EXPLORING FACTORS ASSOCIATED WITH TIBIAL FRACTURE COMPLICATIONS

EXPLORING PROGNOSTIC FACTORS ASSOCIATED WITH ADVERSE OUTCOMES IN PATIENTS WITH FRACTURES OF THE TIBIAL SHAFT

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LAY ABSTRACT

The enclosed thesis work evaluates outcomes in patients with fractures primarily of the tibial shaft. In particular, the comprised studies assess whether certain characteristics, such as injury factors, treatment variables and early healing progression, are associated with adverse outcomes in these patients. One study found that delays in timing to appropriate surgical care for patients with open fractures (open wound at the site of the fracture) leads to greater risk of infection. Furthermore, two studies found that both the level of radiographic healing and functional status of patients at three months from surgery can help predict if the patient will ultimately heal radiographically at one year from injury. The findings of this thesis work should help orthopaedic care providers identify patients at high risk for infections and nonunions, such that these patients can be closely monitored to minimize the risk of such complications.

ABSTRACT

The following graduate thesis aims to identify important clinical variables, including injury, treatment and healing characteristics, that serve as prognostic indicators for complications in patients with fractures of the tibial shaft. In particular, the complications of focus in this thesis are surgical site infections and nonunion. The three analytical studies comprising this thesis were derived from large data sets arising from two randomized controlled trials and an observational cohort study.

The first chapter (*Open Tibial Fractures: Updated Guidelines for Management*) is a published literature review that provides an overall introduction to the thesis. It highlights the paucity of high-quality evidence currently available to inform many of the treatment strategies for patients with open fractures of the tibial shaft.

The second chapter (*Timing of Irrigation & Debridement and Infection Risk in Severe Open Fractures*) is a sub-study of all open fracture patients recruited in the International Orthopaedic Multicenter Study (INORMUS) in Fracture Care. The findings of this study suggest that timing delays to irrigation and debridement for patients with open fracture injuries is associated with an increased risk of surgical site infection.

The third and fourth chapters evaluate the association between early healing measures and nonunion in patients with tibial fractures. Specifically, chapter three (*Exploring the Association of 3-Month Radiographic Union Score for Tibia Fractures (RUST) with Nonunion in Tibial Shaft Fracture Patients*) demonstrates that radiographic healing at three months post-operatively is strongly associated with nonunion at one year. Similarly, chapter four (*Nonunion in Patients with Tibial Shaft Fractures—Can Early

Functional Status Predict Healing?) demonstrates that functional status at three months post-operatively is also correlated to eventual healing. Both of these studies include patients from the randomized controlled trials, SPRINT (Study to Prospectively Evaluate Reamed Intramedullary Nails in Patients with Tibial Fractures) and FLOW (Fluid Lavage of Open Wounds).

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DECLARATION OF ACADEMIC ACHIEVEMENT

I (Raman Mundi) was significantly involved in the design, analysis and manuscript drafting of all studies enclosed in this thesis, such that primary authorship for all studies was warranted and granted by my thesis supervisor (Dr. Mohit Bhandari).

All contributing co-authors have been acknowledged and listed in the respective cover pages of each chapter.

CHAPTER I

Open Tibial Fractures: Updated Guidelines for Management

Open Tibial Fractures: Updates Guidelines For Management

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I. INTRODUCTION

Tibial diaphysis fractures represent the most common major long bone fractures that currently confront practicing orthopaedic surgeons[1,2]. The overall incidence has been estimated between 17- to 23 per 100,000 person-years, and it is young males in particular who carry the highest risk of sustaining these fractures, with a reported incidence of 39 per 100,000 person-years in males aged 10-19 [3,4].

Unfortunately, up to 24% (study n=523) of all tibial diaphyseal fractures present as open injuries and are second only to phalanx fractures as the most prevalent type of open fracture[3,5]. Furthermore, a considerable proportion of open tibial fractures are associated with severe soft-tissue compromise (Gustilo and Anderson type III)[3]. Road-traffic accidents, inclusive of pedestrians and cyclists, have been implicated as the predominant causative mechanism, as they account for 43-65% (study n=1,275[4]; study n=123[3]) of open tibial shaft fractures[3,4]. Furthermore, falls represent the second most common mechanism and are responsible for up to 25% (study n=1275[4]; study n=67[6]) of these fractures[4,6]. Although sporting injuries remain a common cause of closed tibial shaft fractures, they infrequently result in open injuries (<10%, study n=502)[7].

Given that up to 1 in 4 patients with tibial shaft fractures present with an open injury, surgeons are often required to make a series of acute management decisions that carry substantial prognostic implications for these patients who are at higher risks for infection, fracture nonunion, and wound complications[8]. The importance of proceeding with evidence-based interventions that optimize patient outcomes in the setting of these potentially devastating injuries cannot be overstated. Despite the growing body of literature surrounding the treatment of open tibial shaft fractures, several crucial aspects in the surgical management of these patients remain equivocal and thus varied across the global orthopaedic community[9].

In this review, we explore the practice patterns and emerging clinical evidence within four aspects of treatment that are central to the management of open tibial diaphyseal fractures, including: i. Irrigation and debridment techniques; ii. Antibiotic prophylaxis; iii. Fracture stabilization; and iv. Wound management. Type of fracture will refer to its Gustilo and Anderson classification throughout this review.

II. IRRIGATION & DEBRIDEMENT

There are several issues regarding the irrigation and debridement of open tibial shaft fractures that are currently controversial. The true urgency of initial surgery has been called into question and the optimal techniques of irrigation remain equivocal. At present, there are several variations of irrigation solution, pressure and volume to select from, including normal saline with or without additives (antiseptics, antibiotics, soaps), delivered at low- or high-pressures[8].

Although emergent irrigation and debridement within 6 hours of injury has been advocated and adopted as the standard of care, there remains a paucity of evidence to conclusively support such practice[8]. Several retrospective series have demonstrated no significant difference in infection rates for those patients who undergo initial surgery before or after 6 hours of injury/presentation, including those patients with type III fractures[6,10,11]. These findings have been validated in a recent meta-analysis, in which a pooled analysis of 14 prospective and retrospective studies demonstrated no significant difference in overall infection rates between late and early debridement (Odds Ratio 0.91 favouring late debridement, 95%CI: 0.70-1.18)[12]. The time threshold for defining late versus early debridement in this analysis was based on the varying definitions set by the individual studies, although the majority used a 6-hour threshold[12].

Fittingly, an assessment of national practice trends across the United States involving 6099 patients with open tibial fractures demonstrated that 42% of patients waited greater than 6 hours from hospital arrival for initial surgery. Factors associated with delayed treatment included both patient characteristics (severe head or thoracic injury, presentation after 6:00pm) and hospital characteristics (level-1 trauma center and university hospital)[13].

Ultimately, in the absence of evidence from randomized trials, formal irrigation and debridement within 6 hours of injury remains the historically established recommendation of care. However, there is a growing recognition that delayed surgery for less severe fractures (type I) may be acceptable practice, so long as debridement is performed as a priority procedure no later than the morning after admission[8].

An international survey of 984 orthopaedic surgeons assessing practice preferences for irrigation techniques of open fractures found no global consensus on the preferred choice of irrigation solution or pressure. Although the predominant preferences were normal saline solution alone and low-pressure irrigation, only 71% of respondents endorsed these practices[9]. Furthermore, it has been suggested that type I, II and III fractures should be irrigated with 3L, 6L, and 9L of solution respectively[8]. However, practice patterns regarding volume of irrigation solution used for open fracture management remains varied and may in large part be attributable to insufficient clinical evidence[8,9].

There are recent randomized clinical trials that are providing further insight into the relative efficacy of these irrigation techniques. Anglen randomized 400 patients with open fractures of the lower extremity (111 tibial shaft fractures) to irrigation with either castile soap or antibiotic (bacitracin) solution and found no significant difference in regard to infection risk between the two agents (13% castile soap versus 18% bacitracin). There was, however, an increased risk of wound healing failure with the antibiotic solution (4% castile soap versus 9.5% bacitracin)[14]. The Fluid Lavage of Open Wounds (FLOW) study is an international, multi-center, 3 x 2 randomized trial that has recruited over 2500 patients to evaluate the efficacy of high-pressure, low-pressure and bulb syringe lavage, as well as normal saline to castile soap solution[15]. The initial pilot study of 111 patients suggested that low-pressure lavage may reduce re-operation rates due to infection, nonunion and wound healing problems, but ultimately, the final results of this landmark trial will provide more definitive guidance[16] (CME 1).

The merits of meticulous irrigation and debridement of open fracture wounds in mitigating infection risk are universally accepted[8,16]. Beyond this uncontested matter, however, strong recommendations for specific solutions or irrigation pressures for the management of open tibial shaft fractures cannot be put forth.

III. ANTIBIOTIC PROPHYLAXIS

Infection is a known complication related to open fractures, as open injuries are prone to microbial contamination[17]. Numerous studies have been carried out over the years investigating the role of antibiotic prophylaxis in the setting of open fractures. A Cochrane review of randomized trials (n=913 patients) demonstrated a pooled relative risk reduction in acute infection of 59% for patients with open fractures treated with prophylactic antibiotics[18]. It was concluded that for every thirteen patients treated with prophylactic antibiotics, one acute infection would be circumvented[18].

Although the merits of administering systemic antibiotic prophylaxis are well established, there are few randomized trials that inform the urgency of administration, the necessary duration of treatment, and the optimal regimen of antibiotic therapy.

As per accepted practice, antibiotic prophylaxis should be commenced as early as possible post-injury. Earlier work by Patzakis and Wilkins identified timely antibiotic administration as the most important factor in reducing infection risk[19]. In this case-control study of over 1100 open fractures, antibiotics administered after 3 hours of injury was associated with a 1.63 greater odds of infection in comparison to treatment within the first 3 hours of injury[19].

It has been recommended that both type I and II open fractures require antibiotic coverage for 24 hours post-wound closure[20,21]. For type III injuries, it is suggested that antibiotic administration continue for 72 hours post-injury but no longer than 24 hours after wound closure[20,21]. As demonstrated by Dellinger *et al* in their blinded, randomized trial comparing a one-day course of antibiotic prophylaxis to a five-day course, there is no clear benefit to prolonged antibiotic prophylaxis in preventing fracture-site infections in open fractures, including those of type III severity[22].

In regard to specific antibiotic selection, there is strong evidence supporting coverage against gram-positive organisms for all open fractures, typically with a first generation cephalosporin unless specific contraindications exist (ie. allergy)[8,20,23].

Additional coverage of gram-negative organisms is indicated for type III injuries and the use of an aminoglycoside has been suggested[20] (CME 2). The best-available evidence in the form of randomized trials, however, has not conclusively validated the optimal regimen. In a randomized study by Patzakis *et al*, antibiotic prophylaxis of type III open fractures with a combined regimen of cefamandole and gentamicin substantially reduced infection rates compared to prophylaxis with ciprofloxacin alone (7.7% vs. 31%, respectively)[24]. It must be noted that the sample size of patients with type III injuries was relatively small (n=52) and statistical significance was not reached despite the magnitude of difference in infection rates[24]. Sorger *et al* were unable to substantiate such a low infection rate in their randomized trial, as 10-25% of patients with type III open fractures (n=20) developed an infection despite prophylaxis with a similar antibiotic course consisting of cefazolin and gentamicin[25]. Other antibiotic options for type III open fractures have also been explored in randomized trials. Prophylaxis using a third-generation cephalosporin (cefotaxime) alone for type II and III open tibial fractures was evaluated in an earlier trial by Johnson *et al*. Despite finding a considerably lower infection rate with cefotaxime compared to cefazolin in type III fractures (18% vs. 37%), the effect size was statistically insignificant as they recruited only 27 patients with such high-grade injuries[26]. Vasenius and colleagues further underscored the need for appropriate gram-negative coverage of type III injuries in their randomized trial that demonstrated unacceptably high infection rates using clindamycin or cloxacillin alone for antibiotic prophylaxis[27].

In light of the available evidence, a combined regimen consisting of an aminoglycoside in conjunction with a first-generation cephalosporin appears reasonable for type III injuries (Table 1). However, the above mentioned studies must be interpreted with an understanding that trials consisting of small sample sizes are susceptible to spurious findings-- small changes in the number of outcome events could substantially alter the percentage of infections reported and possibly the significance of results. Accordingly, sufficiently powered trials with large sample sizes are still needed to provide unequivocal guidance on the optimal antibiotic regimen for type III open fractures.

