported incidence of fibula non-union. This is an overall rate and does not discern between fixation methods, fracture patterns and metaphyseal tibial fractures including open and closed injuries. Although the large scale of the cohort is welcomed, the authors have still had to make approximations to confound for the difficulties in extracting tibia specific data from national registry-based data.

The SPRINT trial reported on their non-union rate while investigating the results of reamed and un-reamed IMN. This is welcome due to the large and multinational scale of the trial. The report and overall non-union rate of 4.6% (6.8% in open fractures and 2.4% in closed fractures). Non-union in this instance was defined as any patient who underwent exchange nailing or bone grafting to progress union and not using FDA definition or any radiological criteria. In addition, it would be interesting to evaluate the rates of non-union in other treatment modalities.

There have been several studies attempting to elucidate the risk factors for the development of non-union. These are generally separated into general and local risk factors. General factors shown to play a role include female gender, smoking status and poorly controlled diabetes mellitus among others(68). Local factors relate to the injury and associated soft tissue damage. Open fractures have consistently demonstrated higher rates of non-union than closed injuries. This may be in part due to the higher rate of infection and disruption of the soft tissue envelope and therefore vascular supply of the fracture site. In addition, fracture morphology has also been implicated with unstable multi-fragmented fractures and those with associated bone loss adding risk. The mechanical environment produced by fixation methods, persistence of fracture gap and the degree of soft tissue stripping required to achieve reduction are the modifiable operative factors that have been incriminated(65,69–71). Despite this seemingly exhaustive list there is also an evolving suspicion over a genetic predisposition for the development of non-union and owing to the wide variation in union times among patient, injury and fixation matched individuals. This is a topic of ongoing and extensive research(72). Zura et al(68) investigated the risk factors for non-union in the adult population using a private healthcare database in North Carolina with a total of 309 patients with 330 fractures included. Several demographic risk factors were included such as male gender, opioid and NSAID use, Type I diabetes, multiply injured patients and open fractures. Interestingly smoking was not deemed a significant risk factor, but the authors acknowledge that reliable data on this demographic was probably incomplete. This study was limited however as patients older than 63 were excluded as they would have transitioned to a different healthcare database.

Unfortunately, the product of a non-united tibia fracture is deleterious to both patient and health care systems alike. According to Kanakaris et al. the estimated cost of managing non-union in the UK is £16,330. This is based on a ‘best case’ scenario whereby management followed an uncomplicated course with optimal and timely recovery with no additional complications(11). This is unlikely given that almost one third of all tibial fractures require secondary operations(73). A large study by Antonova et al in the U.S. found the median total healthcare cost of patients with tibial non-union to be $13,870, more than twice that of patients without non-union. They also found a higher rate and longer duration of strong opioid prescriptions. The study did not follow all patients up to union within the study period and so there may be further healthcare costs not included within the estimates. The study also did not consider indirect costs such as loss of patient earnings, legal costs and residential or nursing care. It is estimated that this may represent 80% of the total cost of musculoskeletal conditions(74). A literature review by Stewart in 2019 concluded that, based on the current UK population of 67 million, the annual bill for managing non-union could be £320 million(75).

From a patient perspective non-union has a detrimental impact on patient quality of life. Brinker et al(13) reported the result of various patient reported quality of life scores in patients who had sustained tibial non-unions. They employed a 'Time Trade-Off' (TTO) score, whereby patients were asked how much of their remaining life span they would be willing to 'trade in' to regain perfect health with patients willing to trade in 36.5% of their remaining life span in order to achieve this. The Short-Form 12 Physical Component Summary (SF-12 PCS), a measure of patients overall physical health and function, was lower than all other musculoskeletal and non-musculoskeletal conditions including end-stage arthritis, myocardial infarction, sciatica and depression.

A systematic review conducted by Johnson et al in 2019(76) pooled 4 non-randomised studies concerning the physical and psychosocial health of patients suffering tibial non-unions. Despite overall poor methodology in the included studies, the authors showed a significant reduction in SF-12 physical and mental component scores compared to the normal population. In a further by Tay et al(77), similar effects on SF-12 scores were found amongst non-union patients but in addition, they found that 56% of patients were not able to return to work and 72% of patients had ongoing pain at 12-month follow up.

### 4.4 Fracture Healing and Non-Union

At a cellular level, fracture healing is a complex orchestration of various complex processes and key mediators that is initiated from the time of injury. The process begins with the coagulation and inflammatory cascade and the formation of a haematoma. This generates several key mediators including platelet-derived growth factor (PDGF), insulin-like growth factor (ILGF) and transforming growth factor β (TGF-β) proteins, of which bone morphogenic proteins (BMP) are a member. These osteoinductive agents act to attract, differentiate and mature the osteoprogenitor cells in preparation for tissue regeneration and repair. The osteogenic cells comprise both pluripotent mesenchymal stem cells (MSCs) from the bone marrow and committed osteoprogenitor cells resident in the surrounding periosteum(78). These mediators have been the subject of extensive research due to their implication in fracture repair and the exact mechanism and the inner workings of this complex process is still not fully understood. The third factor in the cellular response to fracture healing is the requirement of a scaffold for the osteogenic cells to base their work. This is the concept of osteoconduction. With well opposed fracture ends, local necrotic and redundant bone can act as a natural canvas until fracture repair and remodelling is complete. In some instances this is insufficient and must be supplemented artificially(78,79).

Further to these complex cell signalling pathways lies the local strain and mechanical environment of the fracture site. Laboratory studies have shown osteocytes have the ability to sense and react to the surrounding mechanical environment through fluid shifts in canaliculi and cell surface mechanoreceptors(80). Perren discusses the interplay between fracture healing and local strain environment in his landmark 1978 paper(81). He states that some level of strain is required to induce callus formation, whereas strain beyond a certain threshold (10 to 30%) is counterproductive and promotes resorption as opposed to callus formation. Consequently, a large component of modern orthopaedic methodology and fracture fixation aims to control the local strain environment through implant choice and fixation methods. It therefore comes as no surprise that these methods are implicated in the development of non-union whereby the mechanical environment has become unfavourable for progression of callus formation or persistent fracture gap impedes healing. Although this concept has remained theoretical, it is still widely used and discussed with regards to fracture healing.

Overlying these cellular and mechanical principles are host, or patient, factors. These include issues with vascularity which can impede the inflammatory cascade and the recruitment of osteoinductive factors and osteogenic cells. This has implications for high energy and open fractures or where operative dissection is excessive and compromises the soft tissue envelope and periosteum. It is also true for conditions such diabetes, immunosuppressive conditions, peripheral vascular disease, endocrine disease and smoking status among others(82).

Infection is also implicated in several non-unions. The presence of bacterial infection has the potential to interfere with previously described biological pathways of fracture healing. It can also lead to localised bone resorption and implant loosening thereby changing the mechanical environment and leading to the development of delayed- or non-union(70). There is suspicion that low grade and sub-clinical infection may be responsible for many cases of seemingly idiopathic and aseptic non-unions. In a fascinating article by Sczerny et al(83), intra-operative tissue samples were collected from the fracture site of patients with closed tibial and femoral shaft fractures. One cohort had their samples taken immediately during their index procedure, the other cohort had their samples extracted on subsequent operations for non-union and delayed union. Microbiological culture grew bacterial pathogens in 35% of non-union cases and 14% of cases with uneventful healing. The implication being that low grade and perhaps sub-clinical infection may have an appreciable effect on the development of non-union.

This complex array and interplay of these various factors is succinctly summarised by the 'diamond concept' proposed by Giannoudis in 2007(79). The concept advocates fulfilling certain criteria in order to achieve successful fracture union. These criteria include availability of osteoinductive mediators, osteogenic cells, an osteoconductive scaffold and an optimum mechanical environment. In addition, adequate vascularity around the fracture site and optimisation of host factors (for example smoking status) are also considered. The concept aims to describe an optimum situation for union but can also provide a framework to guide the management non-union.

There is also the issue of definitively labelling a fracture as united. Several radiographic indices have been proposed to indicate fracture union including restoration of cortical continuity, disappearance of fracture lines and size of callus(84). Unfortunately, even these have not shown to be infallible assessments of fracture union. Hammer et al(85) reviewed 208 tibial shaft fractures for radiographic union and permitted full unrestricted weightbearing only when radiographic measures indicated stability. In 55% of unstable fractures, the films pointed to satisfactory union. In the 93 fractures that were mechanically stable, the films suggested that no union had been achieved in 44% of these.

In 2010, Whelan et al(86) developed the Radiographic Union Scale in Tibial fractures (RUST) score. The aim was to standardise the assessment of tibial union given that presence of callus and disappearance of the fracture line offered the most observer reliability(87). The score was initially developed for tibial fractures that were treated by intra-medullary nails but has been employed to assess union in fractures managed with circular frames and plate osteosynthesis(88). It has shown good inter- and intra-observer reliability(89,90).

## 4.5 Predicting Non-Union and Risk Scores

With mounting evidence demonstrating the burden of non-union, it is no surprise that abolition of this complication would be a great societal gain and improve patient care. Unfortunately, by the nature of the diagnosis a considerable time (9 months according to the FDA definition of non-union) has elapsed before the diagnosis of non-union has even been made. Only then will the clinician and patient embark upon the potentially arduous journey towards union, often with multiple re-operations and uncertain outcome. It is worth noting that in practice this definition is probably not strictly adhered to, and patients may be identified based on unsatisfactory radiological or clinical progress. This is ill-defined and an ideal scenario would be to correctly identify factors leading to non-union and predict which patients are at elevated risk so that they may be followed more closely with potential for earlier intervention. To that end several scoring systems have been developed that incorporate a number of predetermined risk factors in order to achieve this very goal.

The Leeds Genoa Non-Union Index (LEG-NUI) was devised in 2020(15) as a tool to help assess the risk of long bone non-union and plan for early intervention. The score was conducted after a case control of 100 tibial and femoral non-unions against 100 control patients. Ten factors were compiled from previous literature: post-surgical fracture gap > 4 mm, presence of infection superficial or deep, sub-optimum mechanical stability, initial displacement of more than 75% of bone shaft width, fracture of the tibia rather than the femur, soft tissue damage, open method of fracture reduction, wedge or multi-fragmented fracture type, smoking habit, and fracture location in an area of low vascularisation of the bone (distal third). Smoking habit and fracture location were subsequently excluded from the final score due to low adjusted odds ratio (OR 1.39 and 1.31, respectively). The score produced an area under the Receiver Operating Characteristics (ROC) curve of 0.93 and sensitivity and specificity of 86% and 87% at the optimal cut point of ≥ 5. The score was based on tibial and femoral diaphyseal fractures and can be used for both, but therefore is not specific to tibial shaft injuries. All fixation methods were included.

Preceding the LEG-NUI score, the Non-Union Risk Determination (NURD) score was produced by O'Halloran et al(16) in 2016. The methodology was similar to the development of the LEG-NUI score, using logistic regression analysis against a list of risk factors extracted from the current literature. The independent variables included similarities like presence of open fracture, extent of soft tissue and bony injury and quality of reduction. In addition, gender, comorbid disease, compartment syndrome and requirement for soft tissue coverage were also included. A total of 382 patients were studied retrospectively, including 56 patients who developed non-union. Almost 90% of the cohort sustained high energy injuries with an average Injury Severity Score (ISS) of 16.5 and so may not be completely representative of the general population of tibial fractures. Furthermore, patients with anticipated non-unions who underwent prophylactic non-union procedures were excluded from analysis (n = 61), as were a large number of patients (n = 336, 34%) with insufficient follow up data. Unlike the LEG-NUI score, only patients who were managed by IMN were included in the derivation of the score and its subsequent validation.

The external validity of the NURD score was tested in a recent paper using data from the SPRINT trial(91). This was conducted in part by the same authors who produced the NURD score originally and included 382 patients and 56 non-unions. The score did not perform as well with the SPRINT data than during its original conception. In particular, there was a reduction in discrimination with a C-statistic of 0.61 when subject ROC analysis. This was attributed to numerous case-mix differences between the SPRINT trial data and the derivation data and shows poor generalisability of the score to other cohorts of tibial shaft fractures.

Both scores were evaluated by Chloros et al(92). The scores were compared against a cohort of 15 prospectively selected patients (5 non-union cases and 10 uneventful cases). The LEG-NUI score achieving good positive (PPV = 100%) and negative (NPV = 90%) predictive values and the NURD score achieving less favourable outcomes (PPV = 40%, NPV = 100%). Despite the very small numbers used in this comparison there has been no further reported evaluation of these scores in the literature.

# 5. Methodology

## 5.1 Study design

This project took the form of a retrospective cross-sectional study and service evaluation of all patients sustaining a tibial shaft fracture in the city Leeds. A retrospective study design was adopted in order to maximise the number of patients recruited. In addition, trends over time could be evaluated and presented. The time-period ranged from January 2008 to December 2019. These dates were chosen as before 2008, plain radiographic images were not available for viewing via the Picture Archiving and Communications Systems (PACS). This is a software application that allows clinicians to view radiological investigations. Prior to this, plain radiographs were printed and viewed directly on a lightbox and review of these studies would be highly impractical. The year 2019 was chosen as an end date as it was felt that this would allow sufficient time for follow up data and complications to have occurred for study as many of these, for example non-union and osteomyelitis, occur several years following injury. Acknowledgment was given to the fact that the COVID-19 pandemic active during 2020 and the nation entered a national lockdown early in the calendar year. This may have had some impact on outpatient follow up of patients sustaining injuries in 2019.

## 5.2 Population to be studied

The population to be studied was all adult patients (regarded as 18 years and older) presenting to Leeds General Infirmary with a diaphyseal tibia fracture. This included isolated tibial shaft fractures and tibial shaft fractures present in in multiply injured patients. The decision to study diaphyseal fractures in isolation as opposed to the whole bone was three-fold. In the first instance, articular fractures at knee (plateau) and ankle (pilon) fractures have an extra layer of complexity and often require different surgical strategies and priorities including anatomical joint reduction, early range of movement and primary bone healing. Secondly, the diaphysis of the tibia includes the sub-cutaneous antero-medial border where the overlying tissue envelop is thin. This may lead to an increased rate of open fractures. Lastly, distal metaphyseal tibial fractures at the ankle begin a spectrum from distal shaft to extra- and intra-articular pilon fractures to ankle fractures which may include medial malleolar or Volkmann fractures (posterior malleolar fractures). Although tibial fractures also include fracture around the ankle, these metaphyseal and articular fractures have different operative goals of anatomical reduction, interfragmentary compression and absolute stability compared to the diaphyseal portion of the tibia.

Paediatric patients were excluded on the basis that the paediatric skeleton has incredible remodelling and healing potential, and therefore vastly different outcomes and treatment strategies. This group of patients require isolated assessment and investigation.

Tertiary referrals were included only when a substantial amount of management and outpatient follow up had not occurred elsewhere and provided data on the initial injury and presentation was available in the patient notes. These additional patients were included for analysis of complication rates and management outcomes and not for incidence data for the catchment population. In addition, patients who were subsequently transferred out of area for outpatient follow up were included only for basic demographic and incidence reporting, but not for outcome or management data as lack of follow up data precluded it.

Exclusion criteria were patients with insufficient follow up data or patients under the age of 18-years-old. Ideally a follow-up period of 12 months was desired. However, in some instances patients were discharged prior to this after their recovery had been deemed complete by the treating clinician. This was acceptable and therefore these patients were included. If patients failed to complete 12 months follow-up through non-attendance, then this was classed as insufficient follow-up data and patients were labelled as such and excluded from further analysis beyond basic demographic and injury specific data.

## 5.3 How were patients identified

It has been shown that patient identification using hospital coding systems are inaccurate and incomplete with up to 24% of patients given the incorrect diagnosis(93). Therefore, patients were identified using a variety of other sources and cross referenced to ensure that all possible cases were included for analysis. At our institution, daily trauma lists and patient handover documents are completed for each 24-hour period for presentation at the trauma meeting. These are held as paper copies but also stored electronically on the Trust intranet. In addition, operative theatre records are maintained and stored with basic patient and operative details. Both of these records were interrogated in order to identify all patients who underwent, or were considered for, operative intervention. Patients who were not considered for operative intervention or erroneously missing from these records would be potentially overlooked. Therefore, a list of all tibial plain radiographs performed during the study period was obtained from the institution's radiology department. This list comprised a total of 77,000 plain radiographs to screen. Requesting information and radiological reports were used to exclude a substantial proportion of these relatively quickly. The remaining radiographs were assessed included if applicable. Following this it was felt that all possible sources were scrutinised to obtain a complete data set.

## 5.4 Data collected

Online and scanned clinical patient notes, plain radiographs and outpatient correspondence were reviewed. Data was collected and recorded anonymously on a data collection tool using Microsoft Excel. The following data was collected.

### 5.4.1 Demographics and Patient Comorbidities

Patient age and gender were recorded at the time of incident. Comorbidities were recorded using the Charlson Comorbidity Index (CCI)(94). The score is used to calculate the 10-year survival rate of patients as a result of pre-existing comorbid disease. The specific comorbidities considered include:

- Ischemic heart disease and myocardial infarction
- Heart failure
- Peripheral vascular disease
- Cerebrovascular disease or transient ischaemic attack
- Dementia
- Chronic Obstructive Pulmonary Disease
- Connective Tissue disease
- Peptic Ulcer disease
- Liver disease from mild to severe
- Diabetes
- Hemiplegia
- Chronic kidney disease
- Tumour
- Leukaemia
- Lymphoma
- Human immune-deficiency virus or AIDS

A score of 0 indicates no comorbid disease with an estimated 10-year survival of 98% and the maximum score of 37 giving a 10-year survival rate of 0%. The CCS has been used successfully in medical and registry-based research and has been widely validated particularly in post-operative surgical patients(95,96). In addition, the components of the score were applicable to certain factors implicated in fracture healing that would be beneficial to investigate, for example, diabetes, immunosuppressive conditions, and peripheral vascular disease. Comorbidities not included in the index were recorded separately.

### 5.4.2 Injury classification

Fractures were classified according to the AO/OTA fracture and dislocation classification compendium 2018(97). This is an alpha-numeric classification which assigns each bone and segment a numerical label and fracture pattern denoted by an alphabetical suffix (A – simple fracture, B – Wedge fracture and C – Multifragmented fracture). Specifically, types 42 (subtypes A, B and C) were included. The transition between the diaphyseal (Type 42) and metaphyseal (type 41 and type 43) fractures is arbitrary and open to interpretation. Primary fracture lines occurring in the proximal and distal 50mm were classed as metaphyseal fractures and not included. This is in line with previous reported epidemiological studies in order to maintain consistency(17). If *displaced* articular extension was present and in continuity from the diaphyseal fracture, then the fracture was deemed metaphyseal and excluded. If *undisplaced*, the injury was classed as diaphyseal with articular extension and hence included in the cohort. The classification of fractures was performed by a single author.

Open injuries were classified according to the Gustilo-Anderson classification system. This information was derived from the operative notes, the need for free tissue transfer or from clinical photographs where these were available. The Gustillo-Anderson classification is the most widely used classification of open fractures with and therefore beneficial for comparison of other studies(98). It stratifies open fractures into 3 types in order of increasing soft tissue injury. Part of its appeal is to guide soft tissue management and it has shown good correlation with complications, in particular infection(99,100)

### 5.4.3 Injury and Management Details

The date of injury was recorded as the initial contact from care providers or attendance to the emergency department, whichever was available or earlier. If this was not available, then the time of the first diagnostic radiograph was used. Where patients had sustained initial injuries abroad or had a delayed initial presentation then the injury date was estimated from documentation. When this was not available then the first diagnostic radiograph was taken as the time of injury.

The mechanism of injury was recorded from a pre-populated list of options. Road Traffic Collisions (RTC) were stratified into pedestrian, driver/passenger or cyclist RTCs. Falls made up a large proportion of injuries and these were stratified into low energy fall from standing height or high energy fall from greater than standing height. A fall down a full flight of stairs was taken as a fall greater than standing height. The Injury Severity Score (ISS)(101) was used to classify patients into major- or poly-traumatic presentation (ISS >15) or not. To supplement this, any additional injuries sustained at the index event were also recorded.

Subsequent timing of the initial operative intervention was recorded whether this was definitive or temporising management (for example, application of an external fixator). In the event of non-operative management then the time of application of the definitive cast or first check plain-radiograph thereafter was taken. All subsequent operations were recorded and their date. In the event of open fracture, the method of soft tissue coverage was recorded including primary closure at the time of definitive bony fixation.

The length of hospital stay and the duration of outpatient follow up was recorded. Ideally 12 months of outpatient follow up was desirable. This would allow sufficient time for late complications such as non-union or metal work irritation to develop. In some cases, patients were discharged before this time due to satisfactory progress and where the responsible clinician had deemed treatment complete, so this was also acceptable. A proportion of patients did not attend or were lost to follow up and a further subset of patient completed their outpatient journey elsewhere. These patients were included for demographic purposes only.

### 5.4.4 Complication Outcomes

Superficial infection was defined as any surgical site infection involving only the skin and superficial tissue that required antimicrobial therapy. Deep infection was defined as infection involving muscle compartments, abscess formation or infection that required operative intervention.

Malunion, joint contractures and post-traumatic arthritis were based on the outpatient clinical documentation as diagnosed by the treating surgeon rather than on radiological grounds.

## 5.5 Assessment of union

The diagnosis of fracture union is imprecise at best. Bhandari et al conducted a cross-sectional survey of 577 orthopaedic surgeons exploring the definition of union, non-union and malunion. There was considerable variability in the use of, and combination of, several clinical and radiographic indices of fracture healing. There was no consensus on the optimal assessment of fracture healing or the definition of non-union and malunion with large variability on all three (84).

With a lack of standard assessment clinicians continue to employ a combination of clinical signs of union and serial plain radiographic examinations. Clinical signs include the ability of a patient to mobilise pain-free without deformity and the absence of pain and mobility on palpation of the fracture site. This can be misleading particularly in load bearing devices such statically locked intra-medullary nails where pain free mobility may not necessarily guarantee fracture union. In the case of circular frames, this was taken as successful dynamisation of the frame at outpatient follow up whereby certain elements of the frame are loosened in order to allow the tibia and fracture site to transmit bodyweight. This is somewhat artificial as, generally, frames were dynamised only when the treating clinician believed that the fracture has healed radiographically and as standard practice at our institution patients were mobilised for 2 weeks on a dynamised frame prior to definitive removal. Therefore, differences in these two indices may not be apparent for this subset of patients.

