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ORIGINAL ARTICLE

Observational Study

Three predictive scores compared in a retrospective multicenter study of nonunion tibial shaft fracture

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Abstract

BACKGROUND

Delayed union, malunion, and nonunion are serious complications in the healing of fractures. Predicting the risk of nonunion before or after surgery is challenging.

AIM

To compare the most prevalent predictive scores of nonunion used in clinical practice to determine the most accurate score for predicting nonunion.

METHODS

We collected data from patients with tibial shaft fractures undergoing surgery from January 2016 to December 2020 in three different trauma hospitals. In this retrospective multicenter study, we considered only fractures treated with intramedullary nailing. We calculated the tibia FRACTure prediction healING days (FRACTING) score, Nonunion Risk Determination score, and Leeds-Genoa Nonunion Index (LEG-NUI) score at the time of definitive fixation.

RESULTS

Of the 130 patients enrolled, 89 (68.4%) healed within 9 months and were classified as union. The remaining patients (n = 41, 31.5%) healed after more than 9 months or underwent other surgical procedures and were classified as nonunion. After calculation of the three scores, LEG-NUI and FRACTING were the most accurate at predicting healing.

CONCLUSION

LEG-NUI and FRACTING showed the best performances by accurately predicting union and nonunion.

Key Words: Trauma; Bone; Tibial fracture; Nonunion; Scores; Prediction model

Core Tip: Nonunion continues to be one of the most harmful complications after fracture treatment. Preventative strategies and early identification of its development are needed to successfully manage nonunion fractures. In this study, we compared the most prevalent predictive models of nonunion fractures to determine the accuracy and risk factors.

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INTRODUCTION

Bone fracture healing is one of the most important and debated issues in the field of orthopedics. Delayed union and nonunion are the most common terms to describe pseudoarthrosis (the Greek stem "pseudo" means false and "arthrosis" means joint). Although in the literature there are many definitions[1], delayed union can be described as the prolonged fracture healing time for a specific site and type of fracture. Nonunion can be described as the failure of a fracture to heal after twice the period of expected healing time (usually taking at least 6 months after trauma). Nonunion is currently defined according to the Food and Drug Administration (FDA) as a fracture older than 9 months that presents no signs of healing in the prior 3 months[2]. Conversely, Brinker *et al*[3] defined nonunion as a fracture that, in the opinion of the treating physician, has no possibility of healing without further intervention.

Delayed union or nonunion represents one of the most challenging complications for modern orthopedics. Among the long bone fractures, nonunion rate is 5%-10%[4]. However, this rate could increase due to increases in high-energy trauma in which patients survive due to improvements in basic life support techniques. High-energy trauma often involves diaphyseal fractures of several limbs, serious muscle and tendon injuries, and damage to the parenchymal organs[5,6]. A recent population-based study from Scotland estimated the incidence of nonunion at 13 per 1000 pelvis and femur fractures per year, 30 per 1000 humerus fractures per year, and approximately 55 per 1000 tibia and fibula fractures per year[7].

The management of these long fractures is complex, and the risk of malunion, delayed union, and nonunion remains high. Improper healing of a fracture contributes to considerable patient disability, reduced quality of life, and significant treatment costs[5]. Delayed union and nonunion (like fracture healing) are multifactorial events, making prediction of complications challenging. Many risk factors contribute to nonunion. Calori *et al*[8] identified sex, age, diet, diabetes, osteoporosis, muscular mass, smoking and alcohol habits, nonsteroidal anti-inflammatory drugs (NSAIDs) use, fracture personality, type of fracture, exposure, infection, and multiple fractures as risk factors.

Some studies have determined algorithms to predict the risk of nonunion, which is calculated after surgical treatment, and to quantify nonunion high-risk patients[9-11]. The aim of this study was to evaluate the accuracy of predictive scores in a group of patients after surgical treatment of tibial fracture.

MATERIALS AND METHODS

Patient selection

We retrospectively reviewed all consecutive cases of tibial shaft fractures undergoing intramedullary nailing surgery from January 2016 to December 2020. Data were collected from three different hospitals: Azienda Ospedaliera Universitaria delle Marche (71 Via Conca, Ancona 60126, Italy); Ospedale Carlo Urbani Jesi [52 Via Aldo Moro, Jesi (Ancona) 60035, Italy]; and Azienda Ospedali Riuniti Marche Nord, Pesaro (Piazzale Cinelli Carlo, 1, Pesaro 61121, Italy). All patients gave their informed consent during the enrollment period and were included in a retrospective observational database. Both preoperative and postoperative data, including sex, age, type of surgical procedure, *etc*, were collected from the hospital databases and patient medical records. The Declaration of Helsinki and Guidelines for Good Clinical Practice were applied. We included open and closed tibial nonarticular fractures according to the AO/OTA classification [12] in patients older than 18 years of age.