Local delivery of antibiotics has also peaked interest in recent years, as antibiotic-laden polymethylmethacrylate cement beads have been demonstrated to improve antibiotic delivery at the target site[8]. In a retrospective review of 1085 open fractures by Ostermann *et al*, a statistically significant reduction in infection rate (acute and chronic) for type III injuries was demonstrated using systemic antibiotics in conjunction with tobramycin-impregnated cement beads compared to systemic prophylaxis alone (6.5% vs. 20.6%, $p<0.001$). This statistical significance was not found in lower grade injuries[28]. However, a recent meta-analysis of 21 studies demonstrated a significantly lower deep infection risk with local antibiotic administration as an adjunct to systemic antibiotics across all types of open tibia fractures treated with intramedullary nailing. The effect was most pronounced for type III injuries, which demonstrated a pooled infection risk of 2.4% (95% CI 0.0 % to 9.4%) with an adjunct local antibiotic compared to 14.4% (95%CI 10.5% to 18.5%) with systemic prophylaxis alone (odds ratio 0.17, p value not reported)[29].

IV. FRACTURE STABILIZATION

Options for stabilization following open tibial shaft fracture include either internal fixation or external fixation. Internal fixation may be performed with plates (e.g. dynamic compression plates or limited contact dynamic compression plates) or with an intramedullary nail. External fixation may be either definitive or temporary (i.e. preceding a second stage internal fixation procedure). The standard of care for open tibial shaft fractures has evolved considerably over the past several decades, and we present the latest evidence on the stabilization of these injuries.

1. Internal Fixation

a. Plating

There is both biologic and clinical rationale that favours the plating of open tibial shaft fractures over alternative options. First, external fixation is cumbersome and not convenient for the patient. Among internal fixation devices, plating does not risk further injury to bone that is likely already denuded of periosteum (especially in higher grade open fractures), whereas intramedullary nailing has the potential to further compromise the intraosseous blood supply and lead to bony necrosis[30,31]. Arguments against plating have focused on the possibility of chronic infection and resultant infectious non-union, as the inert surface of a metal plate could provide a medium for bacterial growth to flourish. Evidence from clinical studies has largely fallen against plating. Therefore, this option is no longer recommended in the primary treatment of open tibial shaft fractures[32].

Van Der Liden *et al* evaluated 100 consecutive patients in a randomized controlled trial comparing AO-plating to conservative management. Only six patients in each group had open fractures. The investigators reported that healing times were almost double in the plated open fracture group and only two of the six patients that received plating were complication-free. Of note, the protocol used by the investigators waited for the wound to heal prior to surgical management[33].

Bach and Hansen performed a randomized trial in which 59 patients with open type II or III tibial shaft fractures were allocated to either external fixation with half-pins or AO plating with a 4.5 mm plate. The investigators reported higher rates of wound infections (35% vs. 13%), chronic osteomyelitis (19% vs. 3%), and fixation failure (12% vs. 7%) in the plate group. External fixation had a low incidence of pin tract infection (10%) and a slightly higher rate of malunion (10% vs. 4%)[34].

Clifford and colleagues performed a non-comparative chart review of 97 plated fractures (60 of 97 fractures were type II or type III). They reported a deep infection rate of 10.3%; almost half (44.4%) of type III fractures developed a deep infection. Eleven of 95 patients developed stiffness in one or more knee[35]. These results are unacceptable in the context of alternative fixation options.

b. Intramedullary Nailing

Intramedullary nailing has the advantage of avoiding further disruption of soft tissues and periosteum, as well as the potential for immediate post-operative weight-bearing. Further, because incision and nail insertion occurs remotely from the open wound, there is a lower likelihood of hardware being contaminated and colonized by bacteria. Clinical studies have largely upheld the superiority of intramedullary nailing in terms of improved fracture healing and reduced risk of deep infection.

Kakar and Tornetta performed a prospective longitudinal cohort evaluation of 143 type I to III open tibial shaft fractures that were managed with unreamed tibial nailing. All fractures received irrigation, debridement, and closure within 14 days post-operatively. They found an overall low incidence of deep infections (3%) and implant failures (3.5%). Although this study lacked a comparator group, the results are better than those quoted in the aforementioned literature on plating. However, the investigators reported a high incidence of ipsilateral ankle stiffness (21%), knee pain (20%), and fracture site pain despite union (21%)[36].

Inan and colleagues compared circular wire external fixation with unreamed tibial nails in a randomized trial of type IIIA open tibial shaft fractures. They found a statistically significant shorter time to union (19 vs. 21 weeks, p=0.04) and less knee contractures (0% vs. 10%, p value not reported) in favour of the unreamed tibial nails[37]. They were unable to detect any significant difference in the number of deep infections. In another randomized trial, Henley *et al* compared half-pin external fixators to unreamed tibial nails in Type II, IIIA, and IIIB open tibial shaft fractures. The use of an intramedullary nail resulted in better alignment and less re-operations, with no statistically significant difference infection rates[38]. A systematic review that indirectly compared reamed nails to external fixators has also demonstrated a decreased risk of re-operation with the use of intramedullary nails[39].

Overall, the evidence supports the use of intramedullary nailing (either reamed or unreamed) over both plating and external fixation for open tibial shaft fractures owing to lower re-operation rates and faster time to fracture union. If used in place of plating, there is a reduced risk of deep infection as well.

c. Reamed versus Unreamed Nailing

Surgeons have the option of reaming the intramedullary canal of the tibial shaft prior to nail insertion. Reaming before nailing allows for insertion of a larger diameter intramedullary nail with resultant greater stability. However, reaming can disrupt the endosteal bloody supply through thermal injury, physical disruption of blood vessels, increased intramedullary pressure, and fat emboli occlusion of blood vessels[30,31]. Unreamed techniques require smaller nails and therefore result in comparatively less stability, but preserve the endosteal blood supply. The latter consideration is potentially important when periosteum has been denuded during the initial injury. Thermal necrosis during reamed nailing can also lead to increased rates of post-operative infection and other complications[40].

Bhandari and colleagues conducted a systematic review which identified two studies comparing reamed and unreamed nails for open tibial shaft fractures. They were unable to demonstrate statistically significant superiority of one technique over the other in the context of open fractures[39]. Subsequently, the SPRINT Investigators randomized 1319 patients to either reamed or unreamed intramedullary nailing; 406 of these patients had an open fracture and 137 of these fractures were type III injuries. Reamed nailing was shown to be superior in the closed fracture group, but not in the open fracture group, which trended instead in the opposite direction but did not reach statistical significance[41]. Therefore, neither reamed nor unreamed nailing technique has proven superior in the treatment of open tibial shaft fractures (CME 3).

2. External Fixation

Owing to a lack of evidence supporting superiority over intramedullary nailing, as well as patient discomfort and the high incidence of pin tract infections, definitive external fixation is generally not a highly recommended treatment option. However, external fixation can still be an appropriate option for certain injuries. For instance, orthopaedic surgeons may utilize external fixation for severely contaminated type IIIA and IIIB fractures with severe bone loss[42,43]. However, improvements in our knowledge of soft tissue reconstruction techniques and infection control have largely usurped the practice of definitive external fixation in favour of intramedullary nailing.

However, there remains a strong role for temporary external fixation in the management of severely contaminated tibial shaft fracture with extensive soft tissue injury. The literature has demonstrated acceptable results in open tibial shaft fractures that are treated sequentially with external fixation followed by intramedullary nailing[44,45,46,47].

Bhandari and colleagues conducted a systematic review of both tibial and femoral fractures managed with intramedullary nailing secondary to external fixation. The vast majority of tibial fractures in the analyzed studies were open fractures. They found that tibial shaft fractures treated with a shorter duration of external fixation (i.e. ≤ 28 days) had a relative risk reduction of 83% (n=263) for infection ($p<0.001$). Following removal of the external fixator, tibial shaft fractures in which there was a shorter interval between fixator removal and intramedullary nailing (i.e. ≤ 14 days) had a relative risk reduction of 85% (n=268) for infection ($p<0.001$)[48]. Therefore, external fixators should be used for a short duration and the interval between removal and internal fixation should be less than 14 days. Some surgeons have advocated near-immediate conversion, with a very short interval (i.e. less than 10 days) if there are concerns pertaining to pin-tract infections[32] (CME 4).

V. WOUND MANAGEMENT

An optimal time for wound closure of open tibial shaft fractures has yet to be established, although primary closure under specific circumstances is warranted[2]. In a retrospective, cohort study of 95 open tibial fractures (type I-IIIa), Hohmann *et al* found no significant difference in infection rates between those patients who underwent primary closure (4%) compared to delayed closure (2%; average 9 days from initial debridement). It is important to note that only seven fractures were type III injuries, with the study primarily including less severe, isolated injuries of the tibia[49]. There is, however, further evidence endorsing primary closure in type III fractures. In a prospective, non-comparative series of 173 patients with type III A and B open fractures treated with primary closure, Rajasekaran and colleagues found 87% of patients to have an "excellent" result, which collectively entailed bony union, primary wound healing with no or marginal necrosis, and no infection. Stringent criteria for primary closure were utilized in this study, however, including no skin loss, debridement within 12 hours of injury, stable skeletal fixation during primary surgery, skin apposition without tension, and no sewage or organic contamination, among other criteria[50]. In general, primary closure has been suggested for type I to IIIa tibial fractures, where adequate viable soft-tissue allows for tension free closure and the patient has undergone meticulous debridement with timely antibiotic prophylaxis[8]. Intra-operative cultures after debridement have demonstrated poor yield in predicting subsequent infection and should not dictate the timing of wound closure[51].

For those fracture wounds requiring flap coverage, location of the injury, size of the defect, and zone of injury must collectively be assessed to determine if rotational or free flap coverage is optimal. Typically, fractures in the proximal two-thirds of the tibia are treated with rotational muscle flaps, whereas distal third fractures require free flaps[32]. In a study of 174 patients with open distal third tibia fractures, Yazar *et al* found free muscle flaps comparable to free fasciocutaneous flaps with respect to flap survival, bone healing, and infection rates[52].

Negative pressure wound therapy has garnered much attention as a method of providing provisional coverage for such wounds not amenable to primary closure. Stannard *et al* randomized 58 patients with severe open fractures requiring serial debridements to coverage with either negative pressure wound therapy or saline soaked dressings. The predominant fracture type included in this study was that of the tibia (42%) and 92% of the injuries were of type III severity. The study found a significant reduction in total infection rate (acute and late combined) with negative pressure therapy, although this estimate lacked precision as demonstrated by a wide confidence interval (relative risk 0.20, 95%CI: 0.045-0.874). Furthermore, when acute and late infections were assessed independently, no significant difference was detected, likely due to insufficient study power[53].

Irrespective of the use of negative pressure wound therapy, flap closure of open tibial fracture wounds should not be prolonged beyond 7 days of injury, as the risk of subsequent infection and other complications increase[32,54,55] (CME 5). A recent systematic review evaluating open fracture wounds requiring flap coverage corroborated the importance of early coverage. In a pooled analysis of 7 studies—6 of which specifically studied open tibia fractures— early coverage was associated with a significant reduction in infection risk (RR 0.31, 95%CI:0.18-0.53). Surprisingly, several of these studies employed an aggressively early flap coverage practice (<72 hours)[56]. In the absence of any randomized trials, however, the true efficacy of such aggressive timing for coverage remains to be explored.

VI. CONCLUSION

Open tibial shaft fractures are a common, yet challenging injury for the orthopaedic surgeon to manage. Several paramount strides have been made in establishing evidence-based treatment strategies for these patients, as study findings have endorsed the need for meticulous irrigation and debridement, prompt antibiotic prophylaxis, and primary wound closure under the appropriate circumstances. Furthermore, stabilization techniques of tibial shaft fractures have evolved considerably with current evidence demonstrating superior outcomes with either reamed or unreamed intramedullary nailing for definitive management.

Nevertheless, there remains a need for further, high-quality evidence to clarify the efficacy of specific techniques and treatment practices within the umbrella of these accepted treatment areas. For instance, guidelines detailing the optimal irrigation solution and pressure, as well as the ideal duration of antibiotic prophylaxis, are difficult to establish due to a paucity of high-quality trials. Through large-scale, randomized trials, the answers to such fundamentally important questions can hopefully be answered, such that a global consensus on optimizing all aspects of management for these patients is reached.

FIGURES & TABLES

Table 1. Antibiotic Prophylaxis Suggestions

Open Injury Type	Coverage Required	Suitable Antibiotic
Gustilo and Anderson Type I & II	Gram Positive	1st Generation Cephalosporin
Gustilo and Anderson Type III	Gram Positive & Gram Negative	1st Generation Cephalosporin + Aminoglycoside
Farm Injury or Soil Contamination	Anaerobic	As per above + Penicillin

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CHAPTER II

Timing of Irrigation & Debridement and Infection Risk in Severe Open Fractures

Timing of Irrigation & Debridement and Infection Risk in Severe Open Fractures

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ABSTRACT

Background
Open fractures are common injuries in trauma patients. Detailing the open fracture burden and simple modifiable factors associated with infection risk in developing regions remains a global surgical priority.

Objective(s)
Our primary objective was to identify prognostic variables associated with the risk of surgical site infections.