As described, there is no “gold standard” assessment of union. The RUST score was employed to measure progression of union amongst cases as it is still widely used, validated and easily accessible using existing plain radiographs in keeping with the retrospective nature of this study. The score was calculated at 8, 12, 24 and 36 weeks post-operatively. In addition, the highest score achieved and the date of this was also recorded. A RUST score of 3 (bridging callus present) on at least three cortices was deemed to be united giving a minimum score of 9 which appears to be consistent with other orthopaedic trauma surgeons definition of union with regards to the score(88). In some instances, it was not possible to calculate a RUST score since all four cortices must be visualised. This may be the case with the use of circular frames where the metal work can obscure the fracture site. Where all four cortices were not visualised, cross-sectional imaging was used if this had been undertaken. Using a mid-sagittal and mid-coronal slice to recreate an antero-posterior and lateral radiograph, a RUST score could still be calculated. In this absence of cross-sectional imaging, then the fracture was deemed united on clinical grounds if the treating clinician indicated so during outpatient follow up. In the case of plate osteosynthesis there is frequently no callus formation due to primary bone healing and so a RUST score was not recorded, but radiographic union was assumed on the disappearance of the fracture line. Both time to clinical and radiographic union were recorded separately, but radiographic union was used for the purposes of outcome measures as this was deemed to be the most objectively measurable.

As stated previously, there is no accepted or validated definition of non-union. The FDA is the most widely used and is the definition that was adopted for identification of cases. In addition, when a non-union was declared by the treating surgeon or when any additional procedural interventions were required to promote union, then this was also deemed a non-union. With regards to circular frames, this constituted a complete frame revision with or without biological augmentation. Often frame surgeons will dial in incremental compression and/or distraction at the fracture site in the outpatient department with the aim of creating micro-motion and stimulation at the fracture site to progress union. This was not taken as an additional procedure as most would regard this as a standard practice of management using circular frames and the Ilizarov technique and does not require an anaesthetic, procedural sedation or a theatre environment.

## 5.6 Statistical analysis

The majority of the analysis of data will rely on simple descriptive statistics and are presented by the use of simple descriptive tables and graphs where applicable. Rates of complications or injury categories for example are reported as a count and percentage of the total number of cases included in that analysis. When continuous data did not follow a normal distribution, the median will be reported along with the interquartile range to describe the spread of data.

Where associations between two or more categorical outcomes were investigated, a Pearson chi square test for independence was calculated. Where the expected counts of more than 20% of the cells in the contingency were less than 5, then a Fisher exact test was calculated instead(102). This will be indicated in the text.

For continuous outcome variables, student t-tests and one-way Analysis of Variance (ANOVA) tests were used to compare means between independent groups. These parametric tests were employed even when the distribution of the outcome variable in each group did not follow a normal distribution. This has been deemed acceptable given a large enough sample size. The central limit theorem suggests that with sufficiently large samples, the sample mean will approximate the true population. The sample size frequently quoted is $n > 30$ for this to hold true. This is of benefit as parametric tests are more robust with higher statistical power than non-parametric tests(103). Prior to ANOVA, a Levene's test was calculated to determine if the variance between groups was similar. Post-Hoc multiple comparison analysis was performed using appropriate post-hoc tests according to the specific context and spread of data and followed the suggestions outlined by Toothaker 1993(104).

All descriptive and inferential statistics were computed using IBM statistical program for the social sciences (SPSS v. 27)(105) and Microsoft Excel. A significance value of less than 5% was used for all statistical tests.

## 5.7 Data Recording

Data was recorded anonymously using a data extraction tool produced on Microsoft Excel. Data was recorded as ordinal categorical or continuous scalar variables, without the free text input, to facilitate subsequent analysis.

## 5.8 Clinical governance

The project was registered as a clinical audit and service provision project with the clinical governance department at Leeds General Infirmary with identification number #8195. Furthermore, the NHS Health Research Authority Confidentiality Advisory Group guidance (CAG) states that for local audit a CAG application is not required provided that(106):

- the work is conducted by one of the organisations that has delivered the patient's care or treatment
- The work is carried out in accordance with clinical governance guidelines
- It has been approved by the NHS Trust's medical director/Caldicott Guardian.

The results of this retrospective cohort study have been presented in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) cross-sectional checklist(107).

## 5.9 Appraisal of methodology

There are several benefits and limitations to the study design that will now be discussed. First of all, it is retrospective in nature. As such, only data that is available and has been reliably recorded is available for extraction. If certain data points are missing in particular cases, it may be impossible to remedy this and so the quality and completeness of data extraction relies on the quality and completeness of the patient records, termed information bias. An attempt to account for this was done by performing a pilot of 20 patients randomly selected from all study years to ensure the required data was available. In addition, the basic demographics and outcome data desired from case notes was thought to be commonly recorded data and therefore easily available. However, other factors for example smoking status and BMI which would be beneficial were missing. A retrospective design does however provide some benefits. It was estimated that in excess of 1,000 cases would be extracted from the proposed study period. This would not be possible using prospective methods without several years of study and data gathering. In addition, by looking retrospectively, trends over time can be observed and reported on. A further benefit is in the reporting and analysis of complications. Although complications such non-union are deemed ‘common’ in tibial fractures, this is a relative statement, and these cases will still occur infrequently. With a retrospective design these rare cases can be accumulated from previous years in order to help statistical analysis and investigation.

The cases come from a single centre where all patients in the study were managed exclusively. This is a level 1 Trauma Centre and so the case mix may not be entirely transferrable to the general orthopaedic trauma unit and multi centre studies are preferable for their generalisation. However, by capturing all tibia shaft fractures in the study period, it was possible to gain a high degree of accuracy that may not have been possible with a multicentre trial. In addition, by capturing all shaft fractures and not just those that require specialist trauma care, the results described should still be of use to other sites.

# 6. Results

## 6.1 Incidence and demographics

The methodology for identification of cases and data collection has been previously described in chapter 3. Population estimates for the city of Leeds were obtained from the Office of National Statistics (ONS) and Census data(108) for each year. The mean population estimate for the entire study period was used for gender and age specific incidence calculation and are reported per 100,000 population and year.

A total of 1220 tibial shaft fractures in 1201 Patients (8915 male were identified from January 2008 to December 2019. There were 815 males (66.8%) and 405 females (33.2%). Twenty-two patients suffered bilateral tibial shaft fractures. The population of Leeds was 741,665 in 2008 and has increased to 793,139 in 2019, an increase of 7%. During this time the incidence per 100,000 population and year has shown an increasing trend from 2008 (8.08 cases per 100,000 and year) to 2019 (13.1 cases per 100,000 population and year), an increase of 62% [Figure 1.] There is a sharp increase from 2013 which may correspond to the introduction of the Major Trauma Network (MTN). Furthermore, there is a fall in incidence during 2019. Both males and females followed the same trajectory.

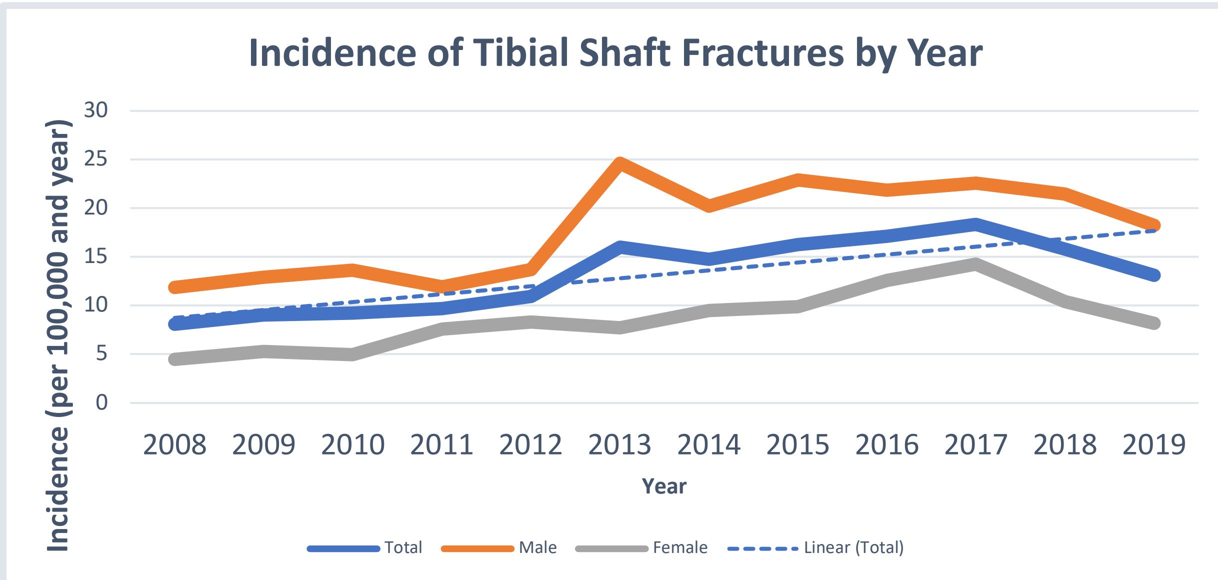


*Figure 1: Incidence of diaphyseal tibia fracture by year*

Patient age ranged from 18 to 101. The spread of data was positively skewed with a median age of 40 years-old (Interquartile range 26) [Figure 2]. The range of patient ages increased during the study period with no patients 85-years and older during 2008 and 2009. The incidence of fractures per 100,000 population and year has increased for all age groups, but this increase was steepest in the 40 to 65-year-old and the over-65 age groups. This is shown in [Figure 3]. The gradient of the linear trend lines of each age group are as follows:

- 0.84 for 18 to 40 years
- 1.34 for 40 to 65 years
- 1.01 for 65+ years

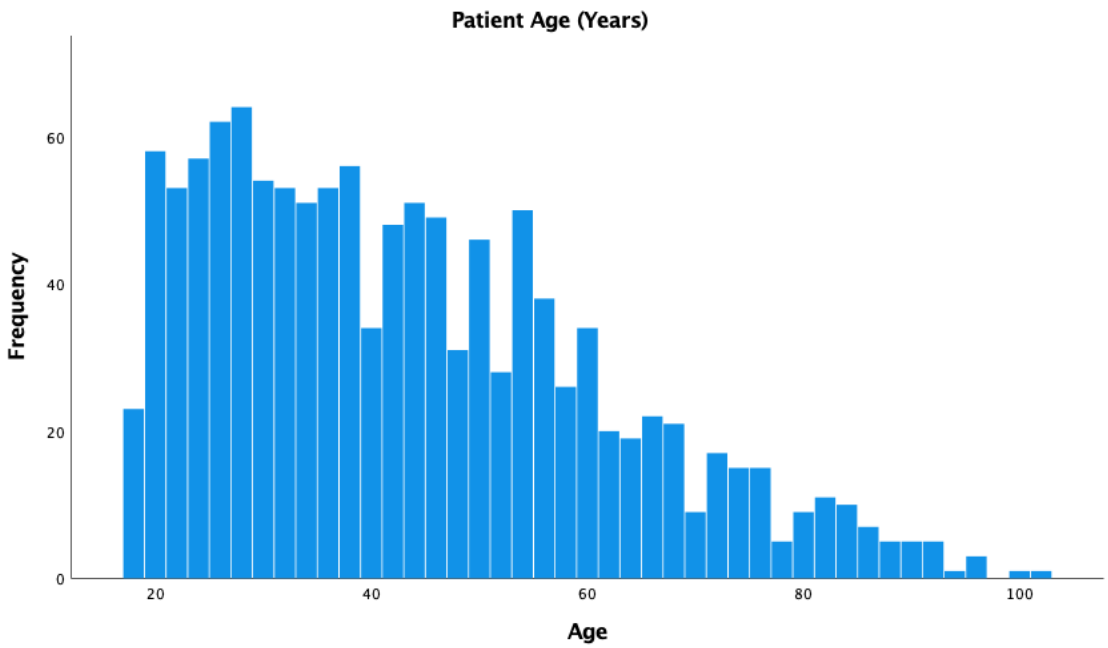


*Figure 2: Frequency count of patient age in years*

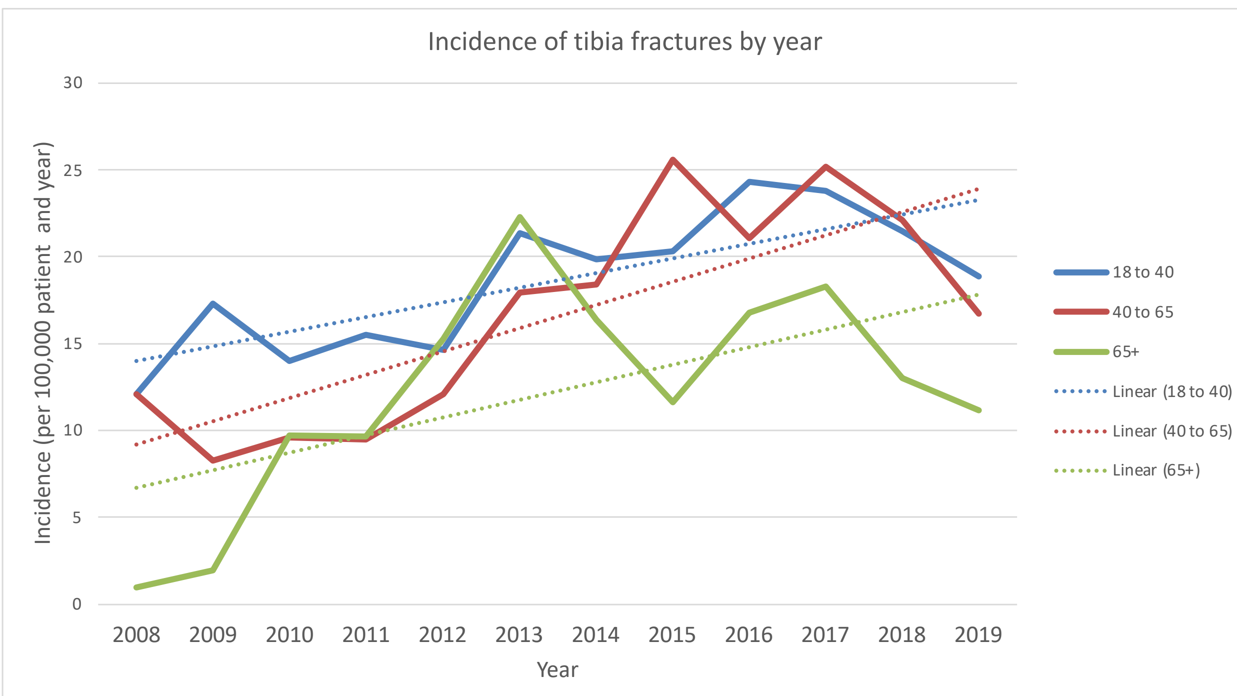


*Figure 3: Incidence of tibial fracture by age group over time*

When accounting for difference between gender, the data showed the incidence of tibial shaft fractures in the female population increased with increasing age, largely accounting for the increase in this age group. The inverse was true of male patients, where injuries predominated in the younger population and tailed off with increasing age [Figure 3].

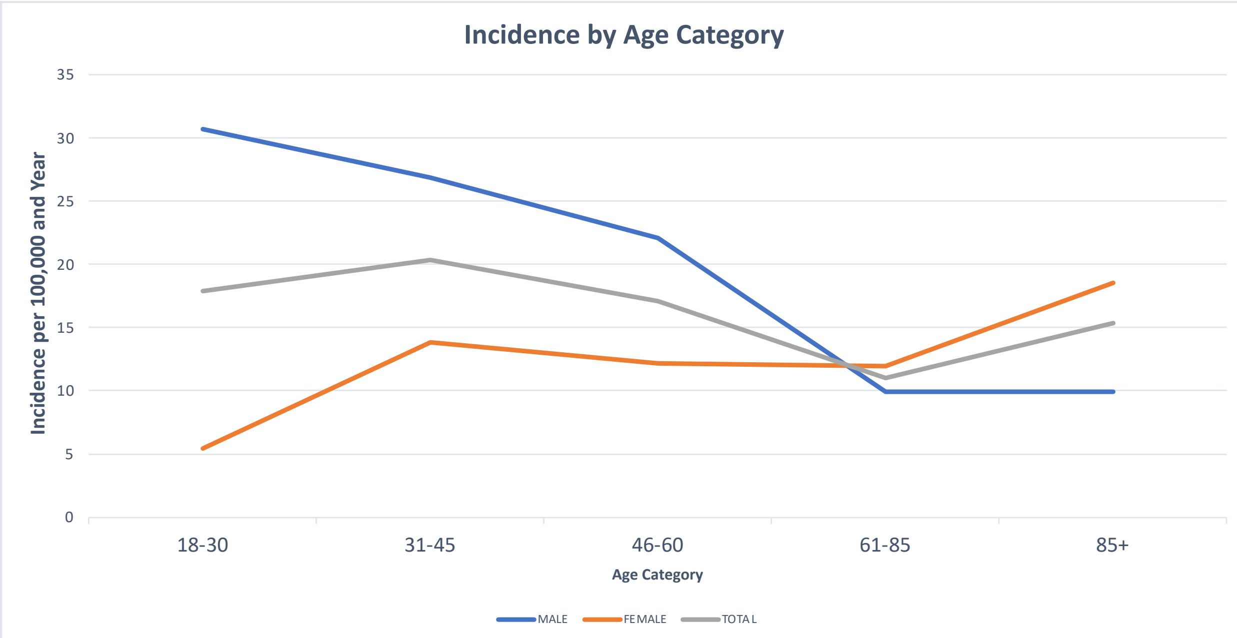


*Figure 4: Age specific incidence of diaphyseal tibia fractures*

Co-morbidities were recorded using the Charlson Comorbidity Score (CCS)(94). This allocates a numerical score and predicts the ten-year mortality for patients based on pre-existing health conditions. It has been externally validated by several sources(109). The majority of patients were fit and well with a CCS of 0 (n = 771, 63.2%). This was largely made up of younger patients aged 18 to 50 years-old with only 8.5% of these patients logging additional co-morbid disease. As patient age contributes to the CCS, older patients by default have a higher co-morbidity score. When this was accounted for, we see that 69.8% of patients over the age of 80 years have additional comorbidities [Table 2].

*Table 1: Charlson Comorbidity Score (CCS) by age group. Highlighted cells are not achievable for each age category as they are given a minimum score based on age and cannot be compared when assessing medical comorbidities*

| | | Age Category (Years) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 18 to 50 | | 50 to 59 | | 60 to 69 | | 70 to 79 | | 80+ | |
| | | n = | % of Age Group | n = | % of Age Group | n = | % of Age Group | n = | % of Age Group | n = | % of Age Group |
| Charlson Comorbidity Score | 0 | 771 | 91.5% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| | 1 | 49 | 5.8% | 112 | 71.8% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| | 2 | 11 | 1.3% | 18 | 11.5% | 64 | 59.8% | 0 | 0.0% | 0 | 0.0% |
| | 3 | 6 | 0.7% | 17 | 10.9% | 24 | 22.4% | 22 | 36.1% | 0 | 0.0% |
| | 4 | 2 | 0.2% | 3 | 1.9% | 10 | 9.3% | 19 | 31.1% | 16 | 30.2% |
| | 5 | 0 | 0.0% | 3 | 1.9% | 7 | 6.5% | 6 | 9.8% | 10 | 18.9% |
| | 6 | 3 | 0.4% | 2 | 1.3% | 1 | 0.9% | 6 | 9.8% | 13 | 24.5% |
| | 7 | 0 | 0.0% | 1 | 0.6% | 0 | 0.0% | 4 | 6.6% | 7 | 13.2% |
| | 8 | 0 | 0.0% | 0 | 0.0% | 1 | 0.9% | 3 | 4.9% | 5 | 9.4% |
| | 9 | 1 | 0.1% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 1 | 1.9% |
| | 10 | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 1 | 1.6% | 0 | 0.0% |
| | 11 | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 1 | 1.9% |

The most frequently occurring co-morbidities of all patients were diabetes (n = 77, 24.3%), ischaemic heart disease (IHD) and myocardial infarction (MI) (n= 49, 15.5%) and Chronic Obstructive Pulmonary Disease (COPD) (n = 41, 12.9%). The calculated rates of these three conditions were considerably larger than those reported for the general population of the UK and England(110–112) [Table 3].

*Table 2: Differences in prevalence of common comorbidities compared to the general population*

| | | Prevalence in Study | Prevalence in population |
|---|---|---|---|
| Comorbidity | Diabetes | 6.48% | 5.84% |
| | IHD | 4.02% | 3.36% |
| | COPD | 3.36% | 1.85% |

Body mass index (BMI) was available for 562 patients. The median BMI was 26.19 kg/m$^2$ (range 15.4 to 55.0 kg/m$^2$).

Smoking status, alcohol intake and illicit substance misuse were not available for all cases and so accurate prevalence of these indices cannot be reported.

*Table 3: Missing data on substance misuse*

| | Smoking | Alcohol | Illicit Drugs |
|---|---|---|---|
| Data available | 1044 | 829 | 1004 |
| Data missing | 176 | 391 | 216 |

## 6.2 Mechanism of Injury (MOI)

The most common documented mechanism of injury (MOI) was a fall from standing height accounting for 40% of all fractures. This was followed by Road Traffic Collision (RTC, 18%) and sports injuries (13.4%). The gender and age specific breakdown of MOI is shown in [Table 5 and 6].

A low energy fall from standing was the most common mechanism found in female patients overall (64%). This was followed by pedestrian RTC (8.9%) and fall from height (7.7%). After 30 years of age, a fall from standing accounted for over half of all injuries, comprising 89.5% of injuries in the over 85 age group [Table 5].