We excluded patients with articular fractures, periprosthetic fractures, and open fractures IIIC according to Gustilo classification[13] as well as patients with active neoplasia, with the doubt of a pathological fracture, and with genetic disorders with bone involvement (*i.e.* Paget's disease, osteogenesis imperfecta). Pregnant women and patients younger than 18 years of age were also excluded. Patients who underwent amputation or who had died because of complications related to the trauma were also excluded from the study. We excluded the polytrauma patients according to the definitions reported in the literature[14,15].

Prediction scores

To obtain a homogeneous sample and to compare the three scores, we considered only tibial fractures treated by intramedullary nailing. The patients underwent clinical examination and biprojective X-rays to assess the type of fracture. Tibia FRACTure prediction healING days (FRACTING) score, Nonunion Risk Determination (NURD) score[10], and Leeds-Genoa Nonunion Index (LEG-NUI)[11] score were applied after the definitive fixation for the FRACTING and NURD scores and within the first 12 wk for LEG-NUI, as indicated by the authors.

FRACTING score: The FRACTING score can be used to predict fracture healing time and to identify patients with a prolonged healing risk immediately after surgical treatment. The FRACTING score was validated in a prospective, multicenter, observational study[9]. The FRACTING score parameters include age, malnutrition, smoking status, diabetes, use of NSAIDs, fracture exposure grade, location (diaphysis, metaphysis, or epiphysis), synthesis device (nail, plate, external fixator, angular stability plate, instability, misalignment (> 5°), bone graft use, type of fracture, loss of bone substance, bone diastasis (> 2 mm), surgery duration (> 2 h), cast, and blood loss before and after treatment (hemoglobin < 10 g/dL). The values of the score range from 3 to 18. The FRACTING score can predict fracture healing time in five post-trauma time intervals: ≤ 3 months; 4 months; 5 months; 6 months; and > 6 months.

NURD score: The NURD score was developed in a retrospective cohort study to reliably predict tibia shaft nonunion at the time of initial intramedullary nail fixation[10]. The NURD score assigns points based on seven commonly collected variables: American Society of Anesthesiologists score; percent cortical contact; male sex; open fractures; chronic disease status; compartment syndrome; and use of a flap. It assigns 5 points for flaps, 4 points for compartment syndrome, 3 points for a chronic condition (s), 2 points for open fractures, 1 point for the male sex, and 1 point per grade of American Society of Anesthesiologists Physical Status and percent cortical contact. One point each is subtracted for spiral fractures and for low-energy injuries, which were found to be predictive of union. A NURD score from 0 to 5 indicates a 2% chance of nonunion, from 6 to 8 indicates a 22% chance of nonunion, from 9 to 11 indicates a 42% chance of nonunion, and > 12 indicates a 61% chance of nonunion.

LEG-NUI score: The LEG-NUI score was developed in a retrospective case-controlled study[11]. The LEG-NUI score supports the surgeon's assessment of the risk of long-bone nonunion and plan for appropriate early intervention. Eight factors are evaluated: site of the fracture; soft tissue damage; type of fracture; displacement; method of reduction; postsurgical fracture gap; mechanical stability; and infection. The LEG-NUI predicts union for 0-4 risk factor scores and nonunion for 5-8 risk factor ones. LEG-NUI can be calculated within 3 months from definitive fixation.

All the patients underwent follow-up for at least 12 months. We collected patients' data, including age, sex, type of fracture, surgery approach and pseudoarthrosis scores (Table 1). FRACTING and LEG-NUI scores were calculated using their app, which is available for free on a smartphone or tablet. NURD was calculated using the appropriate automatic calculator on the website (www.shocknurd.org). An excerpt of data gathered for each patient is shown in Table 1.

Table 1 Example of data collection

Patient	Age at the surgery	S1DE	Sex	Type of fracture (AO/OTA)	Fracting score	NURD score	LEG-NUI score	Union	Non-union	Follow-up (months)
1	22	DX	M	4.2C	9	7	5		X	18
2	28	SN	M	4.2A	6	5	6	X		12
3	82	DX	M	4.2A	6	5	4		X	12

NURD: Nonunion Risk Determination; LEG-NUI: Leeds-Genoa Nonunion Index.

Definitions and procedures

We used the FDA definition of nonunion[2]. The endpoint of fracture healing was radiological and usually clinical (the patient could handle full weight-bearing without pain). The most common clinical features used for the definition of nonunion were pain over the fracture site, pain during weight bearing, and mobility at the fracture site. Nonunion was also designated in all cases that underwent reoperation, according to the Brinker *et al*[3] definition. All fractures were nailed within 21 d from the injury (range: 1-21 d).