Methods
We conducted a prospective, observational, cohort study of 4612 patients recruited from 14 private and public hospitals across India between October 2011 and June 2012. Adult patients admitted to hospital with a fracture and/or dislocation were eligible for inclusion. This sub-study considered only those patients with open fractures. Patients were followed for 30-days or until discharge, whichever occurred first, to assess for the occurrence of deep wound infection. Multivariable binary logistic regression was performed to examine the association between delayed irrigation and debridement (I&D) and infection.

Findings
Seven hundred patients presented with 820 open fractures. The mean patient age was 37 (Standard Deviation [SD]14) years, with the majority being male (570/700, 81%) and sustaining an open fracture of the lower extremity (480/700, 69%). Thirty-four percent of patients had severe open fractures classified as Gustilo-Anderson Type 3 (238/700). Timing to irrigation and debridement (I&D) varied, with less than half (336/700, 48%) of patients treated within 6 hours of injury. The overall rate of deep infection was 14% (100/700), varying from 5% in those undergoing I&D within 6 hours, to 11% and 42% in those patients with delays of 6 to 12 hours and greater than 12 hours, respectively. After controlling for open fracture severity, number of open fractures, and hospital type (public vs. private), delays to I&D beyond 6 hours of injury was associated with a 4- to 13-fold increase in the odds of infection compared to I&D within 6 hours (I&D 6-12 hours: OR 3.87, 95% confidence interval [CI]: 1.37-10.95; I&D >12 hours: OR 13.27, 95%CI: 5.41-32.56).

Interpretation
Infection rates following severe open injuries in India are high and associated with longer time to wound irrigation. Irrigating open wounds urgently after injury may decrease the burden of infection.

INTRODUCTION

The overall incidence of open fractures is 31 per 100,000 patients annually, and approximately one in every four patients with high-risk fractures, such as those of the tibial shaft, will present with an open injury[1-3]. These patients are at a heightened risk for devastating infections, which have shown to vary from 4% to 63%[4].

Given this infection risk and the precipitous rise of traumatic injuries across the developing world, open fractures have garnered considerable attention as a global surgical priority[5-7]. Timely and appropriate care of open fractures has been recognized as one of three essential surgical services that should be available across all first-level (district) hospitals in low- and middle-income countries (LMICs). Termed the 'Bellwether Procedures', open fracture care, laparotomy, and caesarean delivery, have not only been identified as acute, high-value procedures, but collectively serve as markers of an adequate surgical infrastructure in a LMIC health system[7].

Unfortunately, the mobilization of resources and implementation of surgical programs for trauma care in LMICs has been hindered, in part, by a dearth of reliable research evidence[8,9]. Further compounding the care of open fractures is conflicting research evidence surrounding the importance of timing to surgical care on mitigating infection risk[10]. Historically, clinical guidelines have endorsed that patients should undergo urgent irrigation and debridement (I&D) of fracture wounds within 6-hours, as delays to care would predispose patients to greater infection risk[4,10]. In a recent systematic review evaluating the efficacy of timing to I&D on infection risk in open fractures, Schenker *et al* demonstrated that the methodology of existing studies are largely varied and that most studies are retrospective with limited sample sizes. Furthermore, only one study was conducted in the setting of a LMIC (Nigeria). The authors could not confirm the efficacy of a 6-hour time window and recommended large prospective studies to inform this issue[4].

The International Orthopaedic Multicenter Study in Fracture Care (INORMUS India), was a prospective observational study of 4612 adult fracture patients performed in hospitals throughout India. Our objectives for the current study were to: (1) describe the burden of open fractures, their mechanisms and treatment characteristics in an LMIC and (2) identify prognostic variables associated with the risk of serious surgical site infections.

METHODS

Study Design

The INORMUS India study was designed as a multicenter cohort study of musculoskeletal trauma patients admitted across 14 hospitals in India. Patients were followed prospectively in hospital for 30 days, or until discharge, to assess for the occurrence of major complications, including mortality, infection and reoperation. Here, we present outcomes for the subset of patients presenting exclusively with open fracture injuries. The human subject committees at each participating site approved the INORMUS study protocol (REB# 11-275) and with the exception of two participating sites, a waiver of consent was granted.

Study Oversight

This study received funding from the Canadian Institutes of Health Research and McMaster Surgical Associates. The Center of Evidence-Based Orthopaedics (CEO) at McMaster University coordinated the study. The CEO was responsible for the maintenance of the database, data validation, data analyses, and study-center coordination. No funder had a role in the design or conduct of the study, the collection or analyses of the data, or the preparation of the manuscript. The steering committee, chaired by the study principal investigators, designed the study and assume responsibility for the completeness and accuracy of the data and analyses and adherence to the trial protocol.

Study Eligibility and Recruitment

Patients were enrolled in the INORMUS study between October 2011 and June 2012 from 14 participating hospitals, including seven public and seven private centers throughout India. Each individual center actively recruited patients for a two-month period during the overall study period.

All consecutive patients presenting to each hospital were considered for inclusion in the current study if they met the following eligibility criteria: (1) Age ≥ 18, (2) sustained at least one open fracture or open dislocation of the appendicular skeleton (extremities, shoulder girdle, pelvis) or spine (3) presented to hospital within three-months of sustaining their open injuries, and (4) required hospital admission. We excluded patients with fractures isolated to the facial bones, cranium, or rib cage, as these injuries are not typically treated by orthopaedic surgeons.

Data Collection and Follow-Up

Following acquisition of informed consent and enrollment at 2 sites, and direct enrollment at 12 sites, patients were assessed for baseline information, including: demographic information (age, gender, medical comorbidities, and household income); injury event data (location of injury (ie. road, home, etc), mechanism of injury, transportation to hospital, and time from injury to admission); injury characteristics (body region, number of open fractures, open fracture severity, and non-orthopaedic injuries of the head, chest or abdomen); and treatment characteristics (hospital type, temporary stabilization, type of definitive care, time to definitive care, and time from injury to I&D).

We categorized open fracture severity according to the Gustilo-Anderson classification: Type 1 (wound < 1 cm), Type 2 (wound 1-10cm), or Type 3 (wound >10cm or less if severely contaminated) injuries. We categorized time from injury to I&D as follows: < 6 hours, 6 to 12 hours, and > 12 hours.

Patients were followed in hospital for up to 30 days after admission or until discharge, whichever occurred first. The primary outcome of interest was the occurrence of a deep surgical site infection as defined by criteria put forth by the Center for Disease Control and Prevention (CDC)[11]. Briefly, this entails an infection of the fascia, muscle or bone, with a diagnosis based on a constellation of signs and symptoms. All sites were trained with respect to the CDC criteria prior to commencing enrolment, which were also provided to each site in a study manual.

All data were collected on standardized case report forms and transferred electronically through a secure online data system to the study methods center (Center for Evidence-Based Orthopaedics, McMaster University, Canada).

Data Analysis and Sample Size

We present descriptive statistics for continuous variables as means with associated standard deviations (SDs) and categorical variables as frequencies with correlating percentages.

For our primary objective of identifying factors associated with deep infection, we carried out a multivariable binary logistic regression analysis. A preliminary assessment identified 100 patients with deep infections, of which, 40 patients with complete data sets were amenable for inclusion in the regression model. Up to five variable levels were permited for inclusion in the regression analysis (8 events per variable) so as to not over-fit the model[12]. As such, four independent variables were included in the regression model: number of open fractures (1 vs. $\geq$ 2), open fracture severity (Gustilo-Anderson Grade 1 and 2 vs. Gustilo-Anderson Grade 3), hospital type (public vs. private), and time to I&D (<6 hours, 6-12 hours, >12 hours). Patients with incomplete or missing data for these four variables were excluded from the regression analysis. The correlation matrix of the regression model was assessed to ensure there was no significant multicollinearity amongst predictor variables (correlation coefficient >0.9).

We report odds ratios (OR) with corresponding 95% confidence intervals (CIs) and associated p values for all factors in our adjusted regression model. All tests were two-sided with a significant p value set at alpha = 0.05. All analyses were performed using IBM SPSS (Version 21).

RESULTS

Patient, Injury and Treatment Characteristics

Among the 4612 patients enrolled in the INORMUS study, 707 patients presented with an open fracture. All but seven patients had a reported outcome regarding surgical site infection, allowing for 700 patients to be included in the current study. Thirty-five patients died during the study, but were included in the final analysis based on the occurrence or absence of infection prior to death (**Figure 1**).

The average age of the study cohort was 36.6 (SD 14.1) and the majority of patients were male (81%, n=570) with no medical comorbidities (79%, n=553). Over 99% of patients had a fracture or fracture-dislocation, with very few patients having an isolated open dislocation.

Road traffic crashes were the predominant mechanism of injury (76%, n= 535), among which, motorcyclists were the most common type of road user presenting with an open fracture (n=329). Fifty percent of patients were transported to hospital by methods other than an ambulance. Although the majority of patients presented to hospital within six hours of injury (67%, n=472), 31% of patients had delays exceeding six hours and 21% had delays exceeding 12 hours (**Table 1**).

The overall fracture and treatment characteristics are presented in **Table 2**. In regards to fracture characteristics, 69% of patients (n=480) had fractures of the lower extremity, comprised mostly of the tibia/fibula and femur. Only 16% of patients had Type 1 open fractures (n=114), whereas the majority had higher-grade open fractures wounds classified as Type 2 (25%, n=174) or 3 injuries (34%, n=238). The open fracture severity of 174 patients (25%) was not documented. An assessment of treatment characteristics demonstrated that a higher volume of patients with open fractures presented to public hospitals (65%, n=454) compared to private hospitals (35%, n= 246). With respect to definitive fracture care, 90% of patients (n=628) received some form of surgical stabilization, whereas 10% (n= 70) underwent non-operative care.

Timing of Irrigation & Debridement

Timing to irrigation and debridement of the open fracture wounds varied broadly. Approximately half of all patients underwent I&D within six hours of injury (48%, n=336), whereas 15% (n=104) and 16% (n=112) of patients had delays between six to 12 hours and greater than 12 hours, respectively. The timing to I&D in 148 patients was not documented.

Surgical Site Infection

During the hospital follow-up period, a total of 100 patients developed deep infections of the muscle, fascia or bone, for an overall deep infection rate of 14%. The rate of infection increased with successive delays to I&D, varying from 5% for those with treated within six hours of injury to 11% and 42% in those with delays of six to 12 hours and greater than 12 hours, respectively (**Figure 2**).

When controlling for the number of open fractures, Gustilo-Anderson type, hospital type and timing to I&D in the multivariable regression analysis, timing to irrigation and debridement was the only variable with a significant association to deep infection risk (**Table 3**). As compared to patients undergoing I&D within six hours of injury, delays between six to 12 hours conferred a four-times greater odds of infection (OR 3.87, 95%CI: 1.37-10.95) and delays greater than 12 hours conferred a thirteen-times greater odds of infection (OR 13.27, 95%CI: 5.41-32.56).

DISCUSSION

In this prospective observational study of 700 patients presenting to hospital with severe open fractures in India, delays greater than 6 hours from injury to I&D were associated with increased risk of infection .

The findings of our current study build upon recent evidence that suggests the importance of timely I&D in mitigating infection risk for open fractures has gone unrecognized[13,14]. In the most comprehensive meta-analysis on this topic to date published in 2012, Schenker *et al* could not validate the efficacy of a six-hour time window from injury to initial I&D (Deep Infection OR 1.07, 95%CI: 0.74-1.54). However, several limitations were recognized in the existing studies. Only nine of the included 16 studies provided ample data for a pooled analysis of deep infection, and among these nine studies, seven were retrospective, seven evaluated only lower extremity fractures, and the definitions of "deep infection" varied[4]. Furthermore, while a pooled analysis weights studies according to sample size, it does not necessarily control for multiple confounding variables. This review was unable to control for potentially important prognostic factors such as antibiotic administration and irrigation methods due to limited reporting in the primary studies. Given these limitations, it was acknowledged that additional prospective studies were warranted.

Several trials with relatively larger sample sizes have since been published. In a recent observational study of 364 patients with open fractures presenting to a North American trauma center, Hull and colleagues noted a deep infection rate of 10%. In a multivariable regression analysis, it was demonstrated that every hour in delay to debridement was associated with a 3% increased risk of deep infection for patients with severe open fractures (Grade 2 and 3)[13]. These findings generally coincide with our observed deep infection rates based on timing to I&D. In another recent study of 404 patients with open fractures conducted by Malhotra *et al*, the overall rate of infection was 13%, with a 19% rate of infection for those with delays to I&D exceeding eight hours compared to 11% in those with early I&D (<8 hours). These authors also concluded using a multivariable regression analysis, that delays to I&D resulted in a significantly increased risk of infection[14]. Nevertheless, recent studies have continued to emerge that cast doubt on the importance of timing to I&D[15,16]. In a prospective study of 315 patients, Srour *et al* found no difference in infection risk associated with timing to debridement. Of note, however, their deep infection rate was very low (3%) and the regression model did not include open fracture severity[15].