By comparison, males had a tendency for high injury mechanisms. Although a fall from standing height was still the most common mechanism, it only accounted for around a quarter of all injuries (26.3%). This was followed by RTC (24.2%) and sports injuries (18.5%). Males differed from females in the 18 to 30 age group where RTC (35.0%) and sport injuries (29.3%) were the most common and a fall from standing height only accounting for 33% of injuries in over 85s [Table 6].

*Table 4: Breakdown of MOI by age category for female patients*

| | Age Category (Females) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 18-30 years | | 31-45 years | | 46-60 years | | 61-85 years | | Over 85 years | |
| | n = | % of Total | n = | % of Total | n = | % of Total | n = | % of Total | n = | % of Total |
| Crush | 2 | 3.5% | 3 | 2.4% | 2 | 2.0% | 1 | 1.0% | 0 | 0.0% |
| Direct blow | 5 | 8.8% | 0 | 0.0% | 5 | 5.1% | 0 | 0.0% | 0 | 0.0% |
| Fall down stairs | 0 | 0.0% | 0 | 0.0% | 1 | 1.0% | 1 | 1.0% | 0 | 0.0% |
| Fall from height | 9 | 16% | 12 | 9.4% | 7 | 7.1% | 2 | 1.9% | 1 | 5.3% |
| Fall from horse | 1 | 1.8% | 3 | 2.4% | 1 | 1.0% | 0 | 0.0% | 0 | 0.0% |
| Fall from standing | 16 | 28% | 82 | 65% | 66 | 67% | 80 | 78% | 17 | 89.5% |
| insufficiency | 0 | 0.0% | 0 | 0.0% | 1 | 1.0% | 0 | 0.0% | 0 | 0.0% |
| Other high energy | 0 | 0.0% | 2 | 1.6% | 1 | 1.0% | 0 | 0.0% | 0 | 0.0% |
| Other low energy | 2 | 3.5% | 1 | 0.8% | 0 | 0.0% | 3 | 2.9% | 0 | 0.0% |
| Pathological | 0 | 0.0% | 0 | 0.0% | 1 | 1.0% | 3 | 2.9% | 0 | 0.0% |
| RTC | 6 | 11% | 9 | 7.1% | 3 | 3.0% | 3 | 2.9% | 1 | 5.3% |
| RTC (Pedestrian) | 11 | 19% | 10 | 7.9% | 6 | 6.1% | 9 | 8.7% | 0 | 0.0% |
| RTC (Push Bike) | 0 | 0.0% | 1 | 0.8% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| Sports injury | 4 | 7.0% | 4 | 3.1% | 4 | 4.0% | 0 | 0.0% | 0 | 0.0% |
| Unknown | 1 | 1.8% | 0 | 0.0% | 1 | 1.0% | 1 | 1.0% | 0 | 0.0% |

*Table 5: Breakdown of MOI by age category for male patients*

| | Age Category (Men) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 18-30 years | | 31-45 years | | 46-60 years | | 61-85 years | | Over 85 years | |
| | n = | % of Total | n = | % of Total | n = | % of Total | n = | % of Total | n = | % of Total |
| Assault | 12 | 3.8% | 17 | 6.9% | 4 | 2.3% | 0 | 0.0% | 0 | 0.0% |
| Blast | 0 | 0.0% | 2 | 0.8% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| Crush | 10 | 3.2% | 9 | 3.7% | 22 | 12.5% | 1 | 1.4% | 0 | 0.0% |
| Direct blow | 10 | 3.2% | 10 | 4.1% | 3 | 1.7% | 1 | 1.4% | 0 | 0.0% |
| Fall down stairs | 0 | 0.0% | 1 | 0.4% | 0 | 0.0% | 1 | 1.4% | 0 | 0.0% |
| Fall from height | 16 | 5.1% | 18 | 7.3% | 7 | 4.0% | 7 | 9.6% | 0 | 0.0% |
| Fall from standing | 28 | 8.9% | 73 | 29.7% | 75 | 42.6% | 36 | 49.3% | 2 | 33.3% |
| Gunshot Wound | 0 | 0.0% | 1 | 0.4% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| Other high energy | 1 | 0.3% | 0 | 0.0% | 1 | 0.6% | 1 | 1.4% | 0 | 0.0% |
| Other low energy | 3 | 1.0% | 0 | 0.0% | 0 | 0.0% | 1 | 1.4% | 0 | 0.0% |
| Pathological | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 1 | 1.4% | 0 | 0.0% |
| RTC | 110 | 35.0% | 40 | 16.3% | 36 | 20.5% | 10 | 13.7% | 1 | 16.7% |
| RTC (Pedestrian) | 25 | 8.0% | 18 | 7.3% | 20 | 11.4% | 12 | 16.4% | 3 | 50.0% |
| RTC (Push Bike) | 6 | 1.9% | 5 | 2.0% | 2 | 1.1% | 0 | 0.0% | 0 | 0.0% |
| Sports injury | 92 | 29.3% | 51 | 20.7% | 6 | 3.4% | 2 | 2.7% | 0 | 0.0% |
| Unknown | 1 | 0.3% | 1 | 0.4% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |

## 6.3 Injury Classification

The most common fracture pattern overall was a simple spiral fracture (AO/OTA 42A1 n = 342, 28.0%) with all simple (type A) fracture patterns accounting for over half of cases. This was followed by wedge fractures (n = 376, 30.8%) and finally multifragmented patterns (n = 170, 13.9%). However, simple type A fractures have been reducing as an overall proportion of injuries from 2008 where it accounted for more than 60% of all fractures to 2019, when it accounted for under half. There has been a reciprocal increase in more complex fracture patterns, particularly type B wedge fractures, [Figure 4].

Almost all tibial shaft fractures were associated with a concurrent fibula fracture (n = 1173, 97.1%). Tibial fractures in 44 patients (3.6%) were complicated by the presence of previous metalwork. Peri-implant fractures (n = 35, 2.9%) occurred in the setting of previous fixation or arthrodesis implants of the tibia and/or fibula. Peri-prosthetic fractures (n = 9, 0.7%) occurred on the background of a previous prosthetic joint replacement of the ankle or knee. In addition, an undisplaced articular extension of the fracture was identified in 16.2% of patients (n = 198). In the majority of these patients this extension travelled to the ankle (86.9%) as opposed to the knee (13.1%).

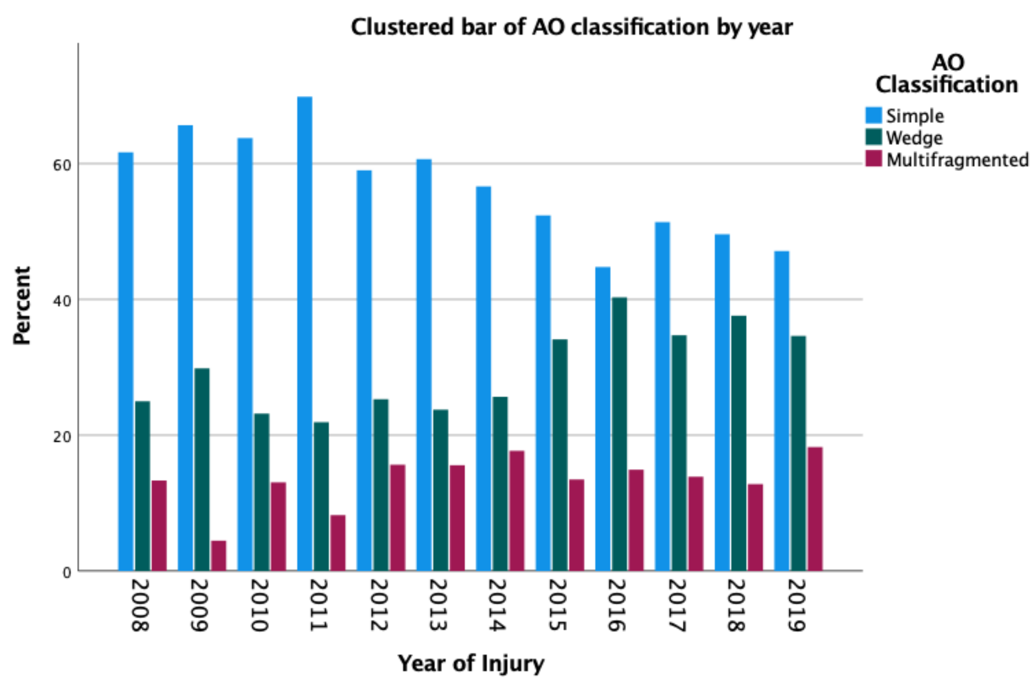


*Figure 5: Stacked bar of AO classification by year of study*

Complexity of injury also increased with age. Type B and C fractures represented an increasing proportion of injuries at each successive age group, representing 72% of fracture patterns in the over 85s compared with just 40.7% in those under 30-years [Figure 5]. This is despite the prevalence of high energy injuries dominating the younger age groups and low energy mechanisms in older patients.

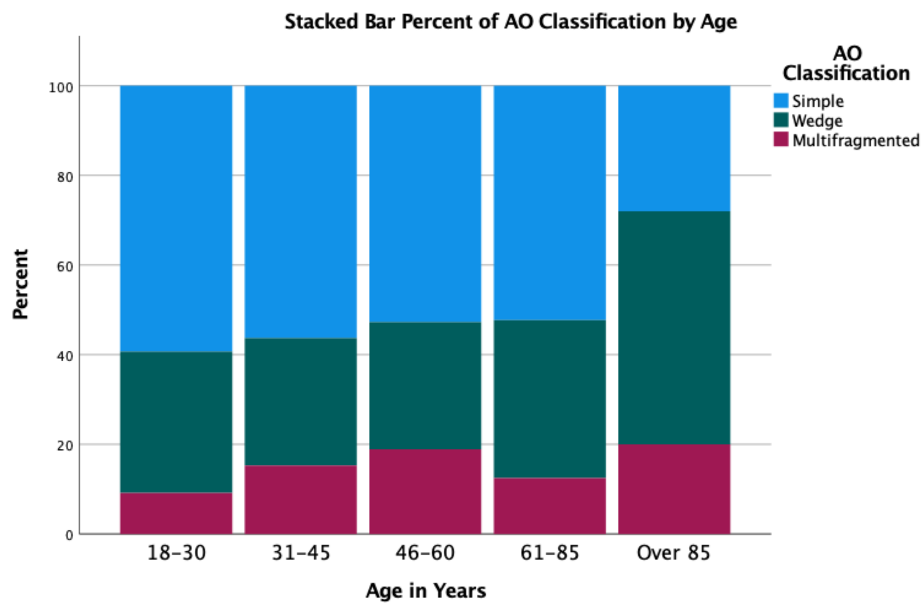


*Figure 6: Stacked bar chart of fracture pattern by age category*

Open injuries accounted for 32.4% (n = 395) of cases. Gustilo-Anderson type 3 injuries accounted for the majority of these (n = 270, 68.3%) with type 3B (those requiring soft tissue coverage) predominating (n = 143, 36.2% of open fractures, 11.7% of total cases). This was followed closely by type 3A injuries (n = 119, 30.1% of open fractures, 9.8% of total cases) and type 2 injuries (n = 91, 23% of open fractures, 7.5% of total cases). Only 8 patients (2.0% of open fractures, 0.7% of total cases) sustained type 3C injury with concurrent vascular compromise.

The same trend of fracture classification over time can be seen with open injuries. There is an increasing proportion of more complex type 3 soft tissue injuries [Figure 6]. In addition, there appeared to be a significant association between patient age and the risk of open fracture. A Chi Square goodness of fit test was computed to compare the proportion of open fractures between age groups. The proportions differed significantly [$X^2(4) = 17.18$, $p = .002$] with patients aged over

85-years sustaining a higher rate of open fracture (64.0%) compared to other age groups (28.2% to 37.5%) which did not differ significantly from each other.

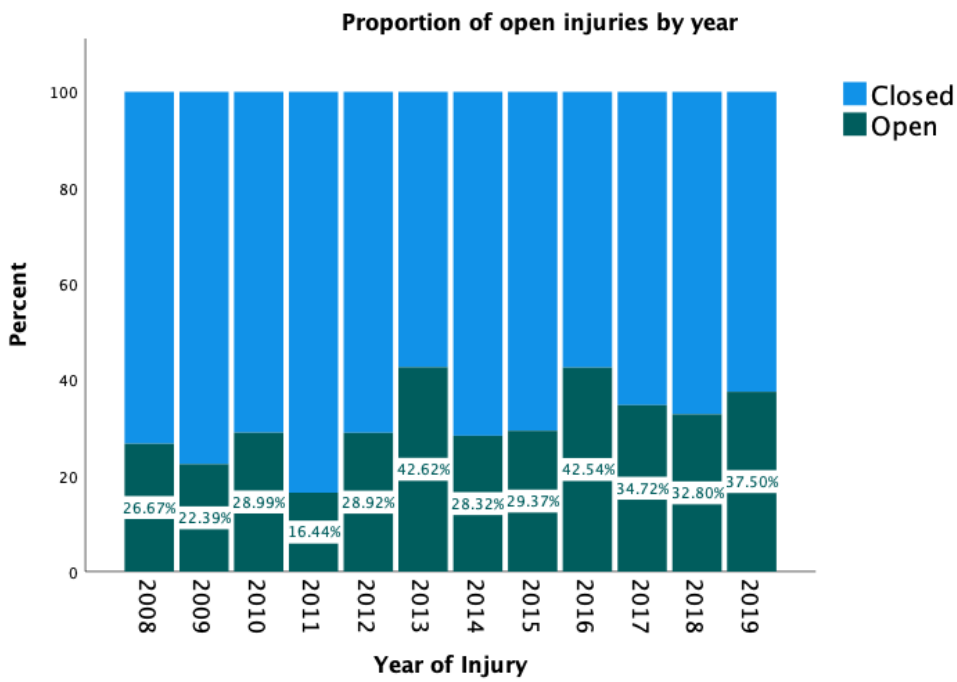


*Figure 7: Proportion of open injuries by year*

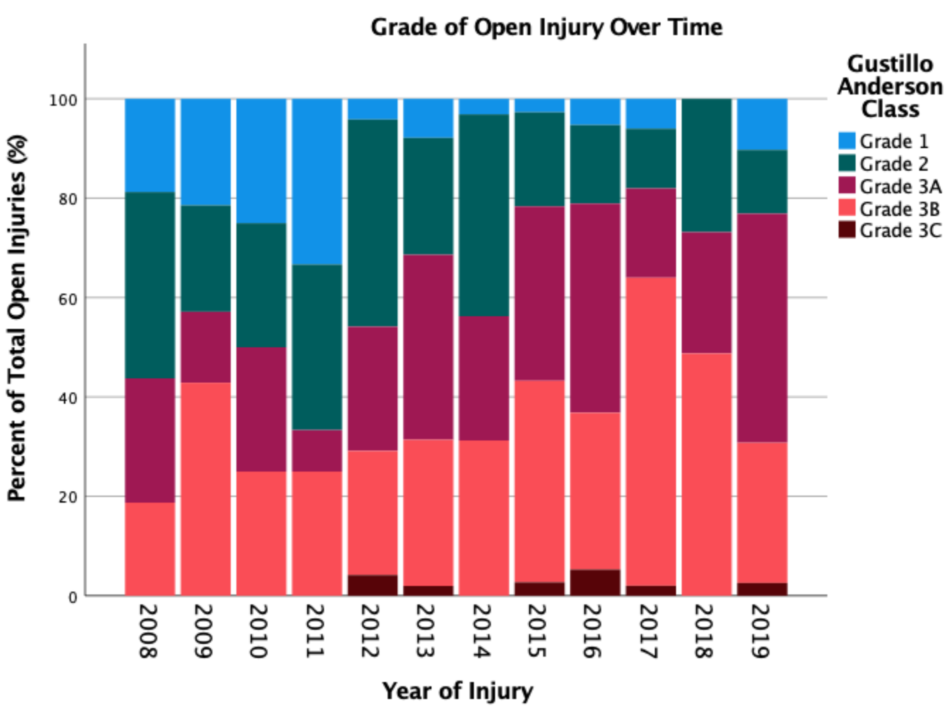


*Figure 8: Stacked bar chart of open injury classification by year of study*

Bone loss was present either at initial injury or after initial debridement in 74 (6.1%) of cases. The mean segmental defect was 37.13mm ± 18.77mm and ranged from 10 to 110mm. Where cortical continuity still remained after excision or bone loss, this defect was recorded as a butterfly fragment. The mean maximum length of butterfly bone loss was 46.95mm ± 22.56 and ranged from 13 to 83mm. The size of these defects was measured either from digital radiographs or if this was stated in the operative notes. Bone loss almost always happened in the setting of open fractures with 95% of cases occurring in open tibial fractures.

The increase in both injury complexity, open injuries and type 3 Gustillo-Anderson injuries may be accounted for by the introduction of the MTN and the import of more complex injuries. This is depicted in [figure 9]. The graph shows a noticeable jump in the transfer of patients from 2013, the same time that the MTN was introduced in Leeds.

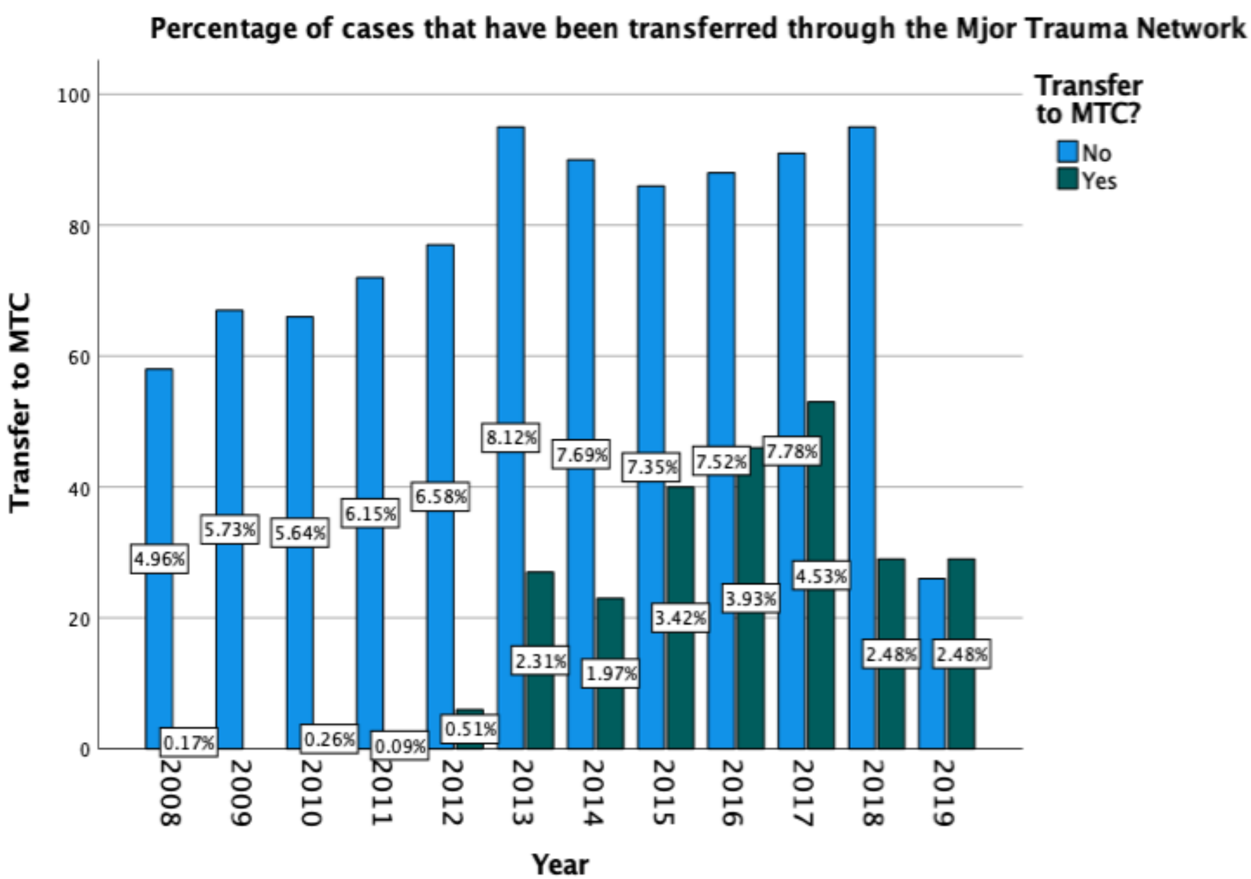


*Figure 9: Proportion of patients that were transferred to Leeds through the Major Trauma Network by year of presentation*

## 6.4 Other Injuries

The majority of patients sustained isolated tibial fractures (n = 908, 74.5%). Of the remaining 312 patients, upper limb injuries (n = 117, 9.6%) and chest injuries (n = 85, 7.0%) were the most frequently associated injury. A complete breakdown of additional injuries can be found in [Table 6]. A small proportion of patients (n = 154, 12.6%) achieved an injury severity score greater than 15 which is deemed a major- or poly-trauma scenario. Thirty-three patients (2.7%) presented with a floating knee injury where the ipsilateral femur was concomitantly fractured, and nineteen patients (1.6%) presented with bilateral tibial shaft fractures.

*Table 6: Other injuries present on admission*

| | N | Percent of Cases |
|---|---|---|
| Isolated Injury | 908 | 74.5% |
| Head Injury | 55 | 4.5% |
| Spinal Injury | 67 | 5.5% |
| Pelvic Injury | 62 | 5.1% |
| Chest Injury | 85 | 7.0% |
| Intra-Abdominal Injury | 23 | 1.9% |
| Upper Limb Injury | 117 | 9.6% |
| Ipsilateral Femur | 33 | 2.7% |
| Ipsilateral Ankle or Foot | 69 | 5.7% |
| Ipsilateral Knee | 27 | 2.2% |
| Contralateral Tibia | 38 | 3.1% |
| Contralateral Femur | 18 | 1.5% |
| Contralateral Knee | 14 | 1.1% |
| Contralateral Ankle or Foot | 24 | 2.0% |
| Vascular Injury | 3 | 0.2% |
| Nerve Injury | 6 | 0.5% |

## 6.5 Complications

After excluding patients with insufficient follow up (n = 53), it was found that more patients suffered a complication during recovery (53.5%) than patients who completed an uneventful recovery without complications (46.5%). In total pin site infection was the most common complication (27.4% of patients, or 49.5% of all complications). This happened exclusively in patients managed by circular frame. This was followed by metalwork irritation (8.4%) and non-union (6.6%). Open fractures developed higher rates of almost all complications recorded with only 34.5% of patients completing an uncomplicated recovery compared with 52.1% of closed injuries. The rates of non-union, deep and superficial infection were statistically worse in open fractures compared to closed. Failed frame removal was also worse for open fractures. This complication is exclusive to patients managed with frames, which are the treatment modality of choice in open fractures at our institution, so this relationship displays selection bias. Although not significant there was a trend towards increasing rates of CRPS, medical complications including respiratory tract infections and embolic disease in open injuries [Table 7].