Fourteen patients with open fractures, soft tissue wide injuries, or life-threatening polytrauma were treated according to the damage control orthopedics principles and received a temporary external fixation. Conversion to definitive surgery was performed as soon as soft tissue conditions allowed and when the patient overcame the immunodeficiency period after trauma[16].

All nailing procedures were performed prior to antibiotic prophylaxis and with the patient in the supine position on a fracture table with fluoroscopic-guided imaging. The surgical technique was performed both by infrapatellar and suprapatellar incision according to the type of fracture and the surgeon's preference. The tibial shaft was both reamed and unreamed, and a guide wire was used for all procedures. All nails were of the same brand and type, with different length and diameter. All nails were locked with at least two proximal and two distal locking screws. In cases with concurrent tibial and fibular fractures, the fibular fracture was never fixed.

There were no intraoperative complications. Patients were weight-bearing as tolerated postoperatively. Participating surgeons did not offer stimulation modalities to promote bone growth (such as ultrasound and electrical stimulation) during the follow-up.

Statistical analysis

The descriptive analysis was computed as follows. The total sample size was first divided into sex (female = 47; male = 83). Then, each sex sample was divided into the nonunion and union groups. Results for each sample size were presented as minimum and maximum values, median and interquartile range, and mean. As described, a nonunion score assumed an integer value calculated as the sum of risk factors, clinical parameters, and/or demographic variables observed.

RESULTS

A total of 174 patients with tibial shaft extra-articular fractures, surgically treated, were assessed for eligibility. However, 17 patients did not satisfy the inclusion criteria, 11 patients did not consent to participate, and 16 patients were lost during follow-up. Finally, 130 patients with tibial shaft fractures were entered into the database and completed the follow-up (Figure 1). Overall, 23 patients (17.6%) had open fractures, and 9 patients (6.9%) experienced loss of bone tissue. Overall, 109 patients (90.8% of fractures) sustained concurrent tibia and fibula bone fractures. According to the AO classification, 64 fractures (49.3%) were type 4.2A, 31 fractures (23.8%) were type 4.2B, 17 fractures (13.07%) were type 4.2C, and 8 fractures (6.6%) were 4.3A type.

Among the 130 patients with tibial shaft fractures, 89 patients (68.0%) healed within 9 months and were classified as union. The remaining patients (n = 41, 31.5%) healed in more than 9 months or underwent other surgical interventions and were classified as nonunion. The second surgery interventions included nail dynamization, bone grafting, renailing, compression plating, and external fixation.

Among the nonunion group, the male patients had a mean age of 45 years, with an average FRACTING score of 7.8 ± 1.8, an average NURD score of 4.9 ± 2.8, and an average LEG-NUI score of 4.1 ± 1.4. Female patients in the nonunion group had a mean age of 52 years, with an average FRACTING score of 7.7 ± 2.1, an average NURD score of 2.4 ± 2.4, and an average LEG-NUI score of 3.1 ± 1.7 (Table 2). The cutoff value for the nonunion score was identified for each score. The FRACTING score suggested a cutoff value ≥ 8, and the NURD score had a cutoff value ≥ 9. Both scores were calculated at the immediate postoperative period. The LEG-NUI score had a cutoff value ≥ 5 calculated and was calculated within 12 wk after definitive fracture fixation.

Increasing age did not affect nonunion (Table 3). By applying the decision rule of each score to the patients, which was dependent on the cutoff value, the prediction was computed (Tables 4-6). Then, the score performances were evaluated to compare the reliability of the decision rule (Table 7). The distribution of scores for nonunion and union patients based on the cutoff were determined (Figure 2).

The presence of class imbalance ratio[17] was 41.1% and determines the ease of predicting union patients. We calculated the sensitivity, specificity, positive predictive value, negative predictive value, and F-test. As shown in Table 7, the FRACTING score had the highest ability to identify patients at risk of nonunion according to the highest sensitivity of 63.4% and an F-test of 67.0%.

DISCUSSION

Malunion or nonunion of long bones are one of the most challenging complications for orthopedic surgeons. There are many definitions of nonunion. In this study we followed the FDA definition of nonunion: a fracture older than 9 months that presents no signs of healing in the prior 3 months[2].