Our study has several inherent methodological strengths. First and foremost, we conducted an observational study with a prospective design. This represents the highest level of evidence that can be used to feasibly address this research question given the ethical concerns that would be associated with actively randomizing patients to delayed I&D. Our sample size of 700 patients also represents one of the largest studies to evaluate timing of I&D on infection risk. Our study cohort was recruited from multiple centers across the country of India, including both private and public hospitals, which increases the generalizability of our findings. Finally, our conclusions regarding the effect of timing delays on infection risk stem from a multivariable regression analysis in which we controlled for important prognostic factors, including open fracture severity.

There are certain limitations to our study. Given the high volume of patient recruitment in the INORMUS study, in which nearly 5000 patients were recruited over nine months, our data collection forms were designed to minimize burden on research staff. Unfortunately, we did not collect information on important variables prognostic of infection in open fractures, such as timing and method of antibiotic administration, irrigation pressure, and timing to wound closure, among other factors[17-22]. Although it is anticipated that antibiotic prophylaxis was administered upon presentation to hospital for most patients, approximately 30% of patients had delays to admission exceeding six hours. Furthermore, despite performing routine quality checks as data was submitted through the online data system, the high volume of patient recruitment precluded us from ensuring case report forms were completed in full for all patients. As such, missing data was prevalent for certain variables, including open fracture grade and timing to I&D.

In conclusion, our findings suggest that infection rates in LMICs following severe open injuries are high and associated with delays to wound irrigation. These findings endorse the Lancet Commission on Global Surgery's position on the need for appropriate surgical services for open fracture injuries across national level hospitals in LMICs. Ensuring urgent hospital admission and timely care for such patients, including the irrigation of open wounds urgently after injury, may decrease the burden of devastating infections.

FIGURES & TABLES

Figure 1. INORMUS Study Flow Diagram

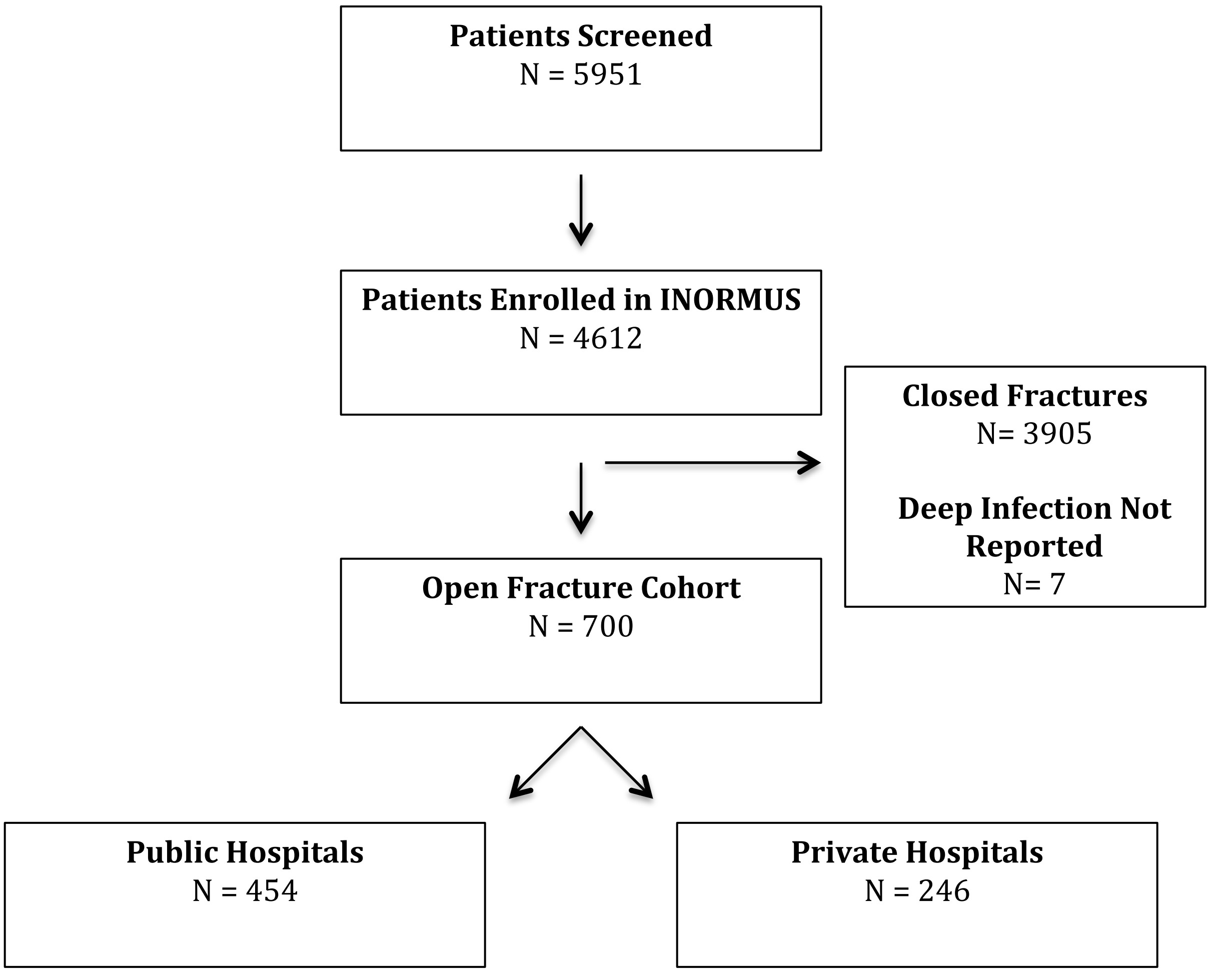


Table 1: Demographic and Injury Event Characteristics (n=700)

Demographic Characteristics	Number of Patients (Statistic)	Deep Infection (Statistic)	No Infection (Statistic)
Age (Mean ± SD): years	36.6 (14.1)	35.9 (12.9)	36.7 (14.4)
Gender: n (%)			
Male	570 (81%)	82 (82%)	488 (81%)
Female	130 (19%)	18 (18%)	112 (19%)
Medical Comorbidities: n (%)			
None	553 (79%)	81 (81%)	472 (79%)
1	97 (14%)	13 (13%)	84 (14%)
≥ 2	50 (7%)	6 (6%)	44 (7%)
Household Income (Indian Rupees): n (%)			
> 500, 000	80 (11%)	4 (4%)	76 (11%)
300,000 – 500,000	131 (19%)	20 (20%)	111 (19%)
100,000 – 300,000	213 (31%)	37 (37%)	176 (29%)
<100,000	230 (33%)	36 (36%)	194 (32%)
Refused/Not Reported	46 (7%)	3 (3%)	43 (7%)
Injury Event Characteristics			
Injury Location: n (%)			
Road	564 (80%)	80 (80%)	484 (81%)
Home	24 (3%)	6 (6%)	18 (3%)
Industrial	76 (11%)	8 (8%)	68 (11%)
Railway	12 (2%)	3 (3%)	9 (2%)
Other	21 (3%)	3 (3%)	18 (3%)
Not Reported	3 (0%)	0 (0%)	3 (1%)
Injury Mechanism: n (%)			
Road Traffic Crash	535 (76%)	77 (77%)	458 (76%)
Motorcycle	329	40	289
Motor Vehicle	116	22	94
Pedestrian	59	10	49
Other (Rickshaw, Bicycle)	31	5	26
Fall	42 (6%)	9 (9%)	33 (6%)
From standing/low height	18	2	16
From height	24	7	17
Struck	70 (10%)	6 (6%)	64 (10%)
By object	62	6	56
By person	8	0	8
Machine Injury	22 (3%)	3 (3%)	19 (3%)

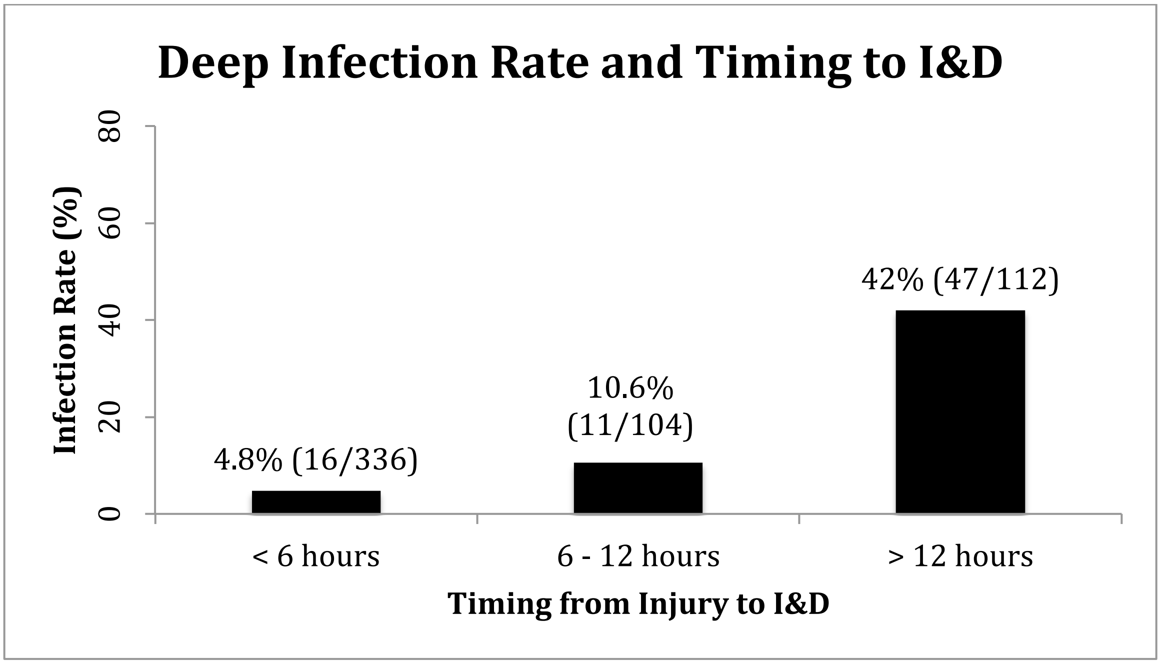
Other (Gunshot, Lifting, etc)	31 (4%)	5 (5%)	26 (4%)
Method of Transportation to Hospital: n (%)			
Ambulance	351 (50%)	55 (55%)	296 (49%)
Car	131 (19%)	15 (15%)	116 (19%)
Rickshaw	128 (18%)	17 (17%)	111 (19%)
Police Vehicle	63 (9%)	13 (13%)	50 (8%)
Motorbike	25 (4%)	0 (0%)	25 (4%)
Walked	2 (0%)	0 (0%)	2 (0%)
Time from Injury to Hospital Admission: n (%)			
<6 hours	472 (67%)	67 (67%)	405 (68%)
6 to < 12 hours	72 (10%)	11 (11%)	61 (10%)
12 to < 24 hours	57 (8%)	9 (9%)	48 (8%)
>24 hours	90 (13%)	12 (12%)	78 (13%)
Not Reported	9 (1%)	1 (1%)	8 (1%)

Table 2: Injury and Treatment Characteristics (n=700)

Injury Characteristics	Number of Patients (Statistic)	Deep Infection (Statistic)	No Infection (Statistic)
Body Region of Open Fracture:			
n (%)	480 (69%)	78 (78%)	402 (67%)
Lower Extremity	281	46	232
Tibia/Fibula	135	23	112
Femur	49	7	42
Foot	17	2	15
Patella	1	0	1
Not Specified			
	214 (31%)	21 (21%)	193 (32%)
Upper Extremity	67	10	56
Radius/Ulna	54	6	48
Humerus	80	3	74
Hand/Carpus	17	2	15
Clavicle	2	0	0
Not Specified			
	1 (0%)	0 (0%)	1 (0%)
Spine			
	5 (1%)	1 (0%)	4 (1%)
Pelvis			
Number of Open Fractures : n			
(%)	605 (86%)	78 (78%)	527 (88%)
1	81 (12%)	20 (20%)	61 (10%)
2	14 (2%)	2 (2%)	12 (2%)
3			
Open Fracture Severity of Worst Injury (Gustilo-Anderson Classification): n			
(%)	114 (16%)	5 (5%)	109 (18%)
Type 1	174 (25%)	20 (20%)	154 (26%)
Type 2	238 (34%)	29 (29%)	209 (35%)
Type 3	174 (25%)	46 (46%)	128 (21%)
Not Reported			
Non-Orthopaedic Injury (Head, Chest, Abdomen): n (%)			