The overall rate of compartment syndrome and embolic events was 5.1% and 3.4% respectively, which is comparable to previously reported studies. Both complications were more common in open fractures compared to closed fractures (6.0% vs 4.6% for compartment syndrome, 4.9% to 2.7% for embolic events). The mean age of patients developing compartment syndrome was 13-years younger than those without [t(72.804) = 8.031, p = <.001; 95% CI 9.449 to 15.687]. Older patients were more likely to suffer embolic events [Mean difference 8.96; t(39.942) = 2.703, p = .01, 95% CI 2.261 to 16.668].

The rates of non-union and compartment syndrome have shown a small but steady decreasing trend since 2008 to 2019. This is not the case for infective complications which have remained static, or for embolic disease which have increased in incidence [Figure 7].

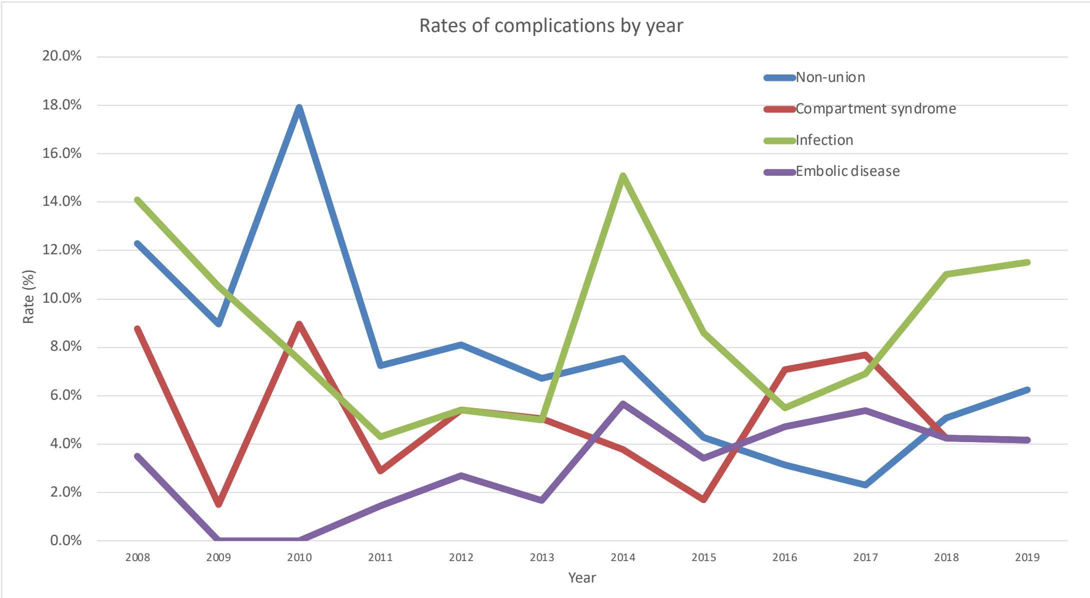


*Figure 10: Rates of complications by year of study*

*Table 7: Complications following tibial shaft fracture in open and closed injuries*

| | Closed | Open | Total | | |
|---|---|---|---|---|---|
| | Number (%) | Number (%) | Number (%) | Test statistic | Significance |
| **No Complications** | 406 (52.1%) | 127 (34.5%) | 533 (46.5%) | $x^2(1) = 31.369$ | $p < 0.001$ |
| **Non union** | 33 (4.2%) | 43 (11.7%) | 76 (6.6%) | $x^2(1) = 22.413$ | $p < 0.001$ |
| **Superficial infection** | 35 (4.5%) | 32 (8.7%) | 67 (5.8%) | $x^2(1) = 8.026$ | $p = 0.05$ |
| **Deep infection** | 13 (1.7%) | 19 (5.2%) | 32 (2.8%) | $x^2(1) = 11.252$ | $p < 0.001$ |
| **Pin site infection** | 189 (24.3%) | 125 (34.0%) | 314 (27.4%) | $x^2(1) = 11.842$ | $p < 0.001$ |
| **Compartment syndrome** | 36 (4.6%) | 22 (6.0%) | 58 (5.1%) | $x^2(1) = 0.959$ | $p = 0.386$ |
| **DVT/PE?** | 21 (2.7%) | 18 (4.9%) | 39 (3.4%) | $x^2(1) = 3.668$ | $p = 0.079$ |
| **Metal work issues** | 67 (8.6%) | 29 (7.9%) | 96 (8.4%) | $x^2(1) = 0.169$ | $p = 0.733$ |
| **Re-fracture** | 4 (0.5%) | 17 (4.6%) | 21 (1.8%) | $x^2(1) = 23.445$ | $p < 0.001$ |
| **Failed frame removal** | 0 (0.0%) | 9 (2.4%) | 9 (0.8%) | $x^2(1) = 19.202$ | $p < 0.001$ |
| **Osteomyelitis** | 9 (1.2%) | 7 (1.9%) | 16 (1.4%) | $x^2(1) = 1.014$ | $p = 0.314$ |
| **CRPS** | 8 (1.0%) | 9 (2.4%) | 17 (1.5%) | $x^2(1) = 3.445$ | $p = 0.063$ |
| **Medical Complications** | 5 (0.6%) | 5 (1.4%) | 10 (0.9%) | $x^2(1) = 1.486$ | $p = 0.223$ |
| **Fat embolus/ARDS** | 3 (0.4%) | 2 (0.5%) | 5 (0.4%) | $x^2(1) = 0.144$ | $p = 0.704$ |

## 6.6 Injury Management

### 6.6.1 Temporary Stabilisation

A large proportion of patients received temporary bony stabilisation with external fixation prior to definitive fracture fixation (n = 474, 38.9%) [Figure10]. This was equally prevalent in open and closed injuries (52.5% open, 47.5% closed). The mean time spent in external fixator was 10.65 days (range 0 to 77 days). Eventual definitive management included IMN (n = 76), circular frame (n = 363), plate osteosynthesis (n = 21), Modular Rail System (n = 4), Hindfoot nail (n = 3), amputation (n = 3), non-operative (n = 2) and one patient treated definitively in an external fixation device. One patient died within 11 days of application of external fixation and therefore did not proceed to definitive management.

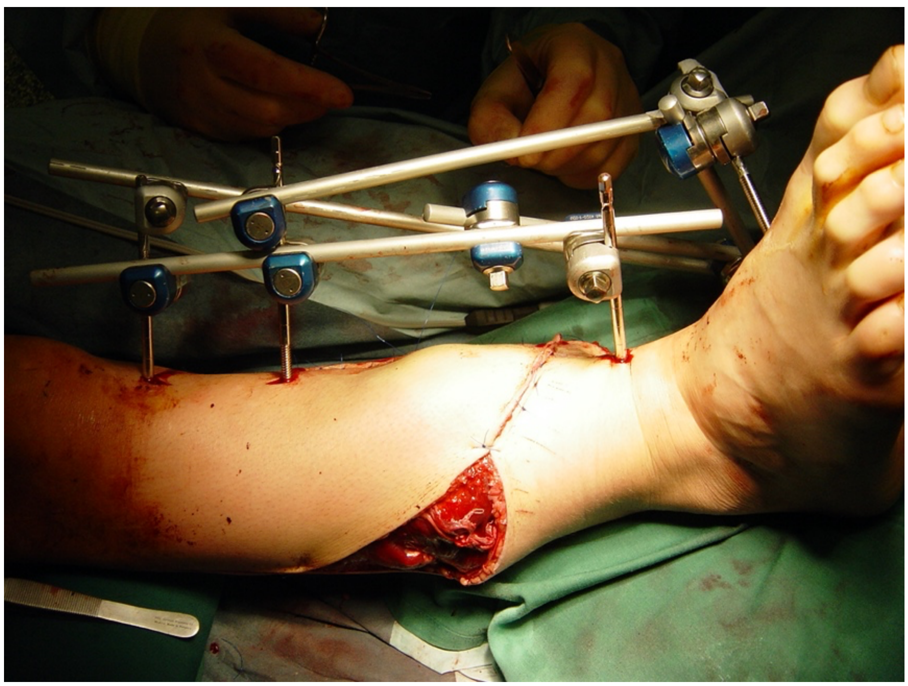

*Figure 11: External fixator with pins and bars used as temporary fixation in a grade 3B open tibial fracture. Note the minimal wound to the soft tissue envelope.*

Binary logistic regression analysis was used to assess the dose related predictive value of the time spent in external fixation in days against certain categorical outcome variables. Of particular interest were infective complications which have been suggested previously in the literature, as well as embolic disease due to the possibility of prolonged bed rest and immobility whilst awaiting definitive management. As open fractures have been shown to be a major predictor of overall complications, open and closed injuries were assessed separately.

Increasing time spent in external fixation before definitive management of all modalities did not significantly predict deep or superficial infection, osteomyelitis or embolic disease for both open and closed injuries. For closed injuries, increasing time spent in external fixator prior to definitive management conferred an increasing risk of 8.5% of non-union for every additional day spent waiting in an external fixator. This may be a result of more severe injuries requiring prolonged time in external fixation. However, these were closed injuries with 67% representing AO type A/B fracture patterns and only one patient had an ISS greater than 16. This trend was suggested in open fractures as well but did not achieve statistical significance.

*Table 8: Simple binary logistic regression analysis for days spent in external fixation as a predictor of various complications for closed injuries*

**CLOSED FRACTURES**

| | | | 95% CI for Exp (B) | | |
|---|---|---|---|---|---|
| | **N** | **OR (ExpB)** | **Lower** | **Higher** | **Sig.** |
| **Infection** | 216 | | | | |
| Intercept | | 0.79 | | | |
| Time in Ex-fix | | 1.031 | 0.989 | 1.075 | p = .147 |
| **Osteomyetlitis** | 216 | | | | |
| Intercept | | 0.008 | | | |
| Time in Ex-Fix | | 1.071 | 0.999 | 1.149 | p = .052 |
| **Emboli** | 216 | | | | |
| Intercept | | 0.142 | | | |
| Time in Ex-Fix | | 0.797 | 0.61 | 1.042 | p = .096 |
| **Non-union** | 216 | | | | |
| Intercept | | 0.027 | | | |
| Time in Ex-Fix | | 1.085 | 1.03 | 1.143 | p = 0.002 |

*Table 9: Simple binary logistic regression analysis for days spent in external fixation as a predictor of various complications for open injuries*

| OPEN FRACTURES | | | | | |
|---|---|---|---|---|---|
| | | | 95% CI for Exp (B) | | |
| | **N** | **OR (ExpB)** | **Lower** | **Higher** | **Sig.** |
| **Infection** | 237 | | | | |
| Intercept | | 1.106 | | | |
| Time in Ex-fix | | 1.012 | 0.986 | 1.04 | p = .365 |
| **Osteomyetlitis** | 237 | | | | |
| Intercept | | 0.022 | | | |
| Time in Ex-Fix | | 1.014 | 0.949 | 1.082 | p = .686 |
| **Emboli** | 237 | | | | |
| Intercept | | 0.084 | | | |
| Time in Ex-Fix | | 0.981 | 0.92 | 1.046 | p = .564 |
| **Non-union** | 237 | | | | |
| Intercept | | 0.08 | | | |
| Time in Ex-Fix | | 1.031 | 0.999 | 1.064 | p = .055 |

In order to try and examine the effect of temporary external fixation in isolation, a case control comparison of patients who underwent temporary external fixation and those who proceeded straight to definitive fixation with an IMN were compared. IMN was chosen as the definitive management of choice as circular frames are a form of external fixation and includes similar elements in terms of retained metalwork that communicate with the external environment. In addition, there were too few case numbers to compare plate osteosynthesis, which has already been shown to produce higher rates of infective outcomes in comparison to other treatment modalities.

A total 145 age, injury and gender matched cases were identified for comparison. Fifteen patients were either lost to follow-up or had follow-up out of region. This left 65 patients who proceeded straight to definitive management with IMN (DM group) and 65 cases who received a temporary external fixator prior to IMN (EF group). The groups were matched for gender, age, AO/OTA fracture pattern and proportion of open injuries. The equality of groups was checked using a Chi-

Square goodness of fit test and an independent samples t-test [Table 10]. There was a higher rate of multiply inured patients (ISS > 15) and grade 3B open injuries in the EF group compared to the DM group.

*Table 10: Demographics and matched variables of case control group*

| | | DM Group | EF Group | Significance value |
|---|---|---|---|---|
| **GENDER** | | | | $x^2$ (1) = 0.003, p = .995 |
| | Female | 23 (50%) | 23 (50%) | |
| | Male | 49 (49.5%) | 50 (50.5%) | |
| **Age (mean)** | | | | t (114) = 0.339, p = .381 |
| | | 42 ±17.8 years | 45.2 ± 18.8 years | |
| **AO Simple Classification** | | | | $x^2$ (s) = 0.01, p = .995 |
| | Simple | 42 (50%) | 42 (50%) | |
| | Wedge | 29 (49.2%) | 30 (50.8%) | |
| | Multifragmented | 1 (50%) | 1 (50%) | |
| **Open Fracture** | | | | $x^2$ (1) = 0.011, p = .918 |
| | Closed | 28 (49.1%) | 29 (50.9%) | |
| | Open | 44 (50%) | 44 (50%) | |

A Chi square test for independence was used to delineate any association between the application of external fixator (EF group) and immediate definitive management (DM group) on categorical complications. Results are displayed in [Table 12]. There did not appear to be a statistically significant association between the prior application of an external fixation device and the development of infective complications, compartment syndrome, embolic events or non-union. This was despite a higher rate of grade 3B open fractures and multiply injured patients in the EF group, which would be expected to produce higher rates of these complications. However, a post-hoc power analysis using the observed frequency of non-union in each group generated a power of only 15% at a significance value of 0.05 for the sample size. This leaves the results liable to a type II error and so a study with several hundred participants in each group would be required.

*Table 11: Comparison of complications with use of temporising external fixation.*

| | | DM Group | EF Group | |
|---|---|---|---|---|
| | | Count | Count | $x^2$ statistic or Fisher Exact |
| **Superficial infection** | No | 58 (89.2%) | 62 (95.4%) | |
| | Yes | 7 (10.8%) | 3 (4.6%) | x2 (1) = 1.73, p = .188 |
| **Deep infection** | No | 62 (95.4%) | 64 (98.5%) | |
| | Yes | 3 (4.6%) | 1 (1.5%) | Fisher exact test, p = .619 |
| **Osteomyelitis** | No | 65 (100%) | 63 (96.9%) | |
| | Yes | 0 (0%) | 2 (3.1%) | Fisher exact test, p = .496 |
| **Compartment syndrome** | No | 62 (95.4%) | 60 (92.3%) | |
| | Yes | 3 (4.6%) | 5 (7.7%) | Fisher exact test, p = .718 |
| **DVT/PE?** | No | 64 (98.5%) | 62 (95.4%) | |
| | Yes | 1 (1.5%) | 3 (4.6%) | Fisher exact test, p = .619 |
| **Non union** | No | 58 (89.2%) | 61 (93.8%) | |
| | Yes | 7 (10.8%) | 4 (6.2%) | x2 (1) = .894, p = .344 |

## 6.7 Definitive Management

The most common modes of definitive bony fixation were either IMN (n = 554, 45.4%) or circular frame (n = 547, 44.8%). The remainder of fixation methods were plate osteosynthesis (n = 86, 7%), non-operative (n = 15, 1.2%), hindfoot nail (n = 7, 0.6%), modular rail system (MRS n = 4, 0.3%), amputation (n = 3, 0.2%) and external fixation (n = 1, 0.1%). The median time to definitive fixation was 3 days (IQR 8 days). It is worth noting the large proportion of circular frames used as definitive management of tibial shaft fractures at our institution. This is down to surgeon preference due to the local expertise and the active lower limb reconstruction practice at our institution. Each of these definitive fixation methods will now be discussed separately.

### 6.7.1 Intramedullary Nail (IMN)

IMNs were used to treat 554 fractures, of which 402 (72.6%) were closed injuries. The predominant fracture pattern was a simple type A1 (spiral) fracture (n = 185, 33.4%) [Figure 11].

This was followed by type A3 transverse (n = 125, 22.6%). There were 152 (27.4%) open fractures managed by IMN. Grade 1 and 2 soft tissue injuries comprised over half of these (n = 84, 55.2%) and 24.3% of open injuries required soft tissue reconstruction (grade 3B). A total of 504 (91.5%) cases had sufficient follow up data to be included in further analysis.

After excluding cases that subsequently developed non-union, the mean time to radiological union was 23.4 ± 10.4 weeks. A students T-Test demonstrated there was a statistically significant difference between the mean time to radiological union between open (27.7 weeks) and closed (22.1 week) fractures [t(112) = -3.696, p = <.001, 95%CI -60.127 to -18.161].

Most patients treated with IMN followed an uneventful post-operative path with 58.5% of patients progressing to union without complication. Metalwork issues were the most frequently encountered problem (n = 81, 15.0%) and 54 patients requiring subsequent implant removal. Superficial surgical site infection affected 37 patients (6.9%) followed by non-union (n = 30, 5.6%), compartment syndrome (n = 23, 4.3%) and embolic disease (n = 14, 2.6%). A comparison of the most common complications between open and closed injuries managed by IMN can be found in [Table 9].

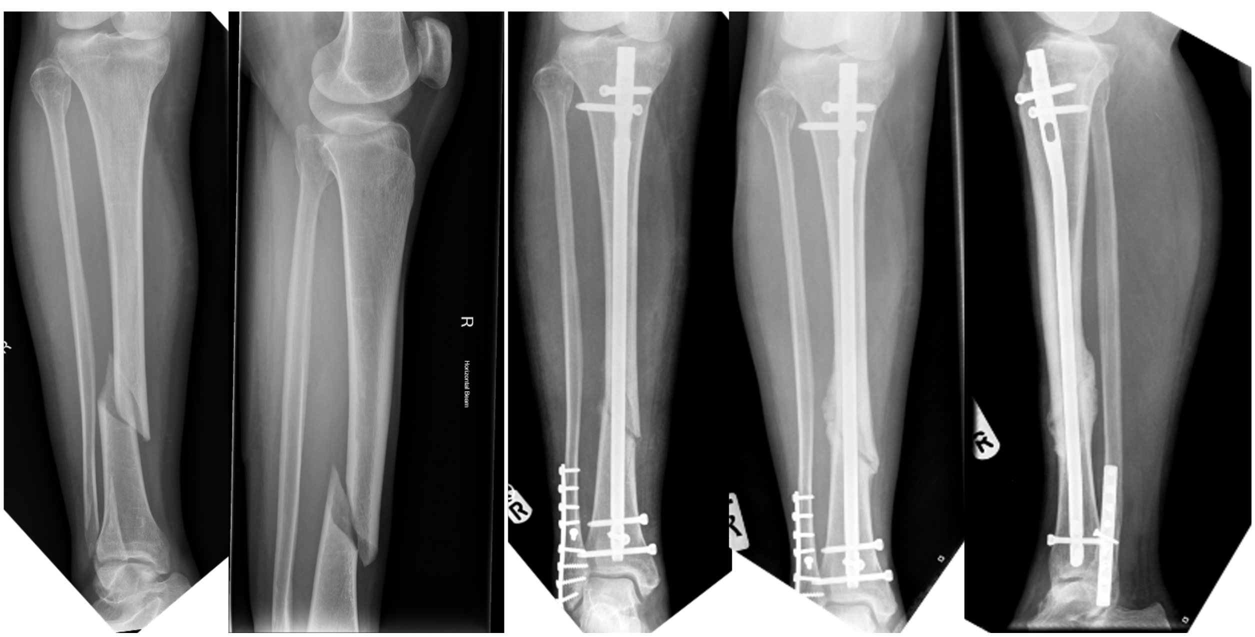

*Figure 12: Simple type 42A1 tibia fracture managed with intramedullary nail (IMN). From left to right: AP of initial radiograph of initial injury, lateral radiograph of initial injury, first post-op radiograph with IMN in situ and fibular fixation, Final AP and final Lateral images showing bridging callus on all four cortices.*

*Table 12: Complications of patients managed with IMN*

| | Fracture Type | | | | | |
|---|---|---|---|---|---|---|
| | Closed | | Open | | | |
| | Count | Total % | Count | Total % | Test Satistic | Significance |
| No Complications | 248/371 | 66.8% | 64/136 | 47.1% | $x^2(1) = 16.463$ | $p < 0.001$ |
| Superficial infection | 23/371 | 6.2% | 13/136 | 9.6% | $x^2(1) = 1.703$ | $p = 0.192$ |
| Deep infection | 7/371 | 1.9% | 5 | 3.7% | Fisher's Exact | $p = 0.319$ |
| Non union | 14/371 | 3.8% | 16 | 11.8% | $x^2(1) = 11.416$ | $p < 0.001$ |
| Compartment syndrome | 14/371 | 3.2% | 9 | 6.6% | $x^2(1) = 2.869$ | $p = 0.09$ |
| Fat embolus/ARDS | 2/371 | 0.5% | 0 | 0.0% | Fisher's Exact | $p = 1$ |
| Metal work issues | 53/371 | 14.3% | 28 | 20.6% | $x^2(1) = 2.945$ | $p = 0.086$ |
| CRPS | 2/371 | 0.5% | 6 | 4.4% | $x^2(1) = 9.611$ | $p = 0.002$ |
| Osteomyelitis | 5/371 | 1.3% | 1 | 0.7% | Fisher's Exact | $p = 1$ |
| DVT/PE? | 11/371 | 3.0% | 3 | 2.2% | Fisher's Exact | $p$ 0.769 |

Open fractures had a higher overall rate of complications. Non-union, surgical site infection, compartment syndrome and chronic regional pain syndrome (CRPS) were all more prevalent in open fractures. However, only non-union and CRPS were statistically significant.