None	519 (74%)	62 (62%)	457 (76%)
Single	130 (19%)	27 (27%)	103 (17%)
Multiple	51 (7%)	11 (11%)	40 (7%)
Treatment Characteristics			
Hospital Type: n (%)			
Public	454 (65%)	91 (91%)	363 (61%)
Private	246 (35%)	9 (9%)	237 (40%)
Type of Definitive Care: n (%)			
Surgical Stabilization	628 (90%)	96 (96%)	532 (89%)
Internal Fixation	474	65	409
External Fixation	84	18	66
Amputation	65	12	53
Other	5	1	4
Non-operative Stabilization	70 (10%)	4 (4%)	66 (11%)
No Stabilization	2 (0%)	0 (0%)	2 (0%)
Time from Admission to Definitive Care (Stabilized, n= 698): n (%)	381 (54%)	17 (17%)	364 (61%)
<12 hours	78 (11%)	21 (21%)	57 (10%)
12-24 hours	78 (11%)	17 (17%)	61 (10%)
1-3 days	111 (16%)	29 (29%)	82 (14%)
4-7 days	47 (7%)	16 (16%)	31 (5%)
> 7 days	3 (0%)	0 (0%)	3 (0%)
Not Reported			
Time from Injury to Irrigation and Debridement: n (%)			
< 6 hours	336 (48%)	16 (16%)	320 (53%)
6-12 hours	104 (15%)	11 (11%)	93 (16%)
>12 hours	112 (16%)	47 (47%)	65 (11%)
Not Reported	148 (21%)	26 (26%)	122 (20%)

Figure 2. Deep Infection Rate by Timing to I&D (n=552)



*The timing to I&D for 26 patients with deep infections was not documented

Table 3. Multivariable Regression Analysis for Odds of Deep Infection

Risk Factor	Multivariable Regression Odds Ratio (95% CI)	Significance (p-value)
Number of Open Fractures		
1	1.94 (0.79-4.77)	0.148
≥ 2		
Gustilo-Anderson Grade		
Type 1 and 2	2.20 (1.00-4.84)	0.051
Type 3		
Hospital Type		
Private	2.24 (0.89-5.64)	0.086
Public		
Time to Irrigation & Debridement		
< 6 hours		
6-12 hours	**3.87 (1.37-10.95)**	**0.011**
>12 hours	**13.27 (5.41-32.56)**	**<0.001**

* Multivariable Regression: 425 patients included in analysis (40 cases of deep infection), 275 patients with missing data

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CHAPTER III

Exploring the Association of 3-month Radiographic Union Score for Tibia Fractures (RUST) with Nonunion in Tibial Shaft Fracture Patients

Exploring the Association of 3-month Radiographic Union Score for Tibia Fractures (RUST) with Nonunion in Tibial Shaft Fracture Patients

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ABSTRACT

Background
Nonunions of tibial shaft fractures have profound implications on patient quality of life, causing both physical and mental suffering. The "Radiographic Union Score for Tibia Fractures" (RUST) may serve as an important prognostic tool for identifying patients at high-risk of nonunion.

Objectives
The objective of this study was to evaluate the 3-month RUST score as a prognostic indicator of nonunion in patients with tibial shaft fractures treated with intramedullary nailing.

Methods
We performed a retrospective cohort study nested within two multi-center, randomized controlled trials. The patients included in the current study: (1) were enrolled in the SPRINT or FLOW randomized trials for a tibial shaft fracture, (2) had initial operative management with intramedullary nailing, (3) had radiographs at 3-month follow-up which demonstrated an unhealed fracture, and (4) their healing status (union or nonunion) was known at 12-months post-operatively. Multivariable binary logistic regression was carried out to identify factors associated with nonunion including open versus closed injury, fracture severity, fracture gap, and 3-month RUST score. The concordance statistic (c statistic) was determined for the regression model both with and without the RUST score.

Results
A total of 155 eligible patients were identified and included in this study. The overall rate of nonunion at 12-months in this cohort was 30% (n=47). The mean 3-month RUST score in patients with nonunion at 12-months was 4.8 (SD 1.1) compared to 6.3 (SD 1.7) for those who eventually healed at 12-months. In the multivariable regression analysis, open fractures conferred a 5-fold greater odds of nonunion at 12-months compared to closed fractures (OR 4.76, 95% confidence interval (CI):1.71-13.30). Furthermore, 3-month RUST scores of < 4 and 5-6 were associated with a 15-fold and 6-fold greater odds of nonunion compared to a score of ≥ 7, respectively (RUST<4: OR 15.49, 95%CI: 4.42-54.33; RUST 5-6: OR 5.70, 95%CI: 1.73-18.75). The c statistic for the regression model improved from 0.70 (95%CI: 0.61-0.79) without the RUST variable to 0.81 (95%CI: 0.74-0.88) with its inclusion.

Conclusion
A third of patients with tibial shaft fractures who have failed to heal by 3 months will show nonunion at one year. Open fractures and lower 3-month RUST scores are associated with higher risk of nonunion at one year. Further research is needed to establish whether timely intervention can improve prognosis in this high risk group.

INTRODUCTION

Tibial shaft fractures represent the most common major long bone fracture surgically treated in the United States, with an annual incidence of 17 per 100,000 people in the developed world[1,2]. Despite a decreasing incidence in developed countries, the overall global incidence of these injuries presumably remains on the rise in direct correlation to increasing rates of road traffic accidents in the developing world[2,3].

It has been estimated that nearly 1 in every 5 patients with a tibial shaft fracture will ultimately fail to heal [4]. The implications of nonunion are profound, as such patients experience significant pain, delayed return to work, physical disability and mental suffering[5,6]. Furthermore, it has been demonstrated that patients with nonunion have worse physical and mental health than patients with congestive heart failure or myocardial infarction[6]. The consequences of nonunion also extend directly to health care systems as a whole, as such patients require significantly greater inpatient and outpatient care, with total expenditures exceeding the costs of an uneventful healing course by more than two-fold[7].

To minimize rates of nonunion associated with tibial shaft fractures, there has been growing interest in delineating risk factors that allow for appropriate identification and timely management of susceptible patients. Several variables have been recognized as predictors of nonunion, such as smoking, unreamed nailing in closed fractures, high-energy injury mechanisms, less cortical continuity/greater fracture gap, and open fractures [4,5,8-13]. However, current studies have focused primarily on identifying baseline injury and treatment characteristics as prognostic factors, while measures of radiographic healing have been less thoroughly investigated. Given the fundamental role of radiographic follow-up in managing patients with such fractures, identifying a radiographic scoring system with strong prognostic capabilities would offer a pragmatic, reliable, and widely applicable method of distinguishing patients at risk for nonunion.

The “Radiographic Union Score for Tibia Fractures” (RUST) is a reliable scoring system that was developed to assess the healing status of tibial shaft fractures stabilized with intramedullary nailing. Our objective was to determine whether RUST scores at 3-months post-operatively are associated with nonunion at 12-months, in a cohort of patients identified from two large, multicenter, randomized controlled trials.

METHODS

Study Design and Eligibility Criteria

This study was designed as a retrospective cohort study nested within two randomized controlled trials (RCTs): the ‘Study to Prospectively Evaluate Reamed Intramedullary Nails in Patients with Tibial Fractures’ (SPRINT) and the ‘Fluid Lavage of Open Wounds’ (FLOW) trial.

We included all patients that met the following eligibility criteria: (1) were enrolled in the SPRINT or FLOW trials for a tibial shaft fracture, (2) initial operative management consisted of intramedullary nailing, (3) had available radiographs at 3-months follow-up which demonstrated an unhealed fracture, and (4) their healing status, at the discretion of the treating surgeon, was documented at 12-months post-operatively.

SPRINT Trial

In brief, the Study to Prospectively evaluate Reamed Intramedullary Nails in patients with Tibial fractures (SPRINT) was a multi-center, international, parallel-group, randomized trial of 1,226 patients comparing reamed versus unreamed intramedullary nailing for tibial shaft fractures. The SPRINT trial consisted of a total of 29 sites across Canada, the United States, and the Netherlands. The study eligibility criteria included skeletally mature patients, with open or closed fractures that were non-pathological and amenable to operative fixation with intramedullary nailing.

The SPRINT study protocol was approved by the human subject committees at each participating site (REB #99-077—Research Ethics Board/Institutional Review Boards). The complete study methods and results have been previously published[1,14].

FLOW Trial

The Fluid Lavage of Open Wounds (FLOW) trial is a multi-center, randomized trial of 2,549 patients with open fracture wounds conducted at 41 sites across Canada, the United States, Australia, India, and Norway. The FLOW trial utilized a 2 x 3 factorial design to compare two different types of irrigation solutions (i.e. soap vs. saline), as well as three different degrees of irrigation pressure (i.e. high, low, and very low) in the treatment of open fractures. The eligibility criteria of this study included skeletally mature patients with an open fracture wound of an extremity, which required operative intervention.

The standardized FLOW study protocol was approved by the human subject committees at each participating site (REB #08-268—Research Ethics Board/Institutional Review Boards). A detailed trial protocol and study results for FLOW have been previously published[15,16].

Data Collection

The following patient demographic, injury, and treatment characteristics were retrieved for all eligible patients from both randomized trials: age, gender, ethnicity, smoking status, diabetes history, non-steroidal anti-inflammatory use, mechanism of injury (high energy vs. low energy), number of injuries, open versus closed fracture, open fracture grade (Gustilo and Anderson Classification), fracture pattern, fracture gap (<1cm vs. ≥1cm), surgical treatment (reamed vs. unreamed), timing to surgery, and wound closure technique. Fracture pattern was classified as complex (comminuted or segmental) or simple (transverse, spiral, oblique). Wound closure technique was categorized as primary closure (closure of wound at initial surgery), delayed primary closure (closure of wound after initial surgery), or secondary closure (closure of wound through flap/grafting). The reported fracture healing status of patients (bone union vs. nonunion) at 12-months was also recorded. Bone union was determined by individual site investigators based on their radiographic assessment of patients.

Two reviewers, who were blind to 12-month outcomes, assigned scores according to the Radiographic Union Score for Tibial fractures (RUST) scale to the 3-month radiographs of all patients. The RUST scoring system evaluates radiographic fracture healing based on bridging of each cortex in two radiographic planes (i.e. Anterior-Posterior and Lateral planes). Each of the 4 cortices is assigned a score of 1 (fracture line, no callus), 2 (bridging callus with visible fracture line), or 3 (bridging callus with no evidence of fracture line) to produce a cumulative score out of 12.

Data Analysis

Descriptive statistics were used to summarize patient, injury, surgery, and radiographic characteristics. Multivariable binary logistic regression was carried out to explore the association of the following factors with nonunion at 1-year: (1) open versus closed injury, (2) fracture pattern (complex vs. simple), (3) fracture gap (<1cm vs. ≥1cm), and (4) 3-month RUST score (≤4 vs. 5-6 vs. ≥7). We limited our regression model to four independent predictor variables (three dichotomous and one three-level ordinal) based on preliminary assessment of the event rate (47 cases of nonunion) to guard against over-fitting (>9 events per variable)[17]. The selected independent variables were purposefully chosen based on the objectives of the study (RUST scores) and previous evidence to suggest an association with nonunion (open fracture, comminuted fracture, fracture gap >1cm)[4,8,11,12]. The concordance statistic (c statistic) was calculated for the regression model with and without the RUST score, to assess the improvement offered by the RUST score for predicting nonunion. A p value of less than 0.05 was used to infer statistical significance. All analyses were performed using IBM SPSS (Version 21).

RESULTS

A total of 155 patients were identified for inclusion, including 83 patients from the SPRINT trial and 72 patients from the FLOW trial. The overall rate of nonunion at 12-months in this cohort of patients was 30% (n=47). For those patients that did heal by 12-months (n=108), the mean time to bone union was 9.4 months (SD 4.2), with only 24% (n=26) of patients achieving union before 6 months.

Patients were predominantly male (80.6%), Caucasian (82.6%), sustained high-energy trauma (81.3%), and had multiple injuries (i.e. non-isolated fracture, 58.1%) (**Table 1**). Furthermore, patients more commonly sustained an open fracture (66.5%), had a complex fracture pattern (i.e. comminuted or segmental, 57.4%), and underwent reamed intramedullary nailing for initial surgical management (65.2%). A total of 119 patients (76.8%) in this cohort experienced fracture-related complications that comprised primary outcomes in the SPRINT and FLOW trials. Specifically, patients most commonly underwent bone grafting, implant exchange, intramedullary nail dynamization and re-operation in response to a surgical site infection (**Table 2**). The 3-month radiographs were performed at a mean of 92 days after initial surgery. The mean RUST score at 3-month follow-up was 5.9 (SD 1.7).

Prognostic Factor Comparison: Nonunion vs. Union

When comparing patients with nonunion to those healed at 12-months, 87% compared to 57% had an open fracture, and 74% compared to 50% had a complex fracture pattern, respectively. Among patients with nonunion, three had a fracture gap of ≥1cm after initial surgical management (6%, 3/47). Although there were also 3 patients who went on to heal at 12-months with a fracture gap of ≥1cm, this accounted for only 3% of such patients (3/108). The mean 3-month RUST score in patients with nonunion was 4.8 (SD 1.1) compared to 6.3 (SD 1.7) in those healed at 12-months (**Figure 1**). Fifty-three percent of patients with nonunion had RUST scores of 4 or less, whereas only 19% of patients healed at 12-months had such low scores (**Table 3**).

When exploring these risk factors (open versus closed, fracture pattern, fracture gap, 3-month RUST score) in a multivariable logistic regression model, only open fracture (OR 4.8, 95% CI 1.7 to 13.3, p=0.003) and 3-month RUST scores (p<0.001) were found to be associated with nonunion at 1-year. Compared to a RUST score of ≥7, a 3-month RUST score of ≤4 was associated with a 15.5 times greater odds for nonunion (95% CI 4.4 to 54.3); a score of 5 or 6 was associated with a 5.7 times greater odds for nonunion (95% CI 1.7 to 18.8). Fracture pattern and fracture gap ≥1cm were not significantly associated with nonunion in our analysis (**Table 4**).

The c statistic for the regression model improved from 0.70 (95%CI: 0.61-0.79) without the RUST variable to 0.81 (95%CI: 0.74-0.88) with its inclusion (**Table 5**).

DISCUSSION

Nonunions of tibial shaft fractures have a devastating impact on patient quality of life and often necessitate extensive treatment with unplanned surgical interventions. Approximately one in every three patients with a tibia shaft fracture who have yet to heal at 3 months and experience a major orthopaedic complication related to their fracture will remain unhealed at one year. In the present study, nearly 80% of these patients underwent re-operations to promote delays in fracture healing, including bone grafting, implant exchange, and dynamization. Despite such intervention, the 3-month RUST score remained highly effective in identifying early those patients who remained at risk for nonunion. Patients with little or no callus at 3-months (RUST scores of 6 or less), had a 5-15 fold increase in odds of remaining unhealed compared to patients with higher RUST scores (≥7). Consistent with previous reports, our study also found a strong association between nonunion and open fractures in this population[4,8,12].

There has been recent recognition that simple radiographic assessments can be used to successfully predict eventual nonunion in patients with tibial shaft fractures. Yang *et al* demonstrated that fellowship trained trauma surgeons can predict nonunion with 74% accuracy when presented with 3-month radiographs in the context of the patients clinical scenario [18]. Predictions in this study were largely based on the degree of callus formation and mechanism of injury[18]. In a retrospective review of 176 open and closed tibial fractures treated with intramedullary nailing, Lack and colleagues found that any cortical bridging within 4-months post-operatively was strongly predictive of eventual union with 99% accuracy[19]. Of note, this predictive model was based on patients who were simply observed beyond 12-months and did not undergo any unplanned operative interventions to promote fracture healing.

Since the RUST score was first introduced in 2010, multiple studies have demonstrated it to have excellent intra- and inter-rater reliability for assessing healing status of tibial shaft fractures treated by intramedullary nailing [20-22]. The RUST score has also been shown to correlate with clinical outcomes, including weight-bearing status, patient-reported functional recovery and the short form-36 physical component score [22,23]. There has been less focus, however, on the prognostic utility of RUST scores in predicting fracture healing, with only a single conference abstract published on the topic to-date[24]. Presented at the 2014 Orthopaedic Trauma Association Annual Meeting, Fowler and colleagues carried out a retrospective case-control study of 97 patients that also demonstrated the 3-month RUST scores and open fractures as strong predictors of nonunion in patients with tibial shaft fractures. Specifically, nonunion occurred in 56% of patients with 3-month RUST scores < 7, compared to 3% of patients with scores ≥ 7 [24]. These findings corroborate the results of our current study, which found a similar risk difference of nonunion based on 3-month RUST scores (43% vs. 7%, with RUST scores of <7 and ≥ 7, respectively).

There are several strengths to our study. First and foremost, data was derived from two large, multi-center, randomized controlled trials with broad generalizability and meticulous data collection. Furthermore, this study employed a nested cohort design in which all eligible patients from the randomized controlled trials were sampled. Finally, our conclusions regarding the prognostic utility of the 3-month RUST score are derived from a multivariable logistic model that controlled for several confounding variables predictive of nonunion, including open fractures, fracture gap, and fracture pattern (comminuted/segmental). The primary limitation of this study was its retrospective nature, which limited analysis to available data. Specifically, 3-month radiographs were primarily only available for patients with fracture-related complications, as these adverse events constituted primary outcomes in the SPRINT and FLOW trials that triggered the collection of 3-month radiographs. This over representation of patients with complications provides the likely explanation for a nonunion rate that is higher than most previous reports. However, the capacity of the RUST score to give consistent findings across distinct patient populations, as in this study and the abovementioned study by Fowler *et al*, underscores the robustness of the 3-month RUST score as a prognostic tool for predicting nonunion[24]. Finally, our analysis was limited to the abovementioned four-predictor variables to prevent over-fitting of our regression model.

In conclusion, patients with fractures of the tibial diaphysis who experience healing complications are at considerable risk for nonunion at one year following their injury. Both 3-month RUST scores and open fractures serve as strong early prognostic indicators of poor healing potential in this population. Future studies evaluating the efficacy of timely intervention in improvng union rates for this patient population are warranted.

FIGURES & TABLES

Table 1. Patient and Injury Characteristics

Characteristic	Union at 12 months N=108	Nonunion at 12 months N=47	Total N=155
Study			
FLOW	46 (43%)	26 (55%)	72 (46%)
SPRINT	62 (57%)	21 (45%)	83 (54%)
Age, mean (SD) years	39.0 (16.4)	40.9 (13.1)	39.6 (15.4)
Gender			
Female	20 (19%)	10 (21%)	30 (19%)
Male	88 (81%)	37 (79%)	125 (81%)
Ethnicity			
Caucasian	91 (84%)	37 (79%)	128 (83%)
African-American	4 (4%)	2 (4%)	6 (4%)
Asian	5 (5%)	3 (6%)	8 (5%)
Other (Hispanic, Native, Other)	8 (7%)	5 (11%)	13 (8%)
Current smoker	35 (32%)	14 (30%)	49 (32%)
Diabetic	5 (5%)	2 (4%)	7 (5%)
NSAID use	5 (5%)	4 (9%)	9 (6%)
Mechanism of injury*			
High Energy	82 (76%)	44 (94%)	126 (81%)
Low Energy	26 (24%)	3 (6%)	29 (19%)
Isolated injury	51 (47%)	14 (30%)	65 (42%)

*High energy defined as: motor vehicle accident (driver/passenger/pedestrian), motorcycle accident, ATV, crush injury, fall from height, direct trauma (blunt)

Low energy defined as: fall from standing, twist, direct trauma (penetrating)

Table 2: Fracture and Surgical Characteristics

Characteristic	Union at 12 months N=108	Nonunion at 12 months N=47	Total N=155
Closed Fracture	46 (43%)	6 (13%)	52 (34%)
Open Fracture	62 (57%)	41 (87%)	103 (66%)
Type I	11	8	19
Type II	18	13	31
Type IIIA	19	12	31
Type IIIB	14	7	21
Type IIIC	0	1	1
Fracture Pattern			
Complex (Comminuted, Segmental)	54 (50%)	35 (74%)	89 (57%)
Not Complex (Spiral, Oblique, Transverse)	54 (50%)	12 (26%)	66 (43%)
Fracture Location			
Proximal Diaphysis	8 (7%)	11 (23%)	19 (12%)
Middle Diaphysis	42 (39%)	18 (38%)	60 (39%)
Distal Diaphysis	58 (54%)	18 (38%)	76 (49%)
Method of Fixation			
Unreamed IM Nail	39 (36%)	15 (32%)	54 (35%)
Reamed IM Nail	69 (64%)	32 (68%)	101 (65%)
Post-Operative Fracture Gap			
<1cm	105 (97%)	44 (94%)	149 (96%)
≥1cm	3 (3%)	3 (6%)	6 (4%)
Time to Surgery			
Median Hours (IQR)	11.8 (6.5-24.0)	11.0 (6.0-20.7)	11.2 (6.4-21.9)
Wound Coverage			
Primary Closure			

Delayed Primary Closure	35 (32%)	20 (43%)	55 (35%)
Secondary closure	8 (7%)	6 (13%)	14 (9%)
Closed fracture	19 (18%)	15 (32%)	34 (22%)
	46 (43%)	6 (13%)	52 (34%)
Fracture Complications	**78 (72%)**	**41 (87%)**	**119 (77%)**
Surgery for Infection*	22	8	30
Bone Graft*	2	11	13
Implant Exchange*	16	21	37
IM Nail Dynamization*	18	11	29
Autodynamization*	27	4	31
Other*	5	1	6

*Patients could have experienced more than one type of complication. For each specific complication, the number listed is the total number of patients experiencing that given complication

* Autodynamization was an adjudicated event only in the SPRINT trial

Definitions:
IQR = Interquartile Range

Figure 1: Comparison of Prognostic Variables between Patients with Nonunion and Union

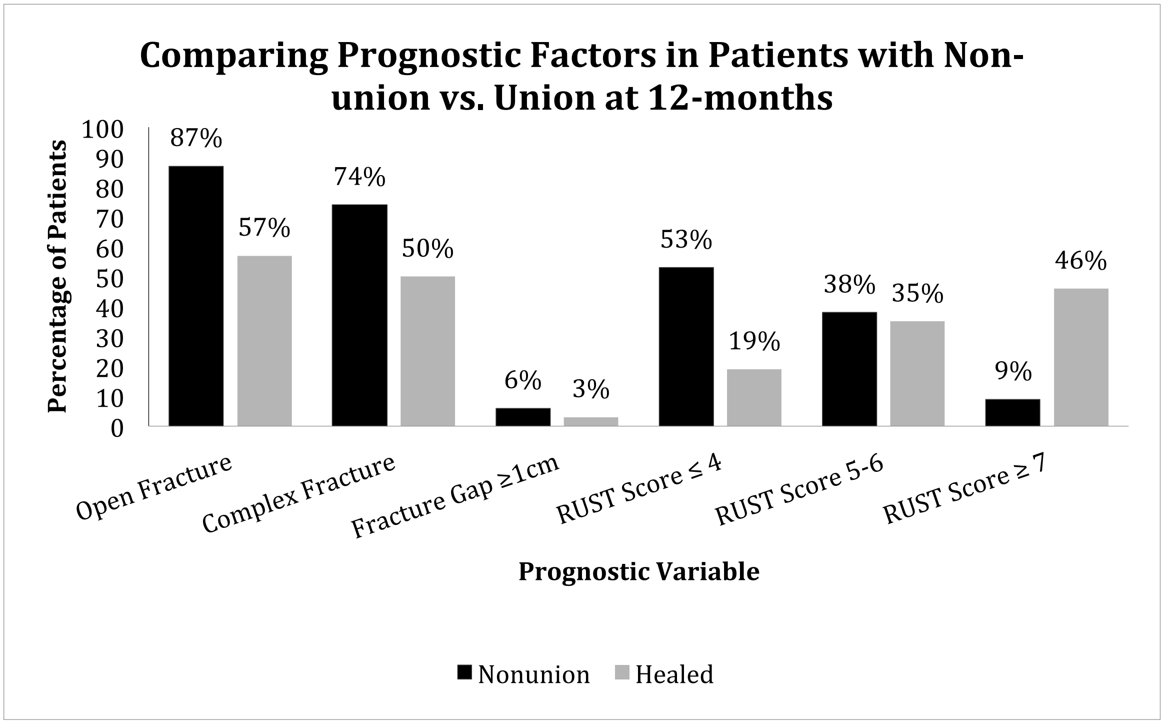

Table 3: Three-Month RUST Scores in Patients with Adjudicated Adverse Events

Characteristic	Union at 12 months N=108	Nonunion at 12 months N=47
Time to 3-month x-ray		
Mean Days (SD)	92.0 (16.8)	91.6 (15.9)
3-month RUST score		
3-4	20 (19%)	25 (53%)
5-6	38 (35%)	18 (38%)
7-12	50 (46%)	4 (9%)
RUST score, mean (SD)	6.3 (1.7)	4.8 (1.1)

Definitions:
RUST: Radiographic Union Score for Tibia Fractures
SD: Standard Deviation

Table 4. Multivarible Logistic Regression (Nonunion at 12-months as outcome, N=155)

Predictor Variable	OR (95% CI)	P-value
Open fracture	4.76 (1.71, 13.30)	0.003
Complex fracture (comminuted or segmental)	1.46 (0.60, 3.54)	0.401
Fracture gap ≥1cm	0.57 (0.09, 3.46)	0.540
3-month RUST score		<0.001
3-4	15.49 (4.42, 54.33)	
5-6	5.70 (1.73, 18.75)	
7-12	1.00	

Definitions:
RUST: Radiographic Union Score for Tibia Fractures

Table 5. Concordance (c) Statistic for Regression Models

Model	C-Statistic	Significance	95% Confidence Interval
Regression (No Rust Score)	0.700	<.001	(0.614-0.786)
Regression (With RUST score)	0.809	<.001	(0.736-0.883)

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CHAPTER IV

Nonunion in Patients with Tibial Shaft Fractures—Can Early Functional Status Predict Healing?