### 6.7.2 Circular Frames

Circular frames were the treatment modality of choice for 547 patients. Closed injuries comprised 341 (62.3%) of these with the remaining 206 open fractures. Unlike injuries managed by IMN, circular frames were employed for more complex fracture patterns. Simple fracture patterns only accounted for 37.3% of injuries versus 72.1% of IMN fractures. Multifragmented wedge fracture (type B3) were the most abundant pattern (21.4%) followed by multifragmented segmental fractures (17.6%). This held true when assessing the soft tissue injury in open fractures with almost half of patients (n = 94, 45.6%) requiring soft tissue reconstruction and coverage to some degree. Fifteen patients had insufficient follow up data to be included in further exploration, leaving 532 patients for assessment of union and complications.

After exclusion of patients who developed subsequent non-union, the mean time to radiological union after management with a circular frame was 189 ± 88.5 days. Again, this was significantly longer in patients who suffered open fractures (229 days) compared to closed fractures (178 days) [t(196) = -5.515, p = <.001; 95% CI -69.71 to -32.99].

A smaller proportion of patients followed an uneventful post-operative course without complications than those managed with IMN (58.5% vs 31.2%). However, this may have been skewed by the several patients (n = 305, 58.8%) developing at least one pin site infection. Some regard this complication as part of the natural course of treatment. Beyond this, non-union (n = 36, 6.9%), compartment syndrome (n = 35, 6.7%), superficial infection (n = 20, 3.9%) and embolic disease (n = 18, 3.5%) were the next most common complications. There were increasing rates of all these complications in the setting of open fractures [Table 10].

*Figure 13: Circular frame employing the Ilizarov technique for tibial shaft fracture. Note the slings around the forefoot to prevent equinus contracture of the ankle*

*Table 13: Complications of patients managed with circular frames*

| | Closed | | Open | | | |
|---|---|---|---|---|---|---|
| | Count | Total % | Count | Total % | Test statistic | Significance |
| **No Complications** | 111/332 | 33.4% | 51/200 | 25.5% | $x^2(1) = 3.710$ | $p = 0.054$ |
| **Superficial infection** | 6/332 | 1.8% | 14/200 | 7.0% | $x^2(1) = 9.302$ | $p = 0.002$ |
| **Deep infection** | 2/332 | 0.6% | 10/200 | 5.0% | $x^2(1) = 10.948$ | $p < 0.001$ |
| **Non union** | 14/332 | 4.2% | 22/200 | 11.0% | $x^2(1) = 9.102$ | $p = 0.003$ |
| **Compartment syndrome** | 24/332 | 7.2% | 11/200 | 5.5% | $x^2(1) = 0.607$ | $p = 0.436$ |
| **Fat embolus/ARDS** | 1/332 | 0.3% | 2/200 | 1.0% | Fischer's Exact | $p = 0.560$ |
| **CRPS** | 6/332 | 1.8% | 2/200 | 1.0% | Fischer's Exact | $p = 0.716$ |
| **Osteomyelitis** | 3/332 | 0.9% | 5/200 | 2.5% | Fischer's Exact | $p = 0.159$ |
| **DVT/PE?** | 6/332 | 1.8% | 12/200 | 6.0% | $x^2(1) = 6.712$ | $p = 0.01$ |

Patients treated by circular frame had a higher rate of superficial and deep infection, non-union, Osteomyelitis, ARDS or embolic disease if they sustained an open fracture. This was statistically significant for superficial and deep infection, non-union and embolic disease.

### 6.7.3 Plate Osteosynthesis

Plate osteosynthesis was used to treat 86 fractures with 20 (23.3%) being open and 66 (76.7%) closed injuries. Seventy-five of these cases employed the minimally invasive plate osteosynthesis technique (MIPO) [Figure 10]. The remaining 11 patients underwent standard open reduction and internal fixation (ORIF). Simple spiral fractures (Type 41A1) were the most common fracture pattern (n = 37, 43%) followed by wedge fractures (Type B2 16.3% and Type B3 20.9%). Of the 20 open fractures, 2 (10%) were Gustilo-Anderson grade 1, 6 (30%) were grade 2, 5 (25%) were grade 3A and 7 (35%) were grade 3B.

Six patients had insufficient follow up data, leaving 80 cases to be included in further assessment. The mean time to radiological union was 168 ± 55.4 days, similar to that of IMN.

The majority of patients led an uncomplicated post-operative period (n = 45, 59.2%). Non-union complicated the recovery of 8 patients (10%) followed by superficial infection and metal work issues (n = 7, 9.2% each), deep infection (n =6, 7.9%) and embolic disease (n = 5, 6.6%).

Most patients did not require any further operations (n = 53, 66.3%). A total of 17 patients required removal of metalwork. This may be from problematic or irritant hardware or as part of further management for deep infection or revision fixation. Three patients required operative intervention for deep infection, one patient required revision of their fixation, one patient underwent further operation to address joint contractures and one patient required correction of a malunion. One patient underwent eventual amputation for an infected non-union.

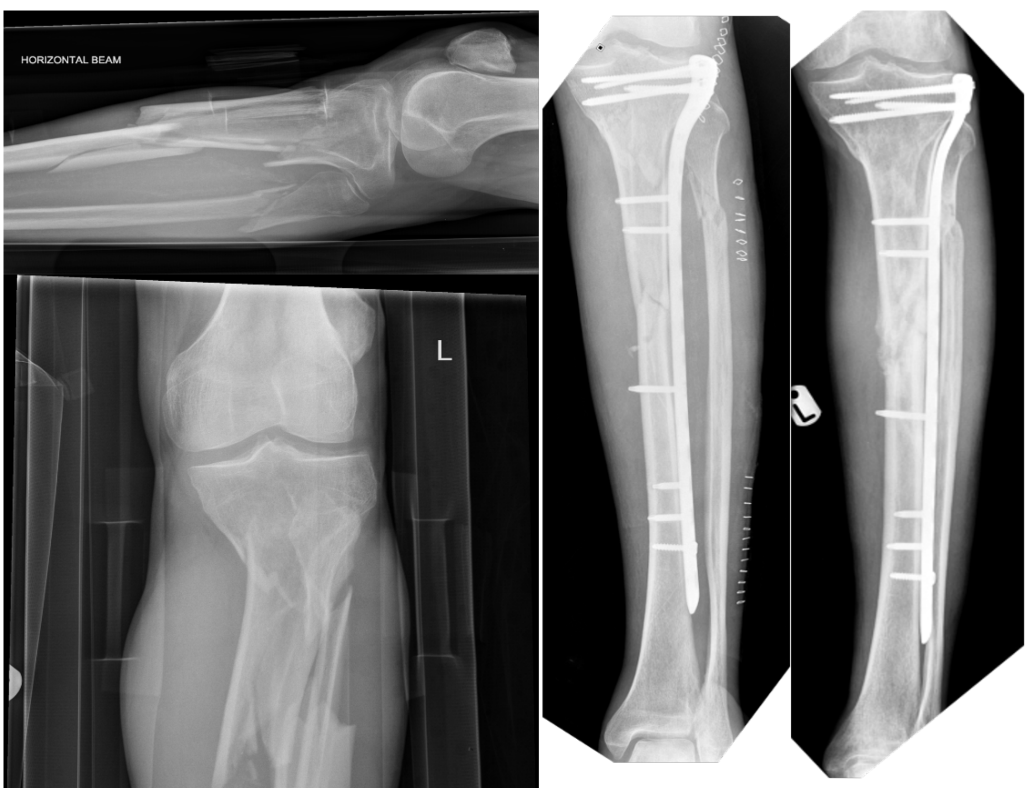


*Figure 14: Proximal multifragmented diaphyseal tibia fracture managed by plate osteosynthesis. LEFTt: initial injury. CENTRE:: first post-operative radiograph. Note the two minimal and discrete operative wounds with staples in situ indicating MIPO technique. RIGHT: Final images showing a untied fracture*

### 6.7.4 Non-operative management

Comparatively few patients underwent non-operative management with only 15 cases (9 female, 6 male). The mean age of patients was higher than with other management modalities at 59 ± 25.23 years-old. More than half of fracture were simple Type A fractures. Four injuries were open fractures, none of which required soft tissue coverage (1 grade 1, 2 grade 2 and 1 grade 3A).

Three patients failed to attend outpatient follow up leaving 12 patients for further assessment. Due to the small number of patients, meaningful analysis is unlikely but the outcomes will be described for completeness.

Seven patients completed an uncomplicated recovery (54.5%). One patient each (9.1%) suffered non-union, deep infection and embolic disease.

Two patients failed non-operative management with one patient's treatment converted to IMN and one patient suffering a deep infection following open fracture. The patient underwent debridement, conversion to an Ilizarov frame and a free tissue transfer. One patient required operative correction for a subsequent malunion.

The median time to union for non-operative patients was 153 days (Inter Quartile Range: 90 days).

### 6.7.5 Other fixation methods

A small proportion of patients were managed using other fixation methods. Seven patients received a hindfoot nail, 4 patients were managed using a modular rail system and 1 patient was treated definitively in an external fixation device. Three patients underwent primary amputation following injury. All three patients presented as a major trauma with an ISS greater than 15. Two of these injuries were grade 3 open fractures.

## 6.8 Comparison of fixation methods

The preferred method of fixation has altered over time. The predominant shift has been away from IMN and towards circular frame in both open and closed injuries. The remaining fixation methods remained constant [Figure 7 and Table 14]. This may correspond with the increasing proportion of complex and open injuries over time as discussed earlier where circular frames appear to be the management strategy of choice given the perceived benefits of minimal soft tissue insult and early weight bearing. It may also be the result of evolving surgeon preference at our institution.

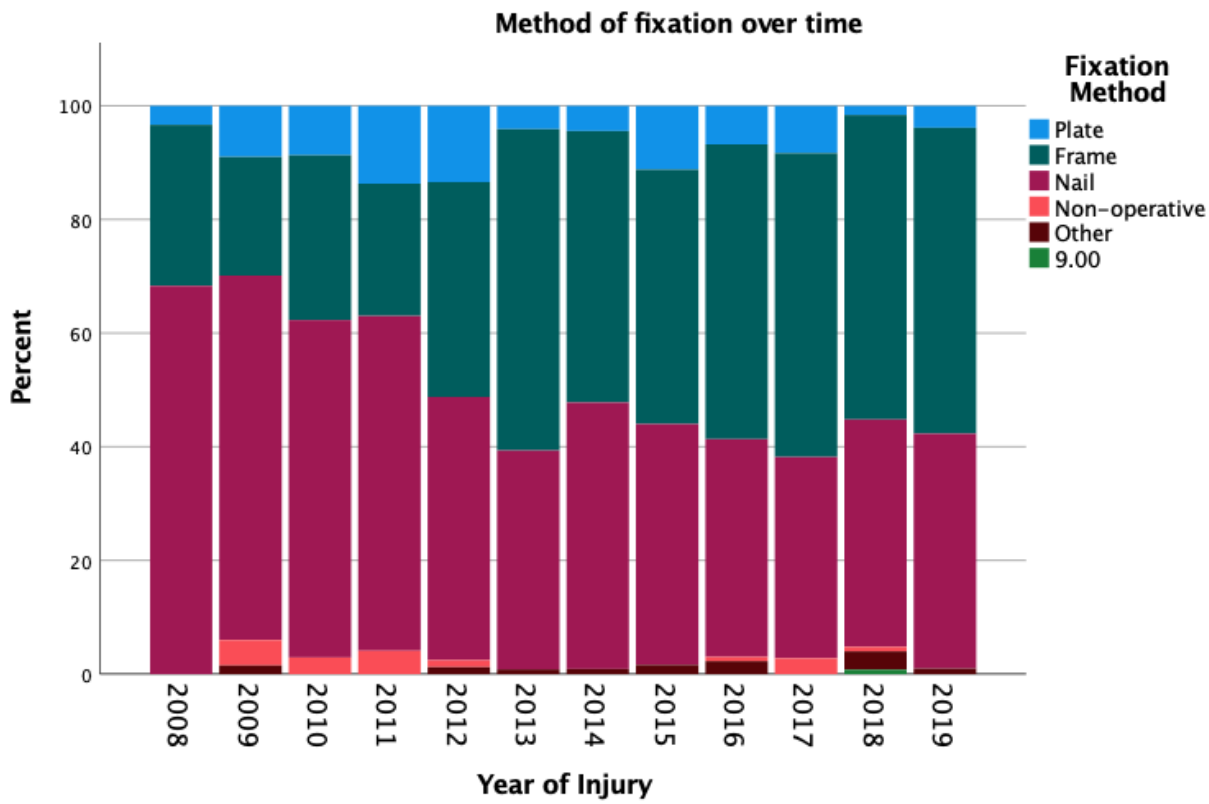


*Figure 15: Method of fixation by year*

*Table 14: change of fixation method over time in open and closed injuries*

| | Closed | | | | Open | | | |
|---|---|---|---|---|---|---|---|---|
| | Frame | | Nail | | Frame | | Nail | |
| Year of injury | n | % of all cases | n | % of all cases | n | % of all cases | n | % of all cases |
| **2008** | 11 | 25.0% | 31 | 70.5% | 6 | 37.5% | 10 | 62.5% |
| **2009** | 10 | 19.2% | 33 | 63.5% | 4 | 26.7% | 10 | 66.7% |
| **2010** | 13 | 26.5% | 32 | 65.3% | 7 | 35.0% | 9 | 45.0% |
| **2011** | 14 | 23.0% | 36 | 59.0% | 3 | 25.0% | 7 | 58.3% |
| **2012** | 20 | 33.9% | 26 | 44.1% | 11 | 45.8% | 12 | 50.0% |
| **2013** | 34 | 48.6% | 33 | 47.1% | 35 | 67.3% | 14 | 26.9% |
| **2014** | 33 | 40.7% | 44 | 54.3% | 21 | 65.6% | 9 | 28.1% |
| **2015** | 34 | 38.2% | 42 | 47.2% | 22 | 59.5% | 11 | 29.7% |
| **2016** | 38 | 49.4% | 34 | 44.2% | 31 | 54.4% | 17 | 29.8% |
| **2017** | 49 | 52.1% | 31 | 33.0% | 28 | 56.0% | 20 | 40.0% |
| **2018** | 48 | 57.1% | 33 | 39.3% | 19 | 46.3% | 17 | 41.5% |
| **2019** | 37 | 56.9% | 27 | 41.5% | 19 | 48.7% | 16 | 41.0% |

The rates of common complications were compared across the various treatment modalities in [Tables 12 and 13].

For both open and closed injuries, the highest overall of any complication occurred with the use of circular frames. However, as stated previously, the majority of these represented low grade pin site infections. These were managed on an outpatient basis with oral antibiotics in the vast majority of cases. In some instances, isolated wires were removed in the outpatient setting if prone to recurrent infection. Frames produced the highest rate of CRPS and compartment syndrome for closed fractures only.

Plate osteosynthesis generated the highest rates of all infective complications (superficial, deep and osteomyelitis) in both closed and open injuries. It also produced the highest non-union rate of 7.9% for closed injuries and 17.9% in open fractures.

*Table 15: Complications per fixation method for closed injuries*

| | Method of Fixation | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Plate | | Frame | | Nail | | Non-operative | | Other | |
| | % | n | % | n | % | n | % | n | % | N |
| **No Complications** | 41.2% | 7 | 25.5% | 51 | 47.1% | 64 | 50.0% | 2 | 30.0% | 3 |
| **Non union** | 17.6% | 3 | 11.0% | 22 | 11.8% | 16 | 25.0% | 1 | 10.0% | 1 |
| **Compartment syndrome** | 5.9% | 1 | 5.5% | 11 | 6.6% | 9 | 0.0% | 0 | 10.0% | 1 |
| **DVT/PE?** | 11.8% | 2 | 6.0% | 12 | 2.2% | 3 | 0.0% | 0 | 0.0% | 0 |
| **Deep infection** | 11.8% | 2 | 5.0% | 10 | 3.7% | 5 | 25.0% | 1 | 10.0% | 1 |
| **Superficial infection** | 5.9% | 1 | 7.0% | 14 | 9.6% | 13 | 0.0% | 0 | 30.0% | 3 |
| **Osteomyelitis** | 5.9% | 1 | 2.5% | 5 | 0.7% | 1 | 0.0% | 0 | 0.0% | 0 |
| **CRPS** | 0.0% | 0 | 1.0% | 2 | 4.4% | 6 | 0.0% | 0 | 0.0% | 0 |
| **Metal work issues** | 0.0% | 0 | 0.5% | 1 | 20.6% | 28 | 0.0% | 0 | 0.0% | 0 |

*Table 16: Complications per fixation method for open injuries*

| | Method of Fixation | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Plate | | Frame | | Nail | | Non-operative | | Other | |
| | % | n | % | n | % | n | % | n | % | n |
| **No Complications** | 60.3% | 38 | 33.4% | 111 | 66.8% | 248 | 50.0% | 4 | 100.0% | 4 |
| **Non union** | 7.9% | 5 | 4.2% | 14 | 3.8% | 14 | 0.0% | 0 | 0.0% | 0 |
| **Compartment syndrome** | 0.0% | 0 | 7.2% | 24 | 3.2% | 12 | 0.0% | 0 | 0.0% | 0 |
| **DVT/PE?** | 4.8% | 3 | 1.8% | 6 | 3.0% | 11 | 12.5% | 1 | 0.0% | 0 |
| **Deep infection** | 6.3% | 4 | 0.6% | 2 | 1.9% | 7 | 0.0% | 0 | 0.0% | 0 |
| **Superficial infection** | 9.5% | 6 | 1.8% | 6 | 6.2% | 23 | 0.0% | 0 | 0.0% | 0 |
| **Osteomyelitis** | 1.6% | 1 | 0.9% | 3 | 1.3% | 5 | 0.0% | 0 | 0.0% | 0 |
| **CRPS** | 0.0% | 0 | 1.8% | 6 | 0.5% | 2 | 0.0% | 0 | 0.0% | 0 |
| **Metal work issues** | 11.1% | 7 | 2.1% | 7 | 14.3% | 53 | 0.0% | 0 | 0.0% | 0 |

An independent samples one-way analysis of variance (ANOVA) test was used to compare the mean time to union between IMN, frame and plate osteosynthesis. Non-operative and other fixation methods were excluded due to low case numbers and to try and maintain power of the statistical test by reducing the number of comparisons during post-hoc analysis. Levene's test was used to ensure that the assumption of homogeneity of variance was met. The resulting one-way ANOVA showed a significant difference in the mean union time between treatment modalities [$F(2, 848) = 17.489$, $p = <.001$].

As group sizes were unequal (Plate n = 41, IMN n = 415, Frame n = 448), a Tukey post hoc test with Tukey-Kramer modification was used to make multiple comparisons. This showed that union time between IMN and frames differed significantly in favour of IMN (163 days vs 195 days, MD -31 days, 95%CI -45 to -19 $p = <.001$). Comparisons between the other methods of fixation were not statistically significant.

Radiological union was used for this analysis. As RUST scores were calculated at defined intervals then the true time of union may have been missed by several weeks, but this limitation is present across all groups in the comparison.

## 6.9 Soft tissue management for open injuries

The median time to the index debridement procedure was 8.56 hours (range 0 to 249.42 hours and interquartile range 9.9 hours). The median time to soft tissue coverage was 18.75 hours (range 0 to 726 hours, inter-quartile range 62.5 hours) with 95 (24%) achieving soft tissue coverage beyond 72 hours. The median time to soft tissue coverage was within 12 hours, which is extremely efficient. In some cases, patients had a recorded debridement and soft tissue closure of less than one hour. However, as the diagnostic radiograph was taken as the time of injury in some cases and the start of operative intervention was taken as the time of debridement and soft tissue coverage, the time to soft tissue coverage may be an underestimate.

*Figure 16: Grade 3B open Tibia fracture. From Left to right: initial debridement, free latissimus dorsi flap, final cosmetic result*

Low grade open fractures (Gustilo-Anderson grade 1 and 2) can be closed primarily by definition, or the open wound can be left to heal by secondary intention. With high energy grade 3 injuries there is a wider variety of coverage options [Figure 15]. The complete breakdown of the soft tissue management for the 395 open injuries is shown in Table 15.

*Table 17: Soft tissue coverage for open fractures*

| | Gustillo Anderson Class | | | | |
|---|---|---|---|---|---|
| | **Grade 1** | **Grade 2** | **Grade 3A** | **Grade 3B** | **Grade 3C** |
| **Primary closure** | 27 (84.4%) | 80 (89.9%) | 89 (70.1%) | 1 (0.7%) | 1 (12.5%) |
| **Secondary intention** | 5 (15.6%) | 2 (2.2%) | 2 (1.6%) | 1 (0.7%) | 0 |
| **SSG** | 0 | 6 (6.7%) | 36 (28.3%) | 0 | 3 (37.5%) |
| **Local flap** | 0 | 0 | 0 | 27 (19.7%) | 1 (12.5%) |
| **Fasciocutaneous flap** | 0 | 0 | 0 | 27 (19.7%) | 0 |
| **Free flap** | 0 | 0 | 0 | 80 (58.4%) | 3 (37.5%) |

Free tissue transfer was the preferred method for Grade 3B open tibial fractures followed by fascio-cutaneous and then local flaps. One patient had his open wound left to heal by secondary intention but unfortunately did not attend any further follow up to assess the outcome of this. One patient with a grade 3B open fracture received a primary amputation and hence the wound was technically closed primarily. After excluding these two patients and those with insufficient follow-up data (n = 4), there were 130 Grade 3B open tibial shaft fractures available for comparison.

Using a Pearson chi square test for independence, an association between the choice of soft tissue coverage and dichotomous complications could be tested. There did not appear to be an association between choice of soft tissue coverage and superficial and deep infection, osteomyelitis, non-union, compartment syndrome, embolic disease or CRPS [Table 18]

Of the 8 Grade 3C injuries, 7 were managed in circular frame. One patient was managed with IMN and free flap, however, after multiple flap failures this patient eventually underwent salvage amputation.