Nonunion in Patients with Tibial Shaft Fractures—Can Early Functional Status Predict Healing?

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ABSTRACT

Background
Nonunions of tibial shaft fractures have devastating physical and psychological consequences for patients. It remains unknown if early functional status can identify patients at risk for nonunion.

Objective
To determine if functional status at three months after surgery, as measured by the SF-36 or SF-12 health survey Physical Component Summary (PCS) score, can serve as a prognostic indicator for nonunion at one year in patients with fractures of the tibial shaft.

Methods
This study was an observational cohort study nested within two multi-center, randomized controlled trials. Patients who met the following eligibility criteria were included: (1) sustained a tibial shaft fracture that was treated with intramedullary nailing, (2) were unhealed at three-month follow-up, (3) had a reported SF-36 or SF-12 PCS score at three months, (4) had final 12 month follow-up with a reported radiographic healing status (bone union or nonunion), and (5) were enrolled in either the SPRINT or FLOW randomized trials. Multivariable logistic regression was performed to evaluate the association between healing status at 12 months and seven prognostic variables (open fracture, fracture pattern, nailing technique, smoking, fracture gap, three-month PCS score, FLOW vs. SPRINT trial).

Results
A total of 940 patients were included in this study with an overall rate of radiographic nonunion of 13.3% (n=125) at 12-month follow-up. Absolute nonunion risk increased with incrementally lower PCS scores (8.2%, 12.8%, 15.9%, 23.7% for scores ≥ 40, 30.0-39.99, 20.0-29.99, and < 20, respectively). In the multivariable regression analysis, PCS scores of < 20 were associated with a 2.6-times greater odds of nonunion compared to scores of ≥ 40 (OR 2.58, 95%CI: 1.02-6.53), whereas scores between 20 to 30 were associated with a nearly 2-times greater odds of nonunion (OR 1.94, 95%CI: 1.08-3.49). Open fractures also conferred a 2.8-fold increase in odds of nonunion compared to closed injuries (OR 2.77, 95%CI: 1.58-4.83), as did complex fractures when compared to simple fractures (OR 2.57, 95%CI: 1.64-4.02).

Conclusion
A considerable portion of patients with fractures of the tibial shaft treated with intramedullary nailing will experience nonunion at one year post-operatively. In addition to open injuries and complex fracture patterns, high-risk patients can be identified early in their healing course, in part, by their functional recovery at three months as measured by the PCS scores of the SF-36 and SF-12 instruments.

INTRODUCTION

Fractures of the tibial shaft are the most frequently fractured major long bone, with an annual incidence of approximately 20 per 100,000 people in the developed world[1-3]. Despite modern surgical techniques of intramedullary nailing for the fixation of these fractures, a considerable number of patients fail to heal (15-19%) and experience significant physical hardship and psychological suffering as a result of nonunion[4-6]. Nonunions of tibial shaft fractures also impose a financial burden for health care systems, as the management of such patients is associated with a greater than two-fold increase in health care costs compared to patients without nonunion[7].

The capacity to identify patients at risk of nonunion early in their healing course would be of substantial value to orthopaedic surgeons in initiating appropriate surveillance and possible intervention for such patients. To date, most variables that have been delineated as prognostic factors that influence healing have been baseline characteristics such as smoking, skin integrity, degree of cortical continuity, and intramedullary nailing technique[4,5,8-12]. It is likely, however, that a patient's early healing response may be a more potent predictor of healing potential than such baseline characteristics. For instance, Lack *et al* recently reported that radiographic assessment demonstrating any cortical bridging within four months post-operatively is predictive of eventual fracture healing with 99% accuracy[13].

Given the significant physical impairment associated with fracture nonunion, early functional recovery may potentially serve as a strong marker for healing potential[6,8]. The Short Form 36-Item (SF-36) health survey—along with its shortened version, the Short

Form 12-Item (SF-12) health survey—are generic health-related quality of life instruments that have found widespread use in the medical literature[14,15]. Both the SF-36 and SF-12 provide a general measure of a patient's physical and mental health measured across eight assessment scales, including: physical functioning, role limitations due to physical health, bodily pain, perceived general health, vitality, social functioning, role limitations due to emotional burden, and mental health. These scales can be aggregated to provide summary measures of overall physical and mental health, represented as the Physical Component Summary (PCS) and Mental Component Summary (MCS) scores, respectively. The PCS score is weighted more heavily on the first four abovementioned health scales that relate to functioning[15,16]. As an inexpensive and time efficient assessment tool that can be readily administered to patients, the SF-36 and SF-12 instruments could be of significant value in identifying patients at high risk for failure of fracture healing.

To that end, we performed an observational study of patients with tibial shaft fractures treated with intramedullary nailing to determine if functional recovery at three months after surgery, as measured by the SF-36 and SF-12 Physical Component Summary score, can serve as a prognostic indicator of nonunion at one year.

METHODS

Study Design

This study was an observational cohort study nested within two multi-center, randomized controlled trials, including: the 'Study to Prospectively Evaluate Reamed

Intramedullary Nails in Patients with Tibial Shaft Fractures' (SPRINT), and the 'Fluid Lavage of Open Wounds' (FLOW) trial.

SPRINT Trial

The SPRINT trial was a randomized trial conducted across 29 centers in the United States, Canada, and The Netherlands, comparing reamed to unreamed intramedullary nailing in 1226 patients between July 2000 and September 2005. Enrolment criteria for the trial included skeletally mature patients with either open or closed fractures of the tibial shaft, which were non-pathological and amenable to intramedullary nailing. Patients in the SPRINT trial were prospectively followed for 12 months post-operatively, with functional outcomes assessed at three months using the SF-36 health survey and radiographic healing status assessed at 12 months.

The full SPRINT study protocol and study results have been previously published[17,18]. The trial received approval from the human subjects committee at each participating site (REB #99-077—Research Ethics Board/Institutional Review Boards).

FLOW Trial

The FLOW trial was conducted across 41 sites from the United States, Canada, Australia, India, and Norway between June 2009 and October 2013. This randomized trial employed a 3x2 factorial design in which 2447 patients with open fractures were randomized to one of three irrigation pressures (high, low, very low) and to one of two irrigation solutions (soap vs. saline). Enrolment criteria for FLOW included skeletally mature patients with open fractures of any extremity requiring operative intervention. Among these patients, 929 had fractures of the tibial shaft. Patients were followed prospectively, with the SF-12 questionnaire administered at three-month follow-up and radiographic healing status documented at follow-up visits up to 12 months.

The FLOW study results and study protocol have been previously published, and the trial received approval from the human subjects committee at all participating centers (REB #08-268—Research Ethics Board/Institutional Review Boards)[19,20].

Inclusion Criteria

All patients from the SPRINT and FLOW trials who met the following eligibility criteria were included in the current study: (1) sustained a tibial shaft fracture that was operatively treated with intramedullary nailing, (2) were unhealed at three-month follow-up, (3) had a reported SF-36 or SF-12 PCS score at three months, and (3) had a reported radiographic healing status (bone union or nonunion) by final 12-month follow-up.

Data Collection and Definitions of Variables

For all patients, baseline data was retrieved and recorded for patient information (age, gender, ethnicity, smoking status, diabetic history, non-steroidal anti-inflammatory use), injury characteristics (mechanism, number of injuries, open versus closed fracture, fracture location, fracture pattern) and surgical factors (reamed versus unreamed nailing, post-operative fracture gap, time from injury to surgery).

In brief, mechanism of injury was classified as either high- or low-energy, with high energy injuries being inclusive of motor vehicle crashes (driver, passenger or pedestrian), ATV/snowmobile crashes, crush injuries, falls from height, and direct blunt trauma. Low energy injuries included falls from standing, twists, and direct penetrating trauma. Open fracture wounds were graded using the Gustilo and Anderson classification. Fracture pattern was recorded as either simple (transverse, oblique, or spiral) or complex (comminuted or segmental). Fracture gap referred to the amount of bone loss between the proximal and distal fragments at the fracture site, and was determined to be either < 1cm or ≥ 1cm from the post-operative radiographs.

The SF-36 and SF-12 PCS scores were recorded for patients in the SPRINT and FLOW trials, respectively. These surveys were either self-administered, or interviewer-administered if needed, at each patient's three-month study follow-up visit in both trials. For both instruments, the PCS score ranges from 0 (worst possible function) to 100 (best possible function). PCS scores were categorized into the following strata based on scoring intervals of ten or greater: <20.0, 20.0-29.99, 30.0-39.99, ≥40.0. Categorization was performed to optimize clinical relevance of our study findings by allowing for reporting of absolute risks of nonunion per strata. It has been previously reported that the minimal clinically important difference (MCID) for the PCS score in an orthopaedic population (osteoarthritis) is a score of two[21]. As such, the above intervals were deemed large enough to be clinically meaningful while allowing for a robust sample size of patients within each stratum.

The radiographic healing status of each patient in both trials was reported as either 'yes' (healed) or 'no' (unhealed), with an associated date of the first radiograph that showed healing. Radiographic interpretation of healing status was at the discretion of the clinical team at each specific site.

Data Analysis

All baseline characteristics, functional scores, and radiographic outcomes are presented using descriptive statistics, consisting of means with associated standard deviations for continuous variables and frequencies with associated percentages for categorical variables. Multivariable logistic regression was performed to explore the association of the following seven factors with nonunion: 3-month SF PCS scores, the trial to which the patient was enrolled (SPRINT or FLOW), and five covariates with previous evidence to suggest an association with fracture healing (skin integrity, fracture pattern, intramedullary nailing technique, smoking status, and fracture gap)[4,5.8-12,22]. Variables were entered into the regression model simultaneously.

It has been demonstrated that the SF-36 and SF-12 PCS scores are strongly correlated[23,24]. As such, patients from both trials were included in a single regression model. Nevertheless, a sensitivity analysis was performed in which an interaction term consisting of 'PCS Score' and 'Study' (FLOW vs. SPRINT) was added to the regression model to explore for an effect modification on nonunion rate based on the instrument used (SF 36 vs. SF 12). An interaction terms consisting of 'skin integrity' (open vs. closed fracture) and 'IM nailing technique' (reamed vs. unreamed) was also included in the sensitivity analysis, given prior evidence to suggest that the effect of intramedullary nailing technique on nonunion rate is dependent on skin integrity at the fracture site[10,11].

With a preliminary assessment of our study sample size (n=940) and an anticipated nonunion rate of approximately 15%, it was expected that all seven independent variables (six dichotomous and one four-level variable) could be included in the regression analysis without risk of over-fitting the model[25]. All analyses were performed using IBM SPSS (Version 21). Statistical significance was set at a p-value of less than 0.05.

RESULTS

A total of 940 eligible patients with fractures of the tibial diaphysis were included in this study, with 626 patients incorporated from the SPRINT trial and 314 from the FLOW trial. The overall rate of radiographic nonunion at 12-month follow-up was 13.3% (n=125). The rate of nonunion, when assessed independently for each trial cohort, was 10% for the SPRINT trial (64/626) and 19% (61/314) for the FLOW trial (**Figure 1**).

Patient, Injury, & Treatment Characteristics

The study cohort was comprised predominantly of young patients (mean age of 40.9), that were male (n=709, 75%) and of Caucasian decent (n=755, 80%). Approximately one third of patients were active smokers (n=299, 32%) (**Table 1**). The majority of patients sustained their fractures as a result of a high-energy mechanism (n=667, 71%). Furthermore, approximately half of patients had open fractures (n=499, 53%) and complex fracture patterns (n=428, 46%) that were either comminuted or segmental. Sixty-seven percent of patients underwent reamed intramedullary nailing (n=632) and few patients had post-operative fracture gaps equal to or exceeding 1cm (n=44, 5%) (**Table 2**).

PCS Scores

The mean PCS score at 3 months for the entire study cohort was 33.5 (SD 9.0). This overall PCS score was consistent for patients in the SPRINT trial assessed with the SF-36 (33.5, SD 9.1) and patients in the FLOW trial assessed with the SF-12 (33.5, SD 8.9). When assessed by strata, 23% of patients had PCS scores of ≥ 40 (n=219), whereas 73% had scores of 20.0 to 29.9 (n=339) or 30.0 to 39.9 (n=344). Relatively few patients scored less than 20 (n=38) (**Table 3**).

Prognostic Factors and Nonunion Rate

The rate of nonunion in smokers was 16.1% compared to 12.0% in non-smokers. Patients with open, high energy, and complex fractures had nonunion rates that were approximately three times greater than patients with closed (19.6% vs. 6.1%), low energy (16.6% vs. 5.1%), and simple fractures (21.0% vs. 6.8%), respectively. In regards to surgical factors, reamed and unreamed intramedullary nailing had identical rates of nonunion (13.3%), whereas patients with a post-operative fracture gap of ≥1cm had a nonunion rate of 31.8% compared to 12.4% in those with a fracture gap of <1cm. The incidence of nonunion increased with every incremental decrease in PCS score strata.