*Table 18: Crosstabulation of complications following different modalities of soft tissue coverage for Grade 3B open fractures*

| | Soft tissue coverage | | | | |
|---|---|---|---|---|---|
| | **Local flap** | **Fasciocutaneous flap** | **Free flap** | **Total** | **Fischer exact test** |
| **Superficial infection** | 5/25 (20%) | 2/27 (7.4%) | 8/78 (10.3%) | 15/130 (11.5%) | p = .349 |
| **Deep infection** | 3/25 (12.0%) | 1/27 (3.7%) | 4/78 (5.1%) | 8/130 (6.2%) | p = .462 |
| **Osteomyelitis** | 2/25 (8.0%) | 0/27 (0.0%) | 3/78 (3.8%) | 5/130 (3.8%) | p = .291 |
| **Non-union** | 3/25 (12.0%) | 2/27 (7.4%) | 13/78 (16.7%) | 18/130 (13.8%) | p = .493 |
| **Embolic disease** | 2/25 (8.0%) | 1/27 (3.7%) | 5/78 (6.4%) | 8/130 (6.2%) | p = .779 |
| **Compartment syndrome** | 1/25 (4.0%) | 1/27 (3.7%) | 6/78 (7.7%) | 8/130 (6.2%) | p = .886 |
| **CRPS** | 0/25 (0.0%) | 1/27 (3.7%) | 0/78 (0.0%) | 1/130 (0.8%) | p = .400 |

## 6.10 Summary of fracture management

At our institution, tibial shaft fractures are primarily fixed with circular frames or IMN. There is a much smaller proportion of fractures managed by plate osteosynthesis. Despite this, these patients still produced the highest rates of non-union, deep and superficial infection and osteomyelitis in open and closed fractures. This further adds to the suspicion of infective complications with this treatment modality. Very few patients are managed non-operatively as was historically the treatment of choice. These patients tended to be older, with only simple fracture patterns, but this also attracted a high failure rate with 13.3% of patients requiring conversion to operative measures.

IMN seemed to have fewer overall complications compared with circular frames. However, as stated, pin site infection was the main driver of complications the circular frame group and is thought to be a normal component of management with circular frames. In addition, circular frames were the treatment of choice for more complex fracture patterns.

The use of external fixation appeared to confer added risk of non-union in closed fractures only. Otherwise, their use appears to be safe in terms of infective complications in both open and closed fractures.

## 6.11 Management of non-union

Seventy-six patients developed a non-union during the study period with 43 open fractures and 33 closed injuries. This is a small cohort of patients so meaningful statistical analysis is difficult. However, the management of non-union in these cases will be described as they still represent an important and substantial aspect of management.

The initial definitive management of the non-union cases comprised 30 IMNs, 36 circular frames, 8 plate osteosynthesis, 1 Modular Rail System (MRS) and 1 non-operative management. Once non-union is diagnosed, patients often undergo multiple further operations at various stages. It then becomes increasingly difficult to tease out the true success of various modalities. Therefore, the index non-union procedure was reviewed and whether this was sufficient in isolation or required further attempts to achieve union [Table 19, 20 and 21]. When infection is the prevailing cause of non-union, these patients frequently require repeat operation to clear the infection and so have been excluded from this analysis but will be described. The treatment and outcomes of each of cohort will be described in turn.

### 6.11.1 Management of non-union after intramedullary nailing

Of the 30 patients who developed non-union, 29 patients (97.7%) went on to achieve union. One patient was left with a permanent pseudoarthrosis after a failed trial of pulsed ultrasound treatment but did not wish to pursue further operative intervention.

Infection was thought to be implicated in 3 patients, who subsequently underwent staged debridement and reconstruction (two patients were converted to a plate and one patient to a circular frame).

26 patients sustained a presumed aseptic non-union and underwent the index procedures shown in Table 19. Nail dynamisation was used to progress union in 13 patients. This was sufficient to achieve union in the first instance for 9 patients, giving a success rate of 76.9%. Two patients required a subsequent exchange nailing with biological augmentation with autologous bone graft (ABG) and BMP. One patient required subsequent conversion to a circular frame, again with augmentation with ABG and BMP.

Exchange nailing was used as the index method of non-union management in 7 patients, with one patient receiving additional augmentation with ABG and BMP at the same time. This was successful for all 7 patients.

Two patients had their fixation converted to a circular frame with the addition of ABG and BMP and was successful. One patient successfully had their fixation augmented with a plate with IMN in situ and the addition of bone marrow aspirate concentrate (BMAC) and platelet-rich plasma (PrP).

Two patients were initially managed with the application of biological therapy only. One patient went onto successful union. However, the other patient was undergoing a Masquelet procedure to address incomplete bone loss (butterfly segment) when non-union developed. Initial treatment with BMAC and PrP failed. Furthermore, exchange nailing, pulsed ultrasound therapy, further biological augmentation with ABG, BMP and bone marrow aspirate were unsuccessful. Union was eventually secured after fixation was converted to a plate.

One patient had no specific management of their non-union and subsequently did not attend follow up. However, radiographs taken several years after injury for an unrelated matter showed complete radiological union.

*Table 19: Procedures used to address non-union after IMN*

**Management of non-union after IMN**

| Index non-union procedure | Number (%) | Need for additional procedures? |
|---|---|---|
| Nothing | 1 (3.3%) | 0 |
| Dynamisation | 13 (43.3%) | 3 |
| Exchange Nail | 7 (23.3%) | 0 |
| Pulsed Ultrasound | 1 (3.3%) | 1 |
| Biologics | 2 (6.7%) | 1 |
| Frame | 2 (6.7%) | 0 |
| Plate | 1 (3.3%) | 0 |
| Infected non-union | 3 (10.0%) | N/A |
| Total | 30 (100%) | |

### 6.11.2 Management of non-union after circular Frame

In patients who were initially treated in a circular frame, 36 developed non-union giving a total non-union rate of 6.5%. This was successfully managed in 32 (88.9%) patients.

Infection was thought to be the driver of non-union in 9 cases and therefore underwent sequential debridement as part of their non-union management. Two of these patients had excision of the infected non-union site and subsequent Masquelet procedure to address the bone defect. An additional two cases underwent eventual amputation and a third cases was left with a permanent pseudoarthrosis.

The remaining 27 patients had presumed aseptic non-union. Seven patients were successfully treated using a ‘watchful waiting’ approach whereby the circular frame was removed and a weight bearing Sarmiento cast applied until union.

A simple frame revision was used in 6 patients, this was supplemented biological stimulation in 2 patients and adjuvant pulsed ultrasound in 2 patients. One patient required resection of the non-union segment followed by bone transport in circular frame. Overall, frame revision proved successful for 4 patients, with one case left with a permanent pseudoarthrosis.

Pulsed ultrasound monotherapy was used to achieve union in 5 patients and biological monotherapy in a further 5 patients. All went on to achieve union.

Three patients had their non-union managed by an additional circular frame with the addition of biological augmentation.

One patient required removal of their circular frame and the application of plate fixation with the addition of ABG and BMP to achieve union in the first instance.

*Table 20: Procedures used to address non-union after management by circular frame*

**Management of non-union after circular frame**

| Index non-union procedure | Number (%) | Need for additional Procedures? |
|---|---|---|
| **Frame revision** | 6 (16.7%) | 2 |
| **Additional Frame** | 3 (8.3%) | 1 |
| **Pulsed Ultrasound** | 5 (13.9%) | 1 |
| **Conversion to plate** | 1 (2.8%) | 0 |
| **Biologics** | 5 (13.9%) | 1 |
| **Watch and Wait** | 7 (19.4%) | 0 |
| **Infected non-union** | 9 (25%) | N/A |
| **Total** | 36 (100%) | |

### 6.11.3 Management of non-union after plate osteosynthesis

Non-union developed in 8 out of 86 fractures, giving a crude rate of 9.3%. Infected non-union was diagnosed in 2 patients who underwent staged debridement, removal of plate and revision fixation with a circular frame. One of these patients who had a background of peripheral vascular disease had a re-vascularisation procedure as part of their non-union management but eventually underwent a below knee amputation due to uncontrolled infection. One further patient did not wish any further operative management and was left with a permanent pseudoarthrosis managed in a removable Sarmiento cast.

The remaining 5 patients all progressed to successful union. Two patients had the plate fixation revised with the addition of ABG and BMP and one of these patients required a repeat procedure before success. Two patients had their plate removed and converted to a circular frame, one of whom returned to theatre several months later to have biological augmentation with bone marrow aspirate and platelet rich plasma injected into the fracture site in order to progress union. One patient was converted to an IMN without the need for further intervention. [Table 20].

*Table 21:Procedures used address non-union after plate osteosynthesis*

**Management of non-union after plate osteosynthesis**

| Index non-union procedure | Number (%) | Need for additional procedures? |
|---|---|---|
| **Infected** | 2 (25.0%) | N/A |
| **Frame** | 2 (25.0%) | 1 |
| **Nail** | 1 (12.5%) | 0 |
| **Nothing** | 1 (12.5%) | 1 |
| **Revision fixation** | 2 (25.0%) | 1 |
| **Total** | 8 (100.0%) | |

### 6.11.4 Management of non-union after other fixation methods

One patient who was managed initially in external factor followed by plaster cast developed a non-union. No further operative intervention was planned due to low functional demand and relative low comorbidity from the non-union.

Finally, one patient who sustained bilateral grade 3B open tibial fracture was managed on one side with a modular rail system (MRS). This progressed to non-union. The MRS was removed, and a period of pulsed ultrasound therapy failed to attain union. At the time of case review the patient was planned for subsequent IMN.

### 6.11.5 Use of biological adjuncts

The use of biological adjuncts is frequently used in order to address the physiological barrier to union in addition to revision fixation, where the mechanical factors are considered. In order to investigate the effect of this, patients with aseptic non-union who underwent an operative procedure as the index non-union procedure were considered. The operative interventions included exchange or dynamisation of IMN, alteration or new circular frame, and conversion of fixation methods (for example from IMN to circular frame). Infected cases were excluded as several of these cases required repeat procedures in order to clear infection and it was felt that the overriding causes of non-union was uncontrolled infection as opposed to any lack of biological stimulus. Patients who had undergone biological therapy alone as their index non-union procedure were also excluded.

A total of 36 cases were identified, all of whom eventually achieved union. In 13 of these patients, biological adjuncts were applied to the fracture site at the time of the procedure. Success was considered when no additional interventions or procedures where required in order to obtain union. Fischer exact test was used to investigate the association between the use of biological adjuncts and success of treatment. There was no statistical association between operative intervention in isolation (87.5% success without further operation) or with the use of biological adjuncts (69.2% success without further operation) [p = .213 by Fisher exact test].

## 6.12 Non-union prediction tools

Non-union prediction scores aim to avoid the dilemma of identifying patients and injuries that will fail to unite. No diagnostic test or prediction tool is 100% accurate but may give insight and additional evidence to support clinicians as a component of the remaining clinical picture. It is often a difficult decision to subject a patient to non-union surgery and the inherent risk of an operation prematurely or without undue evidence. In contrast, when a non-union is developing it is advantageous to act as promptly as possible in order to minimise the social burden to the patient. Two common and recently published tools are the Leeds Genoa Non-union Index and the Non-Union Risk Determination (NURD) score, which will now be evaluated.

### 6.12.1 The Leeds Genoa Non-union Index (LEG-NUI)

The LEG-NUI score and its individual components was recorded for all tibial shaft fracture with sufficient radiological and follow-up data. The score was then used to predict the occurrence of non-union in the data set using the cut-off value of 5 or greater as in the original paper. The performance of the LEG-NUI score could then be assessed in terms of positive and negative predictive values, sensitivity and specificity.

After excluding patients with insufficient follow up data and segmental bone loss, 1096 cases remained. This comprised 319 open fractures and 77 closed injuries. Non-union occurred in 61 patients (6.7%). Scores ranged from 0 to 8, with a median score of 3 (interquartile range 2). The rates of non-union for each score can be found in [Table 22]. Using a cut point of ≥ 5, the LEG-NUI score predicted 177 (16.1%) non-unions. Results are presented in the crosstabulation of non-union prediction based on score against the empirical rates of non-union identified through follow-up. From this we can calculate the following performance metrics:

- Sensitivity 86.0%
- Specificity 49.3%
- Positive predictive value 18.6%
- Negative predictive value 96.3%

*Table 22: Empirical rates of non-union per LEG-NUI score*

| | | Non-union rate |
|---|---|---|
| LEG-NUI Score | 0 | 0/2 (0.0%) |
| | 1 | 3/258 (1.2%) |
| | 2 | 4/256 (1.6%) |
| | 3 | 8/228 (3.5%) |
| | 4 | 19/175 (10.9%) |
| | 5 | 19/95 (20.0%) |
| | 6 | 8/55 (14.5%) |
| | 7 | 4/22 (18.2%) |
| | 8 | 2/5 (40.0%) |

### 6.12.2 The Non-Union Risk Determination (NURD) score

The NURD score was calculated alongside the LEG-NUI score. However, as the score is designed to be used only after intramedullary nailing of tibial fractures, only scores for these patients could be calculated. Once patients with segmental bone loss and insufficient follow up data were excluded, a total of 505 cases were left. These comprised 135 (26.7%) open fractures and 370 closed injuries (73.3%). The scores ranged from -1 to 16 points, with a median of 3 (interquartile range 4). One patient received a score of -1 as the score will deduct points for favourable responses. The score does not give a specific cut off, but instead a range of probabilities based on a range of scores. This was compared to the empirical rate of non-union in the data set and presented in [Table 21].

*Table 23: Comparison of published probabilities of NURD score with observed events*

| | | Non union event | |
|---|---|---|---|
| | | No | Yes |
| | | Published probability | Empircal probablity |
| **NURD Score** | **0 to 5** | 2% | 15/390 (3.8%) |
| | **6 to 8** | 22% | 7/75 (9.3%) |
| | **9 to 11** | 42% | 4/28 (14.3%) |
| | **12+** | 61% | 2/10 (16.7%) |

### 6.12.3 Comparison of scores

The scores were both plotted on a receiver operating characteristic (ROC) curve so that the discrimination of each score could be obtained and compared. Discrimination is the ability of a test to distinguishing between patients with and without the outcome, in this instance non-union. Discrimination was assessed by calculating the area under the ROC curve (AUC, or concordance-statistic). A comparison of the AUC using a paired sample design for both scores was conducted. This was performed using the non-parametric method described by DeLong et al(113) as this is the preferred method of IBM SPSS v. 27 for paired sample design.

Again, as the NURD score only dealt with patients who underwent IMN, only these cases were used to compare score discrimination. The ROC curves for both scores can be found in figure. A diagonal reference line with gradient of 1 is placed for comparison. This line represents a ROC curve where the model is no better than guessing, with 50% chance of predicting the dichotomous outcome. Perfect models have an AUC of 1, where the curve travels through the upper left corner of the graph.

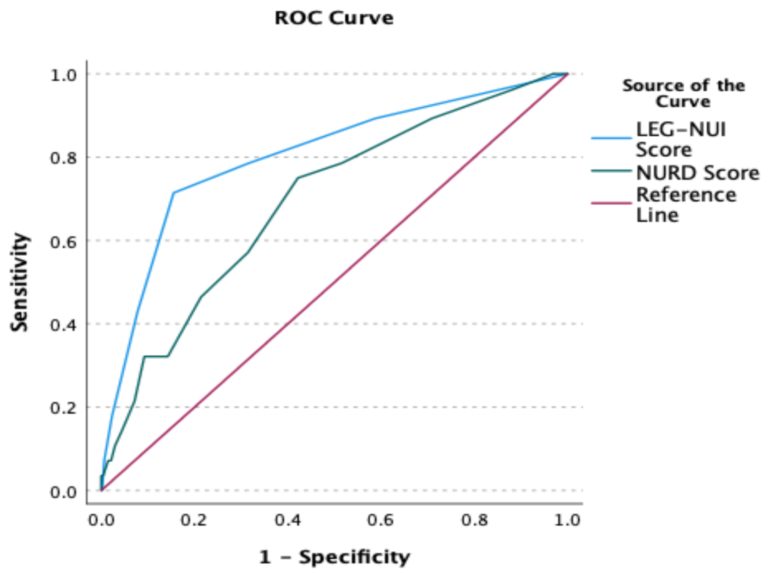


*Figure 17: Receiver Operator Characteristic (ROC) curves for LEG-NUI and NURD scores.*

The LEG-NUI score performed better in terms of discrimination (c = .802, p = <.001, 95% CI .709 to .895) compared to the NURD score (c = .693, p < .001, 95% CI .592 to .793), with a difference of .109 (p = .03, 95% CI, .010 to .208). According to Hosmer and Lemshow(114), concordance statistics of greater than 0.7 indicates a good model fit and greater than 0.8 indicates a strong model.

### 6.12.3 Summary of non-union prediction scores

Both scores performed less well than was reported in their original conception. The discrimination of the NURD score calculated with this cohort was similar to the external validation calculated by the authors of the score using the SPRINT trial database (c-statistic = 0.69 vs 0.61). The LEG-NUI score still provided a strong model fit. However, calibration analysis would be needed in order to fully validate both of these scores.

With a high sensitivity and negative predictive value, the LEG-NUI score is more useful for ruling out problematic union with low scores but is prone to false positive results given the specificity of around 50%. This is demonstrated in the data. If the LEG-NUI score had 100% sensitivity and specificity, then 177 non-unions would have occurred, whereas in reality, only 61 cases were recorded.

It is unlikely that any scoring system can be used in isolation to predict non-union. These scores should be taken in the wider clinical context to aid decision making. In particular, a low LEG-NUI score can be re-assuring, but the clinician must be wary of overestimating non-union risk with higher scores.

# 7. Discussion

The aim of the preceding work was to outline and update the epidemiological and descriptive reporting of diaphyseal tibia fractures, their complications and the current management strategies.

The incidence of diaphyseal tibia fractures has been difficult to ascertain from the literature. There are few epidemiological studies specifically aimed at shaft fractures, particularly from a UK population. Our results demonstrate an evolving picture over the last decade. There has been an increasing trend in the incidence of shaft fractures in Leeds since 2008 (8.08 per 100,000 and year) to 2019 (13.1 per 100,000 and year), an increase of 62%. The majority of injuries occurred in the 18 to 40 age group. This is comparable to previous UK and European studies(1,24,25). The benefit of the prolonged study period in this work allows us to track the change in incidence in age groups over time, from the same population and geographic location. This demonstrated a steeper trend in incidence for those aged 85+ than those in the 18 to 40 age group.

The final incidence of 13.1 per 100,000 and year is similar to the incidence of 15.4 per 100,000 and year given by Wennergren from Sweden(25) and 16.9 per 100,000 and year by Larsen in Denmark(24). However, it is less than previously reported by Court-Brown(1) in the UK of 21 per 100,000 and year. The reason for this difference remains elusive. It may be a result of differing time periods, incomplete population data or changes in road safety, sporting activities and osteoporotic fragility fracture prevention. This latter seems unlikely given that we have demonstrated a steeper upward trend in incidence in the older age groups and may reflect the fragility fracture epidemic brought about by an increasingly elderly population in the UK.

Gender disparity amongst tibial shaft fractures is in keeping with previous studies. Females appear to be the main driving force in the older age group, as opposed to younger patients who tend to be male. This was reported by Court-Brown who showed a similar unimodal distribution of young males and older females sustaining tibial shaft fractures in 2000. It would appear this trend will continue to occur. The dominant mechanism of injury in our cohort was a low energy fall from standing height in females of all age groups, but particularly in those aged over 65 where it accounted for >80% of cases. This contrasts with male patients where a fall from standing accounted for less than half of cases at all age groups. Males had a much a higher rate of RTC and sporting injuries even in the elderly with RTC accounting for over half of cases in the over 85-year-olds. This would suggest different strategies between genders for the prevention of tibial shaft fractures. Improved osteoporosis and fracture liaison services for female patients and more robust road safety measures for male patients.

Over the total study period, type A1 (simple spiral) fractures accounted for 28%, the most common fracture pattern overall. This is similar to the previously mentioned study by Larsen and Wennergren who reported a rate of 34% and 27% respectively(24,25). In contrast, Court-Brown reported a rate of 16.8% type A1 in 1995(17). Although the AO/OTA classification of tibial fractures has changed since then, the classification of type A fractures has remained constant. In their cohort, transverse fractures predominated. These studies are the only epidemiological surveys to include a full breakdown of fracture classification. Unfortunately, they do not comment on the trend in fracture patterns over time, often relying on comparison to other studies performed at different time periods and geographical locations. In this cohort, fracture patterns have been tracked over the last 12 years from the same population and geography. Type A fractures have remained the most common pattern accounting for more than 60% of cases in 2008. This has reduced to under half of cases in 2019. There has been a reciprocal rise in more complex patterns, particularly wedge fractures, which are contributing a larger share of the cohort and appear to be on an increasing trend.

This pattern is replicated amongst open fractures. There has been a slowly increasing proportion of open injuries throughout the study period. Initially representing 26.7% in 2008 to 37.5% in 2019. This is much greater than the rate of 17.7% quoted by Wennergren in Sweden. It is more similar to the UK based survey by Court-Brown of 30%. The complexity of soft tissue insult is also on the increase. Grade 3 injuries, which were once representative of about half of all open injuries in 2008, are now the overwhelming majority with almost 80% of open fractures comprising these. Again, this was consistent with the work from Court-Brown in 1995. This rise of open fractures in our cohort could be accounted for by the introduction of the Major Trauma Network (MTN) in 2012 in the UK. This brought about significant changes, whereby major trauma and complex injuries requiring multidisciplinary tertiary services are brought directly to Level 1 trauma units such as our institution. It may also be accounted for by the rise in elderly patients who have an increased tendency to open injuries (64% open fracture rate in over 85-year-olds in our data). These patients are comorbid with rates of diabetes, COPD and Acute coronary syndrome beyond that reported in the general population. To summarise, tibia fractures are increasing in both incidence and complexity. This is in part caused by the 'MTN effect' at our institution. However, it also appears to be a result of fractures in more complex and frail patients.

The complications following tibial shaft fractures remains substantial. Less than half (46.5%) of all patients followed an uneventful recovery. The majority of these were metalwork issues (8.4%) and pin site infection (27.4%). The rate of embolic events was 3.4% over the 12 year period. Previous studies into the rate of this complication vary widely from 1% to 77%(53,54,56). However, these studies use prospective rates of radiologically proven embolic events which were largely asymptomatic and therefore of unknown clinical relevance. The rate of 3.4% in our study period was of symptomatic embolic events only and may be a more useful estimate. The rate was highest among patients treated with plate osteosynthesis in both closed and open injuries (4.8% and 11.8% respectively). Unlike circular frames and IMN, plate osteosynthesis a larger disruption of the soft tissue envelope. Additionally, it does not frequently allow full and immediate weight bearing as in circular frames and IMN. This fact may account for the steep rates of embolic disease in this cohort of patients. Rates of symptomatic embolic events following circular frame were investigated by Vollans et al(54). They found a rate of 4% in both open and closed injuries, comparable to our rate of 3.4% in this group of patients.

Compartment syndrome complicated 5.1% of patients in the cohort. This is similar to previous estimates of 2 to 10%(57–59). The rate was greatest amongst patients managed with circular frames in closed injuries and (7.2%) and those managed with IMN in open injuries (6.6%). This seems counter intuitive given the minimal soft tissue insult provided by circular frames. It may be that there is an element of selection bias in that more complex fracture patterns tended to management with a circular frame and therefore developed this complication following the injury rather than the management. This warrants further exploration.

Perhaps the most devastating complication of tibial shaft fractures is non-union. This occurred in 6.6% of patients. Previous estimates lacked accuracy. It is frequently quoted as 1 to 10%. At the 4th annual meeting of Danish Orthopaedic Trauma Society 2020 this estimate was questioned. The group found that at least 25 papers quoted this figure from a US textbook dating back to the 1990s. In 2017, Mils et al(67) reviewed data from the national population of Scotland. Tibial non-unions had to be separated from fibular non-union by estimation and a possible range of 5.4% to 7.5% was concluded. Our results corroborate this and lend accuracy to this estimation. Reassuringly, the rate of non-union does appear to be slowly reducing over time. Given the increased risk conferred by open injuries, the introduction of the MTN and comprehensive care of open fractures may have played a role in this. In addition, the reduction in the use of plate osteosynthesis and non-operative management may also have played a part. Plate osteosynthesis produced the highest rate of non-union in closed injuries (7.9%). In open fractures, non-operative management was worse with a rate of 25%, followed closely by plate osteosynthesis (17.6%). This trend is not seen with other major complications. The rates of infection, embolic disease and compartment syndrome have remained constant.

The management of tibial shaft fractures has evolved. Many early studies in the previous century focussed on non-operative management. Sarmiento and colleagues popularised a functional casting technique and demonstrated excellent results(3), but unfortunately these could not be repeated outside their specialist centre. Subsequent studies brought this into question demonstrating high rates of non-union and failure of management(4,5). As a result, very few adult patients now tread this route. A survey by Busse in 2008 showed that 80% of trauma surgeons now favoured operative intervention with IMN and a smaller proportion used plate osteosynthesis. Beyond this there remains little objective descriptions of preference for the management of tibial shaft fractures despite a growing array of fixation methods. This is reflected at our institution where only 15 patients were managed non-operatively over 12 years. These were older patients with high rate of complications and failure of management requiring conversion to IMN. This perhaps demonstrates the largest sea-change in the treatment of tibial shaft management. Intramedullary devices have now become the mainstay of treatment since their conception. There have been numerous studies comparing IM devices and techniques, including the largest randomised control trial in tibial shaft management, the SPRINT trial, comparing reamed and unreamed nails. Coles corroborated this finding through literature review(5). They commented on the shift between non-operative studies towards IMN in more recent years. In addition, a large meta-analysis of randomised trials, comparative studies and case series from 1966 to 1993 by Littenberg(7) included 3,500 patients. Plate osteosynthesis was shown to have a higher rate of union than non-operative management by 20 weeks. Beyond this, the quality of studies was deemed too poor to make any further meaningful comparison between non-operative, IMN or plate osteosynthesis. Each of these reviews focus heavily on plate osteosynthesis and IMN. However, in our institution a substantial proportion of patients (44.8%, n = 547) were managed by circular frame. Furthermore, its use is increasing year by year with a reciprocal decline in the use of IMNs. This may be reactionary to the increasing incidence of open and more complex fracture patterns. However, this trend can be seen in both open and closed injuries. This may be a peculiarity of surgeon preference at our institution where there is a large limb reconstruction practice, and the local expertise favours the use of circular frames for complex tibial shaft fractures. Circular frames share many of the benefits as IMN in that they are minimally invasive, respect the soft tissue envelope and allow early weight bearing. However, the literature surrounding the use of circular frames for tibial shaft fractures concentrate exclusively on open or segmental fractures. In our cohort of patients, many closed and simple fractures were also treated by circular frames and the benefits over conventional IMN is a topic that warrants further research, especially given that IMN fixation is a readily available technique that is in the skill set of most general orthopaedic surgeons and circular frames represent sub-specialty practice. In any case, neither method appears to offer superiority in terms of complication outcomes, but IMN may progress patients to union quicker than with frames.

Plating techniques were used less frequently in all years of study the data did substantiate the finding of increased infective complications as described in the literature. In addition, there was a heightened rate of deep vein thrombosis and pulmonary emboli in patients treated by plate osteosynthesis in both open and closed injuries. The reason for this is not obvious. It may be a result of substantially more soft tissue dissection during the surgical approach on comparison to IMN and circular frames. It may also be a result of the surgeon's reluctance to encourage unrestricted and immediate weight bearing with plate osteosynthesis as opposed to circular frames and IMN fixation.

A total of 76 patients sustained non-union during the study period. The overall success of treatment was generally good in patients initially treated by IMN (97.7%) and circular frame (88.9%). A significant proportion of patients (35.1%) required multiple operations to achieve union. Despite the vast array of management options employed, the eventual outcome is still far from predictable. At our institution several, and often multiple, strategies were employed to address non-union which highlights the tremendous burden to healthcare systems, society and a patient's quality of life following the diagnosis of non-union. Predictive scoring systems like the LEG-NUI score and NURD score described in this work have come some way to risk stratifying patients. However, they may lack generalisability when applied to the general population of tibial shaft fractures. Their use may be valuable as part of the wider clinical picture and may give the clinician the support to intervene sooner when union is not following the desired course. The intervention that this provided is yet to be elucidated. The success rate of non-union management in this study was mixed as was the use of biological adjuncts which have gathered much attention recently. A standardised approach was not adopted over the past 12 years in Leeds. Tanner et al(115) has reported success by using the 'Diamond Concept' of fracture healing as a framework for addressing non-union. In particular, they report a two-stage procedure will benefit those suffering a septic non-union with one stage procedure suitable for all other patients. They found no difference in the method of osteosynthesis for non-union surgery and should be performed at the surgeon's discretion.

The findings of this work must be viewed in the light of its strengths and limitations. This study was retrospective in nature. This is beneficial in terms of cost, time efficiency and a simpler study design. It also allowed a more confident assumption in collating all tibial shaft fractures that have occurred in the city of Leeds leading to a complete population study. Particularly as patients were eventually gathered by reviewing all tibial plain radiographs undertaken during the study period. This was crucial with regards to the aim of accurate and empirical reporting of shaft fractures and their complications. Furthermore, follow up can be prolonged with retrospective data. Complications such as non-union, osteomyelitis and post-traumatic arthritis may take several years to occur and may be missed with short prospective trials. Retrospective chart reviews are subject to information bias and may not contain the desired data for the study question. The study period was subsequently curtailed to 2008 onwards as it was discovered that radiographic investigations were not available through the PACS system until this point. A further limitation was the use of a control or comparative group. This can be difficult to achieve using retrospective data as outcomes, exposures and variable have already occurred.

Radiographic assessment of union using the RUST score was employed. RUST scores could only be calculated from pre-existing radiographs. Typically, patients attended follow-up in intervals of several months and therefore the true date of radiological union may be missed. In a prospective trial, patients could be followed up more frequently so this margin of error could be reduced.

The study aimed to measure some of the basic outcomes of tibial shaft fractures. As discussed in the literature review section, there is a substantial impact on a patient's quality of life and societal and healthcare cost to these injuries, especially when complicated by adverse outcomes. For a more complete overview of tibial shaft fractures, patient reported outcomes, or a cost analysis study would be required. Although this is out with the scope and time scale of this work, it would be valuable in future work. In particular, return to sport and work as a factor of differing fracture patterns and fixation methods would be helpful in providing bespoke treatment for individual injuries and patients based on their functional demand. Anterior knee pain is often suffered by patients with tibial nails and there is ongoing concern over ankle stiffness with the use of circular frames. This association and eventual outcome would also be worth exploring. The large cohort of circular frames in simple closed fractures is underrepresented in the medical literature and the outcomes and patient reported experience of this would be of interest to trauma surgeons. These potential directions for future work would facilitate a more complete informed consent process and help include patients in the decision making in an era of increasing operative options.

# 8. Conclusion

Tibial shaft fractures remain a significant proportion of a trauma surgeon's workload. They are increasing in incidence, complexity and in more complex and frail patients. Despite, this there appears to be headway made in terms of reducing the incidence of non-union, but not other common complications. The management of non-union is extremely varied and unpredictable. Plate osteosynthesis has shown the unfavourable outcomes in terms of non-union and deep infection in both open and closed injuries. There does not appear to be superiority between IMN devices and circular frames in terms of major complications. Hopefully this accurate description of the epidemiology and major complications rates of tibial shaft fractures will help inform healthcare decision and future studies.

# 9. References


1. Court-Brown CM, Caesar B. Epidemiology of adult fractures: A review. Injury. 2006 Aug;37(8):691–7.
2. Estimates of the very old, including centenarians, UK - Office for National Statistics [Internet]. [cited 2022 Aug 6]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/ageing/bulletins/estimatesoftheveryoldincludingcentenarians/2002to2020
3. Sarmiento A. A functional below-the-knee brace for tibial fractures. A report on its use in one hundred thirty-five cases. J Bone Joint Surg Am. 1970;52(2):295–311.
4. Swart E, Lasceski C, Latario L, Jo J, Nguyen USDT. Modern treatment of tibial shaft fractures: Is there a role today for closed treatment? Injury. 2021 Jun 1;52(6):1522–8.
5. Coles CP, Gross M. CLOSED TIBIAL SHAFT FRACTURES: A REVIEW OF THE PROSPECTIVE LITERATURE. 256 JCC. 2000;43(4).
6. Bleeker NJ, van de Wall BJM, IJpma FFA, Doornberg JN, Kerkhoffs GMMJ, Jaarsma RL, et al. Plate vs. nail for extra-articular distal tibia fractures: How should we personalize surgical treatment? A meta-analysis of 1332 patients. Injury. 2021 Mar 1;52(3):345–57.
7. Littenberg B, Weinstein L, McCarren M, JBJS TM-, 1998 undefined. Closed fractures of the tibial shaft. A meta-analysis of three methods of treatment. journals.lww.com.
8. Bhandari M, Guyatt G, Walter SD, Tornetta P, Schemitsch EH, Swiontkowski M, et al. Randomized trial of reamed and unreamed intramedullary nailing of tibial shaft fractures. J Bone Joint Surg Am. 2008 Dec 1;90(12):2567–78.
9. Schmal H, Brix M, Bue M, Ekman A, Ferreira N, Gottlieb H, et al. Nonunion – consensus from the 4th annual meeting of the Danish Orthopaedic Trauma Society. EFORT Open Rev. 2020 Jan 1;5(1):46.
10. Calori GM, Mazza EL, Mazzola S, Colombo A, Giardina F, Romanò F, et al. Non-unions. Clin Cases Miner Bone Metab. 2017;14(2):186.
11. Kanakaris NK, Giannoudis P V. The health economics of the treatment of long-bone non-unions. Injury. 2007;
12. Khunda A, Al-Maiyah M, Eardley WGP, Montgomery R. The management of tibial fracture non-union using the Taylor Spatial Frame. J Orthop. 2016 Dec 1;13(4):360.
13. Brinker MR, Hanus BD, Sen M, O’Connor DP. The devastating effects of tibial nonunion on health-related quality of life. J Bone Jt Surg. 2013 Dec 18;95(24):2170–6.
14. Schottel PC, O’Connor DP, Brinker MR. Time trade-off as a measure of health-related quality of life: Long bone nonunions have a devastating impact. J Bone Jt Surg - Am Vol. 2014 Sep 2;97(17):1406–10.
15. Santolini E, West RM, Giannoudis P V. Leeds-Genoa Non-Union Index: a clinical tool for asessing the need for early intervention after long bone fracture fixation. Int Orthop. 2020 Jan 1;44(1):161–72.
16. O’Halloran K, Coale M, Costales T, Zerhusen T, Castillo RC, Nascone JW, et al. Will My Tibial Fracture Heal? Predicting Nonunion at the Time of Definitive Fixation Based on Commonly Available Variables. Clin Orthop Relat Res. 2016 Jun 1;474(6):1385–95.
17. Court-Brown CM, McBirnie J. The epidemiology of tibial fractures. J Bone Jt Surg - Ser B. 1995;77(3):417–21.

18. Murphy D, Raza M, Monsell F, Gelfer Y. Modern management of paediatric tibial shaft fractures: an evidence-based update. Eur J Orthop Surg Traumatol. 2021 Jul 1;31(5):901–9.
19. Singer BR, McLauchlan GJ, Robinson CM, Christie J. Epidemiology of fractures in 15 000 adults: The influence of age and gender. J Bone Jt Surg - Ser B. 1998;80(SUPPL. 2):243–8.
20. Miller NC, Askew AE. Tibia fractures: An overview of evaluation and treatment. Nursing (Lond). 2007;26(4):216–23.
21. Population Estimates and Projections. 1992;
22. Van Staa TP, Dennison EM, Leufkens HGM, Cooper C. Epidemiology of fractures in England and Wales. Bone. 2001 Dec 1;29(6):517–22.
23. Walley T, Mantgani A. The UK general practice research database. Lancet. 1997 Oct 11;350(9084):1097–9.
24. Larsen P, Elsoe R, Hansen SH, Graven-Nielsen T, Laessoe U, Rasmussen S. Incidence and epidemiology of tibial shaft fractures. Injury. 2015 Apr 1;46(4):746–50.
25. Wennergren D, Bergdahl C, Ekelund J, Juto H, Sundfeldt M, Möller M. Epidemiology and incidence of tibia fractures in the Swedish Fracture Register. Injury. 2018 Nov 1;49(11):2068–74.
26. Wennergren D, Ekholm C, Sundfeldt M, Karlsson J, Bhandari M, Möller M. High reliability in classification of tibia fractures in the Swedish Fracture Register. Injury. 2016 Feb 1;47(2):478–82.
27. Meyer B, Shiban E, Albers LE, Krieg SM. Completeness and accuracy of data in spine registries: an independent audit-based study. Eur Spine J. 2020 Jun 1;29(6):1453–61.
28. Cundall-Curry DJ, Lawrence JE, Fountain DM, Gooding CR. Data errors in the National Hip Fracture Database. https://doi.org/101302/0301-620X98B1037089. 2016 Oct 1;98-B(10):1406–9.
29. Sarmiento A, Sharpe F, research EE-… and related, 1995 undefined. Factors influencing the outcome of closed tibial fractures treated with functional bracing. europepmc.org.
30. Sarmiento A, Latta LL. 450 Closed fractures of the distal third of the tibia treated with a functional brace. Clin Orthop Relat Res. 2004;428:261–71.
31. Sarmiento A, Cech LL-ACOT, 2008 undefined. Functional treatment of closed segmental fractures of the tibia. researchgate.net.
32. Martinez A, Sarmiento A, and LL-CO, 2003 undefined. Closed fractures of the proximal tibia treated with a functional brace. journals.lww.com.
33. Oni OOA, Hui A, Gregg PJ. The healing of closed tibial shaft fractures. The natural history of union with closed treatment. J Bone Jt Surg - Ser B. 1988 Nov 1;70(5):787–90.
34. Duan X, Al-Qwbani M, Zeng Y, Zhang W, Xiang Z. Intramedullary nailing for tibial shaft fractures in adults. Cochrane database Syst Rev. 2012 Jan 18;1.
35. Johal H, Bhandari M, Tornetta P. Cochrane in CORR®: Intramedullary Nailing for Tibial Shaft Fractures in Adults (Review). Clin Orthop Relat Res. 2017 Mar 1;475(3):585.
36. Dodd AC, Salib CG, Lakomkin N, Obremskey WT, Sethi MK. Increased risk of adverse events in management of femur and tibial shaft fractures with plating: An analysis of NSQIP data. J Clin Orthop Trauma. 2016 Apr 1;7(2):80.
37. Upfill-Brown A, Hwang R, Clarkson S, Brodke D, Devana S, Mayer E, et al. Rates and timing of short-term complications following operative treatment of tibial shaft

fractures. OTA Int. 2021 Dec;4(4):e158.
38. Foote CJ, Guyatt GH, Vignesh KN, Mundi R, Chaudhry H, Heels-Ansdell D, et al. Which Surgical Treatment for Open Tibial Shaft Fractures Results in the Fewest Reoperations? A Network Meta-analysis. Clin Orthop Relat Res. 2015 Jul 8;473(7):2179.
39. Schwartsman V, Martin S, research RR-… and related, 1992 undefined. Tibial fractures. The Ilizarov alternative. europepmc.org.
40. Ramos T, Eriksson BI, Karlsson J, Nistor L. Ilizarov external fixation or locked intramedullary nailing in diaphyseal tibial fractures: A randomized, prospective study of 58 consecutive patients. Arch Orthop Trauma Surg. 2014 Mar 25;134(6):793–802.
41. L Foster PA, Barton SB, E Jones SC, M Morrison RJ, Britten S. The treatment of complex tibial shaft fractures by the Ilizarov method. J BONE Jt Surg J Bone Jt Surg Br. 2012;94:1678–83.
42. Costa ML, Achten J, Griffin J, Petrou S, Pallister I, Lamb SE, et al. Effect of Locking Plate Fixation vs Intramedullary Nail Fixation on 6-Month Disability Among Adults With Displaced Fracture of the Distal Tibia: The UK FixDT Randomized Clinical Trial. JAMA. 2017 Nov 11;318(18):1767.
43. Li B, Yang Y, Jiang LS. Plate fixation versus intramedullary nailing for displaced extra-articular distal tibia fractures: A system review. Eur J Orthop Surg Traumatol. 2015 Nov 20;25(1):53–63.
44. Matsumura T, Takahashi T, Miyamoto O, Saito T, Kimura A, Takeshita K. Clinical outcome of conversion from external fixation to definitive internal fixation for open fracture of the lower limb. J Orthop Sci. 2019 Sep 1;24(5):888–93.
45. Nowotarski PJ, Turen CH, Brumback RJ, Scarboro JM. Conversion of External Fixation to Intramedullary Nailing for Fractures of the Shaft of the Femur in Multiply Injured Patients*. JBJS. 2000;82(6).
46. Blachut PA, Meek RN, O'Brien PJ. External fixation and delayed intramedullary nailing of open fractures of the tibial shaft. A sequential protocol. JBJS. 1990;72(5).
47. Bhandari M, Zlowodzki M, Tornetta PIII, Schmidt A, Templeman DC. Intramedullary Nailing Following External Fixation in Femoral and Tibial Shaft Fractures. J Orthop Trauma. 2005;19(2).
48. Maury C, Ramin S, Bonfils J, Dagneaux L, Faure P, Canovas F, et al. Influence of a temporary stabilization device on respiratory status in patients with severe trauma with a femoral shaft fracture treated by damage control strategy. Eur J Trauma Emerg Surg. 2021 Aug 1;47(4):1231.
49. Ye Z, Zhao S, Zeng C, Luo Z, Yuan S, Li R. Study on the relationship between the timing of conversion from external fixation to internal fixation and infection in the treatment of open fractures of extremities. J Orthop Surg Res. 2021 Dec 1;16(1):662.
50. Harwood PJ, Giannoudis P V, Probst C, Krettek C, Pape H-C. The Risk of Local Infective Complications After Damage Control Procedures for Femoral Shaft Fracture. J Orthop Trauma. 2006;20(3).
51. BOAST - Open Fractures [Internet]. [cited 2022 Sep 21]. Available from: https://www.boa.ac.uk/resources/boast-4-pdf.html
52. Waddell JP, Reardon GP. Complications of tibial shaft fractures. Clin Orthop Relat Res. 1983;(178):173–8.