Absolute nonunion risk in patients with PCS scores of ≥ 40 was 8.2%, whereas the risk increased to 12.8% and 15.9% in patients with scores of 30.0-39.99 and 20.0-29.99, respectively. Patients with a PCS score of <20 had the greatest risk of nonunion at 23.7%.

When controlling for these risk factors in the multivariable logistic regression analysis, open fractures, complex fracture patterns, and three-month PCS scores were significantly associated with nonunion at 12 months. Open fractures were associated with a greater than 2.5 increase in odds of nonunion compared to closed injuries (OR 2.77, 95%CI: 1.58-4.83), as were complex fractures compared to simple fractures (OR 2.57, 95%CI: 1.64-4.02). In regards to three-month PCS scores, patients with scores between 20.0 to 29.99 had a nearly two-fold greater risk of nonunion compared to patients with scores of ≥ 40 (OR 1.94, 95%CI: 1.08-3.49), whereas those patients with scores below 20 had an even greater odds of nonunion (OR 2.58, 95%CI: 1.02-6.53) (**Table 4**).

In the sensitivity regression analyses, both interaction terms were non-significant, suggesting no difference in the odds of nonunion for reamed versus unreamed nailing irrespective of skin integrity, as well as in the odds of nonunion across PCS strata irrespective of the SF instrument used (SF-36 vs. SF-12).

DISCUSSION

In this prospective observational study of 940 patients with tibial shaft fractures treated with intramedullary nailing, 13% of patients who had not healed their fractures by three months remained unhealed at one year post-operatively. Open fractures, complex fracture patterns, and low PCS scores (<30) were significantly associated with nonunion. All three risk factors were associated with a two-fold or greater odds of nonunion.

Although there is previous evidence to corroborate our findings that open and complex fractures are associated with a higher risk of tibia fracture nonunion, we are unaware of any previous studies that have directly evaluated early post-operative function as a prognostic marker for eventual healing status[4,12,22]. Previous evidence evaluating the association between functional outcomes and healing has focused rather on the temporal relationship between functional recovery and fracture healing. Timing to successful performance of daily activities, such as prolonged walking, running and jumping, has been noted to moderately correlate with timing to fracture healing[22]. Building on such previous work, our current study directly suggests that functional recovery not only has a temporal relationship with fracture healing, but that early functional recovery serves as a prognostic indicator for a patients ultimate propensity to heal.

Notably, patients in the FLOW trial had nearly double the nonunion rate of patients in the SPRINT trial (19% vs. 10%). This risk difference was most likely attributable to the exclusive enrolment of patients with open fractures in the FLOW trial, as there was no difference in the odds of nonunion between these study cohorts when controlling for open fractures in our regression model (OR 1.14, 95%CI: 0.68,1.91).

Our study has several strengths. First and foremost, this study has a robust sample size of patients stemming from two large, multi-center, randomized controlled trials that were conducted across six countries. Data collection in these trials was done prospectively with quality control checks to ensure accuracy and completeness.

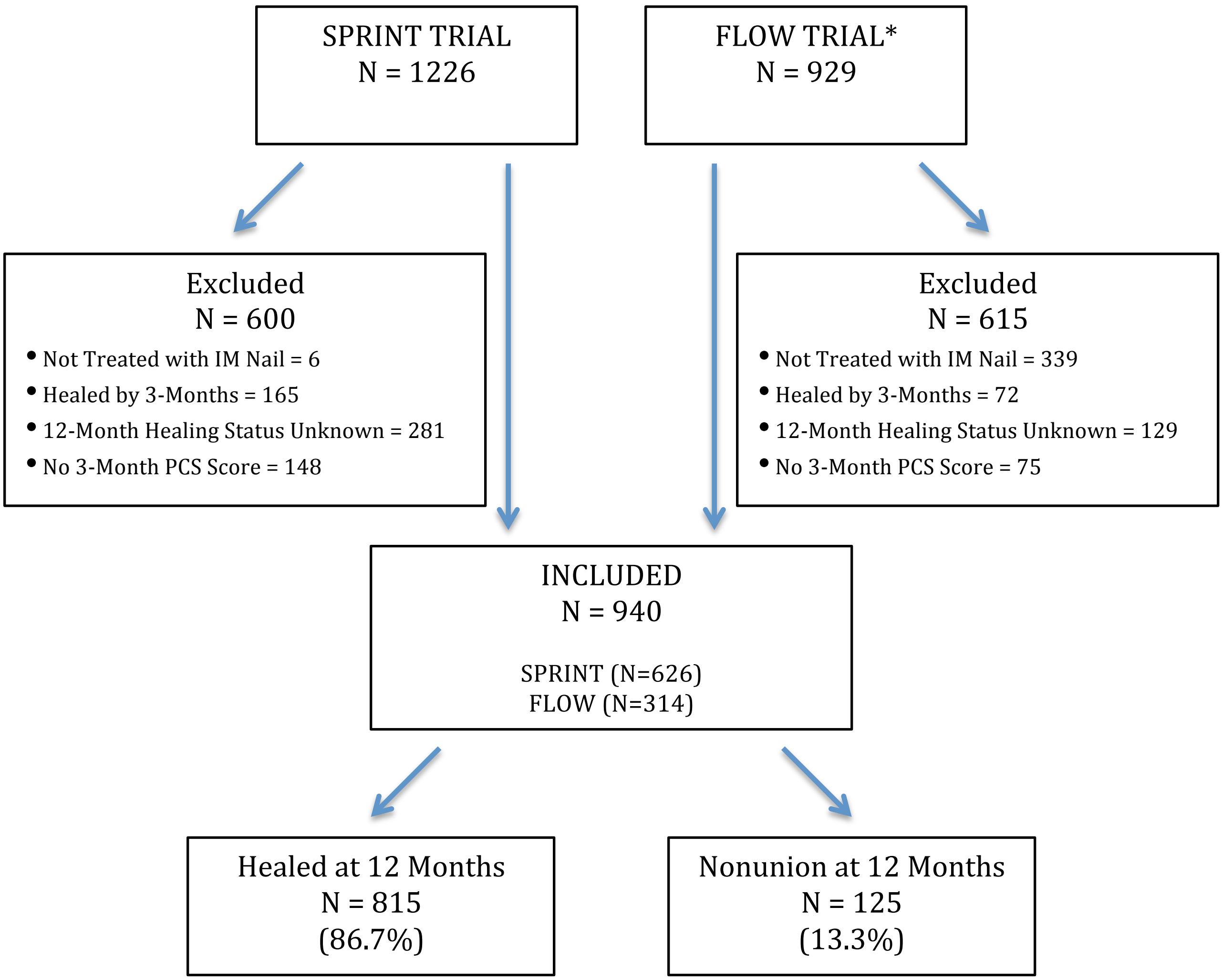
Furthermore, both trials had greater than 90% patient follow-up at one year. Secondly, our chosen measure of physical function is based on a ubiquitous health-related quality of life instrument, with documented validity, reliability and responsiveness[16,21,23,26]. The reliability of the SF instruments is of particular importance for our current study, as the utility of a tool for predicting fracture healing is predicated on its widespread reproducibility. Although to our knowledge, there has been no previous precedent for amalgamating PCS scores across the SF-36 and SF-12 instruments, our findings demonstrated consistent findings as expected between the two instruments. Finally, our conclusions regarding the prognostic utility of the SF-36 and SF-12 PCS scores in predicting nonunion are based upon a multivariable regression model in which several known covariates of fracture healing were accounted for.

The primary limitation of our study is attributable to the lack of a gold standard definition of radiographic and clinical fracture healing[27]. In the current study, we relied upon physician judgment at each center to ascertain healing status (bone union or nonunion) at one year based on radiographic findings. Although this is most commonly defined as radiographic healing in 3 of the 4 cortices seen on anteroposterior and lateral radiographs, this definition was not put forth as a required diagnostic criterion to participating trial centers.

In conclusion, a considerable portion of patients with fractures of the tibial shaft treated with intramedullary nailing will fail to heal their fractures at one year post-operatively. The impact of tibial shaft nonunion on physical and mental health is devastating, such that patients on average would be willing to give up over a third of their remaining lives in exchange for good health[29]. In addition to open injuries and complex fracture patterns, high risk patients can be identified early in their healing course, in part, by their functional recovery at three months as measured by the PCS scores of the SF-36 and SF-12 instruments. Collectively, these prognostic markers should initiate increased surveillance and timely management to avoid prolonged suffering in patients who are more likely to remain unhealed one year from their injury.

FIGURES & TABLES

Figure 1. Study Flow Diagram



* Only those patients with a fracture of the tibial shaft recruited up to March 2015

Table 1. Patient Characteristics

Characteristic	Number of Patients N=940	Healed at 12 Months N=815	Nonunion at 12 Months N=125
Trial			
SPRINT	626	562 (89.8)	64 (10.2)
FLOW	314	253 (80.6)	61 (19.4)
Age, mean (SD)	40.9 (15.6)	40.6 (15.8)	42.4 (14.5)
Gender			
Female	231	203 (87.9)	28 (12.1)
Male	709	612 (86.3)	97 (13.7)
Ethnicity			
Caucasian	755	654 (86.6)	101 (13.4)
African-American	58	46 (79.3)	12 (20.7)
Asian	51	47 (92.2)	4 (7.8)
Hispanic	34	29 (85.3)	5 (14.7)
Native	22	20 (90.9)	2 (9.1)
Other	20	19 (95)	1 (5)
Active Smoker*	299	251 (83.9)	48 (16.1)
Non-Smoker	640	563 (88.0)	77 (12.0)
Diabetic	44	38 (86.3)	6 (13.6)
Non-Diabetic	896	777 (86.7)	119 (13.3)
NSAID Use	60	51 (85.0)	9 (15.0)
Non-NSAID User	880	764 (86.8)	116 (13.2)

* N=939 (814 and 125)

Table 2. Injury and Treatment Factors

Characteristic	Number of Patients N=940	Healed at 12 Months N=815	Nonunion at 12 Months N=125
Mechanism of injury			
High Energy	667	556 (83.4)	111 (16.6)
Low Energy	273	259 (94.9)	14 (5.1)
Isolated Fracture	509	462 (90.8)	47 (9.2)
Multiple Fractures	431	353 (81.9)	78 (18.1)
Closed Fracture	441	414 (93.9)	27 (6.1)
Open Fracture	499	401 (80.4)	98 (19.6)
Type I	104	93	11
Type II	190	151	39
Type IIIA	151	119	32
Type IIIB	54	38	16
Type IIIC	0	0	0
Type of Fracture*			
Complex (comminuted/segmental)	428	338 (79.0)	90 (21.0)
Simple	512	477 (93.2)	35 (6.8)
Diaphyseal Location of Fracture **			
Proximal	84	66 (78.6)	18 (21.4)
Distal	525	470 (89.5)	55 (10.5)
Middle	325	273 (84.0)	52 (16.0)
Nailing Technique			
Reamed IM Nailing	632	548 (86.7)	84 (13.3)
Unreamed IM Nailing	308	267 (86.7)	41 (13.3)
Post-Operative Fracture Gap			
<1cm	896	785 (87.6)	111 (12.4)
≥1cm	44	30 (68.2)	14 (31.8)
Time to surgery from injury in hours, median (IQR)†	12.40 (7.00-24.35)	13.43 (7.30-26.10)	8.72 (6.00-17.65)

* In FLOW more than one type could have been chosen, in SPRINT only one could be recorded on the CRF.
** N=934 (809 and 125)
† N=935 (810 and 125)

Table 3. PCS Score and Nonunion Risk

SF-36/SF-12 PCS Score	Number of Patients N=940	Healed at 12 Months N=815	Nonunion at 12 Months N=125
< 20.0	38	29 (76.3)	9 (23.7)
20-29.9	339	285 (84.1)	54 (15.9)
30-39.9	344	300 (87.2)	44 (12.8)
≥40	219	201 (91.8)	18 (8.2)

Table 4. Multivariable Logistic Regression for Nonunion at 12 Months (n=940)

Risk Factor	OR (95%CI)	P-value
Open Fracture	**2.77 (1.58, 4.83)**	**<0.001**
Complex Fracture	**2.57 (1.64, 4.02)**	**<0.001**
Reamed IM Nailing	0.65 (0.40, 1.04)	0.074
Active Smoker	1.39 (0.92, 2.10)	0.113
Fracture Gap ≥1cm	1.72 (0.85, 3.48)	0.134
3-Month PCS Score		
<20	**2.58 (1.02, 6.53)**	**0.046**
20 to <30	**1.94 (1.08, 3.49)**	**0.027**
30 to <40	1.52 (0.84, 2.77)	0.167
≥40	1.00	
FLOW TRIAL	1.14 (0.68,1.91)	0.628

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