53. Milner SA, Moran CG. (v) The long term complications of tibial shaft fractures. Curr Orthop. 2003 Jun 1;17(3):200–5.
54. Vollans S, Chaturvedi A, Sivasankaran K, Madhu T, Hadland Y, Allgar V, et al. Symptomatic venous thromboembolism following circular frame treatment for tibial fractures. Injury. 2015 Jun 1;46(6):1108–11.
55. Hjelmstedt A, Bergvall U. Incidence of thrombosis in patients with tibial fractures - PubMed. Acta Chir Scand. 1968;134(3):209–18.
56. Geerts WH, Code KI, Jay RM, Chen E, Szalai JP. A Prospective Study of Venous Thromboembolism after Major Trauma. N Engl J Med. 1994 Dec 15;331(24):1601–6.
57. Park S, Ahn J, Gee AO, Kuntz AF, Esterhai JL. Compartment syndrome in tibial fractures. J Orthop Trauma. 2009 Aug;23(7):514–8.
58. Crespo AM, Manoli A, Konda SR, Egol KA. Development of compartment syndrome negatively impacts length of stay and cost after tibia fracture. J Orthop Trauma. 2015 Jul 20;29(7):312–5.
59. McQueen MM, Christie J, Court-Brown CM. ACUTE COMPARTMENT SYNDROME IN TIBIAL DIAPHYSEAL FRACTURES. https://doi.org/101302/0301-620X78B10780095. 1996 Jan 1;78(1):95–8.
60. McQueen M, Gaston P, Court-Brown C. Acute compartment syndrome: WHO IS AT RISK? J Bone Joint Surg Br. 2000 Mar 1;82-B:200–3.
61. Schmidt AH. The impact of compartment syndrome on hospital length of stay and charges among adult patients admitted with a fracture of the tibia. J Orthop Trauma. 2011 Jun;25(6):355–7.
62. Court-brown C, Mcqueen M. Compartment syndrome delays tibial union. Acta Orthop Scand. 1987;58(3):249–52.
63. Reverte MM, Dimitriou R, Kanakaris NK, Giannoudis P V. What is the effect of compartment syndrome and fasciotomies on fracture healing in tibial fractures? Injury. 2011 Dec 1;42(12):1402–7.
64. Stella M, Santolini E, Sanguineti F, Felli L, Vicenti G, Bizzoca D, et al. Aetiology of trauma-related acute compartment syndrome of the leg: A systematic review. Injury. 2019 Jul 1;50:S57–64.
65. Gómez-Barrena E, Padilla-Eguiluz NG, Rosset P. Frontiers in non-union research. EFORT Open Rev. 2020 Oct 1;5(10):574.
66. Tzioupis C, Giannoudis P V. Prevalence of long-bone non-unions. Injury. 2007 May 1;38:S3–9.
67. Mills LA, Aitken SA, Simpson AHRW. The risk of non-union per fracture: current myths and revised figures from a population of over 4 million adults. Acta Orthop. 2017;
68. Zura R, Xiong Z, Einhorn T, Watson JT, Ostrum RF, Prayson MJ, et al. Epidemiology of Fracture Nonunion in 18 Human Bones. JAMA Surg. 2016 Nov 1;151(11):e162775–e162775.
69. Santolini E, West R, Giannoudis P V. Risk factors for long bone fracture non-union: A stratification approach based on the level of the existing scientific evidence. Vol. 46, Injury. Elsevier Ltd; 2015. p. S8–19.
70. Calori GM, Albisetti W, Agus A, Iori S, Tagliabue L. Risk factors contributing to fracture non-unions. Injury. 2007;38(SUPPL. 2).

71. Adams CI, Keating JF, Court-Brown CM. Cigarette smoking and open tibial fractures. Injury. 2001;32(1):61–5.
72. Dimitriou R, Kanakaris N, Soucacos PN, Giannoudis P V. Genetic predisposition to non-union: Evidence today. Injury. 2013 Jan;44(SUPPL.1).
73. Wennergren D, Bergdahl C, Selse A, Ekelund J, Sundfeldt M, Möller M. Treatment and re-operation rates in one thousand and three hundred tibial fractures from the Swedish Fracture Register. Eur J Orthop Surg Traumatol. 2021 Jan 1;31(1):143.
74. Bozic KJ, Rosenberg AG, Huckman RS, Herndon JH. Economic Evaluationin Orthopaedics. JBJS. 2003;85(1).
75. Stewart SK. Fracture Non-Union: A Review of Clinical Challenges and Future Research Needs. Malaysian Orthop J. 2019 Jul 1;13(2):1.
76. Johnson L, Igoe E, Kleftouris G, Papachristos I V., Papakostidis C, Giannoudis P V. Physical Health and Psychological Outcomes in Adult Patients with Long-Bone Fracture Non-Unions: Evidence Today. J Clin Med. 2019 Nov 1;8(11).
77. Tay WH, De Steiger R, Richardson M, Gruen R, Balogh ZJ. Health outcomes of delayed union and nonunion of femoral and tibial shaft fractures. Injury. 2014 Oct 1;45(10):1653–8.
78. Andrzejowski P, Giannoudis P V. The 'diamond concept' for long bone non-union management. J Orthop Traumatol. 2019 Dec 1;20(1).
79. Giannoudis P V., Einhorn TA, Marsh D. Fracture healing: The diamond concept. Injury. 2007 Sep 1;38(4 SUPPL.):S3–6.
80. Rubin J, Rubin C, Jacobs CR. Molecular pathways mediating mechanical signaling in bone. Gene. 2006 Feb 2;367(1–2):1.
81. PERREN SM. Physical and Biological Aspects of Fracture Healing with Special Reference to Internal Fixation. Clin Orthop Relat Res. 1979;(138).
82. Elliott DS, Newman KJH, Forward DP, Hahn DM, Ollivere B, Kojima K, et al. A unified theory of bone healing and nonunion. Bone Jt J. 2016 Jul 1;98B(7):884–91.
83. Szczęsny G, Interewicz B, Swoboda-Kopeć E, Olszewski WL, Górecki A, Wasilewski P. Bacteriology of Callus of Closed Fractures of Tibia and Femur. J Trauma - Inj Infect Crit Care. 2008 Oct;65(4):837–42.
84. Bhandari M, Guyatt GH, Swiontkowski MF, Tornetta P, Srpague S, Schemitsch EH. A lack of consensus in the assessment of fracture healing among orthopaedic surgeons. J Orthop Trauma. 2002 Sep;16(8):562–6.
85. Hammer RRR, Hammerby S, Lindholm B. Accuracy of radiologic assessment of tibial shaft fracture union in humans. Clin Orthop Relat Res. 1985;NO. 199(199):233–8.
86. Whelan DB, Bhandari M, Stephen D, Kreder H, Mckee MD, Zdero R, et al. Development of the radiographic union score for tibial fractures for the assessment of tibial fracture healing after intramedullary fixation. J Trauma. 2010 Mar;68(3):629–32.
87. Whelan DB, Bhandari M, McKee MD, Guyatt GH, Kreder HJ, Stephen D, et al. Interobserver and intraobserver variation in the assessment of the healing of tibial fractures after intramedullary fixation. J Bone Joint Surg Br. 2002;84(1):15–8.
88. Litrenta J, Tornetta P, Mehta S, Jones C, O'Toole R V., Bhandari M, et al. Determination of Radiographic Healing: An Assessment of Consistency Using RUST and Modified RUST in Metadiaphyseal Fractures. J Orthop Trauma. 2015 Nov 1;29(11):516–20.

89. Ali S, Singh A. (PDF) Reliability Of The RUST Score For The Assessment Of Union In Simple Diaphyseal Tibial Fractures [Internet]. Int J Biomed Res. 2014 [cited 2022 Aug 13]. Available from: https://www.researchgate.net/publication/263086827_Reliability_Of_The_RUST_Score_For_The_Assessment_Of_Union_In_Simple_Diaphyseal_Tibial_Fractures
90. Calori GM, Colombo M, Mazza EL, Mazzola S, Malagoli E, Marelli N, et al. Validation of the Non-Union Scoring System in 300 long bone non-unions. Injury. 2014 Dec 1;45(S6):S93–7.
91. O'Hara NN, Slobogean GP, O'Halloran K, Castillo R, Sprague S, Bhandari M, et al. Predicting tibia shaft nonunions at initial fixation: An external validation of the Nonunion Risk Determination (NURD) score in the SPRINT trial data. Injury. 2020 Oct 1;51(10):2302–8.
92. Chloros GD, Kanakaris NK, Vun JSH, Howard A, Giannoudis P V. Scoring systems for early prediction of tibial fracture non-union: an update. Int Orthop. 2021 Aug 1;45(8):2081.
93. Smith SH, Kershaw C, Thomas IH, Botha JL. PIS and DRGs: coding inaccuracies and their consequences for resource management. J Public Health Med. 1991;13(1):40–1.
94. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–83.
95. Brusselaers N, Lagergren J. The Charlson Comorbidity Index in Registry-based Research. Methods Inf Med. 2017;56(5):401–6.
96. Borja AJ, Connolly J, Kvint S, Detchou DKE, Glauser G, Strouz K, et al. Charlson Comorbidity Index score predicts adverse post-operative outcomes after far lateral lumbar discectomy. Clin Neurol Neurosurg. 2021 Jul 1;206.
97. AO/OTA Fracture and Dislocation Classification Compendium-2018 [Internet]. [cited 2022 Sep 2]. Available from: https://classification.aoeducation.org/
98. Yim GH, Hardwicke JT. The Evolution and Interpretation of the Gustilo and Anderson Classification. J Bone Jt Surg - Am Vol. 2018 Dec 19;100(24).
99. Papakostidis C, Kanakaris NK, Pretel J, Faour O, Morell DJ, Giannoudis P V. Prevalence of complications of open tibial shaft fractures stratified as per the Gustilo-Anderson classification. Injury. 2011 Dec;42(12):1408–15.
100. Thakore R V., Francois EL, Nwosu SK, Attum B, Whiting PS, Siuta MA, et al. The Gustilo-Anderson classification system as predictor of nonunion and infection in open tibia fractures. Eur J Trauma Emerg Surg. 2017 Oct 1;43(5):651–6.
101. Baker SP, O'Neill B, Haddon W, Long WB. The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. J Trauma. 1974;14(3):187–96.
102. Kim H-Y. Statistical notes for clinical researchers: Chi-squared test and Fisher's exact test. Restor Dent Endod. 2017;42(2):152.
103. Kwak SG, Kim JH. Central limit theorem: the cornerstone of modern statistics. Korean J Anesthesiol. 2017 Apr 1;70(2):144.
104. Toothaker LE. Multiple Comparison Procedures. SAGE Publications Inc.; 1993.
105. IBM Corp. IBM SPSS Statistics for Macintosh, Version 27. Armonk, NY; 2020.
106. NHS HRA. Guidance for CAG applicants - Health Research Authority [Internet]. [cited

2022 Sep 28]. Available from: https://www.hra.nhs.uk/about-us/committees-and-services/confidentiality-advisory-group/guidance-confidentiality-advisory-group-applicants/

107. STROBE - Strengthening the reporting of observational studies in epidemiology [Internet]. [cited 2022 Oct 1]. Available from: https://www.strobe-statement.org/
108. Population Estimates for UK, England and Wales, Scotland and Northern Ireland - Office for National Statistics [Internet]. [cited 2022 Aug 13]. Available from: https://www.ons.gov.uk/datasets/mid-year-pop-est/editions
109. Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol. 2011 Mar 15;173(6):676–82.
110. Health Intelligence Team B. BHF England CVD Factsheet. 2022;
111. Diabetes Prevalence 2019 | Diabetes UK [Internet]. [cited 2022 Aug 21]. Available from: https://www.diabetes.org.uk/professionals/position-statements-reports/statistics/diabetes-prevalence-2019
112. Chronic obstructive pulmonary disease (COPD) statistics | British Lung Foundation [Internet]. [cited 2022 Aug 22]. Available from: https://statistics.blf.org.uk/copd
113. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the Areas under Two or More Correlated Receiver Operating Characteristic Curves: A Nonparametric Approach. Biometrics. 1988 Sep;44(3):837.
114. Hosmer DW, Lemeshow S, Sturdivant RX. Applied Logistic Regression: Third Edition. Appl Logist Regres Third Ed. 2013 Aug 29;1–510.
115. Tanner MC, Hagelskamp S, Vlachopoulos W, Miska M, Findeisen S, Grimm A, et al. Non-Union Treatment Based on the “Diamond Concept” Is a Clinically Effective and Safe Treatment Option in Older Adults. 2020;

# 10. Appendix A: Search Strategy for literature review

| # | Database | Search term | Results |
|---|---|---|---|
| 1 | EMBASE | "TIBIA FRACTURE"/ OR "DISTAL TIBIA FRACTURE"/ OR "PROXIMAL TIBIA FRACTURE"/ OR "TIBIA SHAFT FRACTURE"/ OR "TIBIA FRACTURE,DISTAL"/ OR "TIBIA FRACTURE,PLATEAU"/ OR "TIBIA FRACTURE,PROXIMAL"/ OR "TIBIA NAIL"/ OR "TIBIA NAIL, NON-STERILE"/ OR "TIBIA NAIL, STERILE"/ | 16163 |
| 2 | EMBASE | ("tibia* fracture*" OR "tibia* trauma*" OR "tibia* nonunion" OR "tibia* non-union").ti,ab | 5304 |
| 3 | EMBASE | ("tibia* distal fracture*" OR "tibia* distal trauma*" OR "tibia* distal nonunion" OR "tibia* distal non-union" OR "distal tiba* fracture*" OR "distal tibia* trauma*" OR "distal tibia* nonunion" OR "distal tibia* non-union").ti,ab | 20 |
| 4 | EMBASE | ("tibia* proxima* fracture*" OR "tibia* promixa* trauma*" OR "tibia* promixa* nonunion" OR "tibia* promixa* non-union" OR "distal promixa* fracture*" OR "promixa* tibia* trauma*" OR "promixa* tibia* nonunion" OR "promixa* tibia* non-union").ti,ab | 4 |
| 5 | EMBASE | ("tibia* eminence fracture*" OR "tibia* eminence trauma*" OR "tibia* eminence nonunion" OR "tibia* eminence non-union").ti,ab | 138 |
| 6 | EMBASE | ("tibia* plateau* fracture*" OR "tibia* plateau* trauma*" OR "tibia* plateau* nonunion" OR "tibia* plateau* non-union").ti,ab | 1538 |
| 7 | EMBASE | ("tibia* diaphysis fracture*" OR "tibia* diaphysis trauma*" OR "tibia* diaphysis nonunion" OR "tibia* diaphysis non-union").ti,ab | 25 |
| 8 | EMBASE | ("tibia* shaft fracture*" OR "tibia* shaft trauma*" OR "tibia* shaft nonunion" OR "tibia* shaft non-union").ti,ab | 1271 |
| 9 | EMBASE | ("tibia* spin* fracture*" OR "tibia* spin* trauma*" OR "tibia* spin* nonunion" OR "tibia* spin* non-union").ti,ab | 92 |
| 10 | EMBASE | ("intercondylar eminence fracture*" OR "intercondylar eminence trauma*" OR "intercondylar eminence nonunion" OR "intercondylar eminence non-union").ti,ab | 59 |
| 11 | EMBASE | ("intercondylar fracture*" OR "intercondylar trauma*" OR "intercondylar nonunion" OR "intercondylar non-union").ti,ab | 176 |
| 12 | EMBASE | ("Segond fracture*" OR "Tillaux fracture*" OR "Tibia* nail").ti,ab | 557 |
| 13 | EMBASE | EPIDEMIOLOGY/ | 209513 |
| 14 | EMBASE | (epidemiology OR cause* OR causation).ti,ab | 3144153 |
| 15 | EMBASE | "CASE MANAGEMENT"/ OR "PATIENT CARE"/ | 307951 |

| | | | |
|---|---|---|---|
| 16 | EMBASE | ("patient care" OR "patient management" OR "case management" OR "patient program*" OR "care program*").ti,ab | 145755 |
| 17 | EMBASE | "CLINICAL OUTCOME"/ OR "TREATMENT OUTCOME"/ OR "CLINICAL PATIENT OUTCOME"/ | 998007 |
| 18 | EMBASE | ("clinical outcome*" OR "treatment outcome*" OR "patient outcome*" OR "therap* outcome*" OR "rehabilitat* outcome*").ti,ab | 441702 |
| 19 | EMBASE | "CLINICAL EFFECTIVENESS"/ | 130882 |
| 20 | EMBASE | ("clinic* effective*" OR "clinic* efhcacy" OR "therap* effective*" OR "therap* efhcacy" OR "treatment effective*" OR "treatment efhcacy" OR "rehabilitat* effective*" OR "rehabilitat* efhcacy").ti,ab | 164590 |
| 21 | EMBASE | (1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12) | 17769 |
| 22 | EMBASE | (13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20) | 4971468 |
| 23 | EMBASE | (21 AND 22) | 4430 |
| 24 | Medline | "TIBIAL FRACTURES"/ | 15202 |
| 25 | Medline | | 4587 |
| 26 | Medline | ("tibia* plateau* fracture*" OR "tibia* plateau* trauma*" OR "tibia* plateau* nonunion" OR "tibia* plateau* non-union").ti,ab | 1335 |
| 27 | Medline | ("tibia* shaft fracture*" OR "tibia* shaft trauma*" OR "tibia* shaft nonunion" OR "tibia* shaft non-union").ti,ab | 1194 |
| 28 | Medline | EPIDEMIOLOGY/ | 12377 |
| 29 | Medline | "CASE MANAGEMENT"/ OR "PATIENT CARE PLANNING"/ OR "MANAGED CARE PROGRAMS"/ | 71901 |
| 30 | Medline | "OUTCOME ASSESSMENT, HEALTH CARE"/ OR "PATIENT OUTCOME ASSESSMENT"/ OR "TREATMENT OUTCOME"/ | 1049037 |
| 32 | Medline | ("clinical outcome*" OR "treatment outcome*" OR "patient outcome*" OR "therap* outcome*" OR "rehabilitat* outcome*").ti,ab | 278170 |
| 33 | Medline | (epidemiology OR cause* OR causation).ti,ab | 2411310 |
| 34 | Medline | ("patient care" OR "patient management" OR "case management" OR "patient program*" OR "care program*").ti,ab | 102097 |
| 35 | Medline | (24 OR 25 OR 26 OR 27) | 17027 |

| | | | |
|---|---|---|---|
| 36 | Medline | (28 OR 29 OR 30 OR 32 OR 33 OR 34) | 3677196 |
| 37 | Medline | (35 AND 36) | 3832 |
| 38 | EMCARE | "TIBIA FRACTURE"/ OR "DISTAL TIBIA FRACTURE"/ OR "PROXIMAL TIBIA FRACTURE"/ OR "TIBIA SHAFT FRACTURE"/ OR "TIBIA FRACTURE,DISTAL"/ OR "TIBIA FRACTURE,PLATEAU"/ OR "TIBIA FRACTURE,PROXIMAL"/ OR "TIBIA NAIL"/ OR "TIBIA NAIL, NON-STERILE"/ OR "TIBIA NAIL, STERILE"/ | 7348 |
| 39 | EMCARE | ("tibia* fracture*" OR "tibia* trauma*" OR "tibia* nonunion" OR "tibia* non-union").ti,ab | 2478 |
| 40 | EMCARE | ("tibia* distal fracture*" OR "tibia* distal trauma*" OR "tibia* distal nonunion" OR "tibia* distal non-union" OR "distal tiba* fracture*" OR "distal tibia* trauma*" OR "distal tibia* nonunion" OR "distal tibia* non-union").ti,ab | 12 |
| 41 | EMCARE | ("tibia* proxima* fracture*" OR "tibia* promixa* trauma*" OR "tibia* promixa* nonunion" OR "tibia* promixa* non-union" OR "distal promixa* fracture*" OR "promixa* tibia* trauma*" OR "promixa* tibia* nonunion" OR "promixa* tibia* non-union").ti,ab | 1 |
| 42 | EMCARE | ("tibia* eminence fracture*" OR "tibia* eminence trauma*" OR "tibia* eminence nonunion" OR "tibia* eminence non-union").ti,ab | 93 |
| 43 | EMCARE | ("tibia* plateau* fracture*" OR "tibia* plateau* trauma*" OR "tibia* plateau* nonunion" OR "tibia* plateau* non-union").ti,ab | 904 |
| 44 | EMCARE | ("tibia* diaphysis fracture*" OR "tibia* diaphysis trauma*" OR "tibia* diaphysis nonunion" OR "tibia* diaphysis non-union").ti,ab | 12 |
| 45 | EMCARE | ("tibia* shaft fracture*" OR "tibia* shaft trauma*" OR "tibia* shaft nonunion" OR "tibia* shaft non-union").ti,ab | 677 |
| 46 | EMCARE | ("tibia* spin* fracture*" OR "tibia* spin* trauma*" OR "tibia* spin* nonunion" OR "tibia* spin* non-union").ti,ab | 65 |
| 47 | EMCARE | ("intercondylar eminence fracture*" OR "intercondylar eminence trauma*" OR "intercondylar eminence nonunion" OR "intercondylar eminence non-union").ti,ab | 34 |
| 48 | EMCARE | ("intercondylar fracture*" OR "intercondylar trauma*" OR "intercondylar nonunion" OR "intercondylar non-union").ti,ab | 68 |
| 49 | EMCARE | ("Segond fracture*" OR "Tillaux fracture*" OR "Tibia* nail").ti,ab | 361 |
| 50 | EMCARE | EPIDEMIOLOGY/ | 38750 |
| 51 | EMCARE | (epidemiology OR cause* OR causation).ti,ab | 538291 |
| 52 | EMCARE | "CASE MANAGEMENT"/ OR "PATIENT CARE"/ | 141755 |

| | | | |
|---|---|---|---|
| 53 | EMCARE | ("patient care" OR "patient management" OR "case management" OR "patient program*" OR "care program*").ti,ab | 53859 |
| 54 | EMCARE | "CLINICAL OUTCOME"/ OR "TREATMENT OUTCOME"/ OR "CLINICAL PATIENT OUTCOME"/ | 275656 |
| 55 | EMCARE | ("clinical outcome*" OR "treatment outcome*" OR "patient outcome*" OR "therap* outcome*" OR "rehabilitat* outcome*").ti,ab | 113613 |
| 56 | EMCARE | "CLINICAL EFFECTIVENESS"/ | 54560 |
| 57 | EMCARE | ("clinic* effective*" OR "clinic* efficacy" OR "therap* effective*" OR "therap* efficacy" OR "treatment effective*" OR "treatment efficacy" OR "rehabilitat* effective*" OR "rehabilitat* efficacy").ti,ab | 30374 |
| 58 | EMCARE | (38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49) | 8007 |
| 59 | EMCARE | (50 OR 51 OR 52 OR 53 OR 54 OR 55 OR 56 OR 57) | 1063216 |
| 60 | EMCARE | (58 AND 59) | 2194 |
| 61 | EMBASE | (21 AND 22) [DT FROM 2018] [English language] [Languages English] [Human age groups Adult 18 to 64 years OR Aged 65+ years] | 474 |
| 62 | Medline | (35 AND 36) [DT FROM 2018] [Human age groups Adult OR Middle Aged OR Aged OR Aged,80 and over] [Languages English] | 242 |
| 63 | EMCARE | (58 AND 59) [DT FROM 2018] [English language] [Languages English] [Human age groups Adult 18 to 64 years OR Aged 65+ years] | 265 |