Nonunion involves residual pain, lameness, use of aids for walking, and the inability to lead a normal lifestyle, which greatly impacts quality of life[18]. Moreover, the healing time of tibial fractures is very variable and affected by many factors. Among the long bones fracture, a comprehensive review of studies reported nonunion rates of 0%-12% in femoral fractures, 0%-33% in humeral fractures, and 1%-80% in tibial fractures[19]. A second surgery is often necessary for complete healing. Reoperations include bone grafts, implant exchanges, or removal for hardware failure. In cases of infected nonunion, irrigation, debridement, and soft tissue coverage procedures are required.

Numerous clinical factors have prognostic value for delayed bone healing or nonunion of tibial shaft fractures. For this reason, there are several different nonunion scores. The FRACTING score was created to predict the time of healing of tibial fractures with parameters analyzed in a retrospective study, called Algoritmo Rischio Ritardo Consolidazione Ossea and was later validated in the prospective, multicenter observational study, called FRACTING[20]. The FRACTING score accounts for the most parameters, which are different for each type of surgery and internal fixation. Moreover, it considers clinical, patient-related, fracture-related, surgical, and perisurgical parameters. The NURD score accounts for some clinical and fracture-related parameters, whereas the LEG-NUI score accounts for no clinical parameters except infection, which can be argued as a perisurgical parameter. Unlike the FRACTING and NURD scores, the LEG-NUI score cannot be calculated immediately after the surgery. Instead, it must be calculated within the first 12 wk after surgery.

There are only three parameters that are common between the three scores: open/closed fracture; cortical contact after reduction; and fracture pattern. Bhandari *et al*[21] identified that a set of three simple prognostic variables (open fracture, transverse fracture, and postoperative fracture gap) can assist surgeons in predicting reoperation following surgical

Table 2 Descriptive statistics for scores and age on outcome of nonunion and sex

	Female (*n* = 47)		Male (*n* = 83)		Total
	Nonunion (*n* = 7)	Union (*n* = 40)	Nonunion (*n* = 34)	Union (*n* = 49)	
Age					
Min/Max	32/84	18/86	19/82	18/87	18/87
Med (IQR)	52 (43; 55.5)	54 (42.2; 62)	45 (28.2; 57.8)	45.0 (27; 60)	46.5 (34; 60)
mean ± SD	52.1 ± 16.4	52.5 ± 17.5	44.6 ± 17.9	44.5 ± 20.0	47.4 ± 18.7
FRACTING					
Min/Max	5.0/10	1.0/10.0	5.0/10.0	2.0/9.0	1.0/10.0
Med (IQR)	8.0 (6.0; 9.5)	5.0 (3.0; 7.0)	8.0 (6.0; 9.0)	4.0 (3.0; 7.0)	6.0 (4.0; 8.0)
mean ± SD	7.7 ± 2.1	5.2 ± 2.3	7.8 ± 1.8	5.1 ± 2.2	6.0 ± 2.4
NURD					
Min/Max	0/7.0	0/8.0	1.0/11.0	0/8.0	0/11.0
Med (IQR)	1.0 (1.0; 3.5)	1.0 (1.0; 3.0)	4.5 (3.0; 7.0)	2.0 (1.0; 4.0)	3.0 (1.0; 4.0)
mean ± SD	2.4 ± 2.4	1.8 ± 1.8	4.9 ± 2.8	2.9 ± 2.1	3.1 ± 2.5
LEG-NUI					
Min/Max	1.0/6.0	0/7.0	1.0/6.0	1.0/6.0	0/7.0
Med (IQR)	3.0 (2.0; 4.0)	2.0 (1.0; 3.0)	4.0 (3.2; 5.0)	2.0 (1.0; 3.0)	2.0 (1.0; 4.0)
mean ± SD	3.1 ± 1.7	2.1 ± 1.5	4.1 ± 4.1	2.2 ± 1.2	2.7 ± 1.6

FRACTING: FRACTure prediction healING days; NURD: Nonunion Risk Determination; LEG-NUI: Leeds-Genoa Nonunion Index.

Table 3 Patients grouped by age

Age	Nonunion (%)	Union (%)	Total (%)
18-45	21 (34)	41 (66)	62 (48)
46-60	13 (35)	24 (65)	37 (28)
> 60	7 (23)	24 (77)	31 (24)

Table 4 Nonunion risk determination confusion matrix

	Union	Nonunion	Total
Predicted union	89	37	126
Predicted nonunion	0	4	4
Total	89	41	130

Table 5 Tibia FRACTure prediction healING days confusion matrix

	Union	Nonunion	Total
Predicted union	77	15	92
Predicted nonunion	12	26	38
Total	89	41	130

Table 6 Leeds-Genoa Nonunion Index confusion matrix

	Union	Nonunion	Total
Predicted union	81	17	98
Predicted nonunion	8	24	32
Total	89	41	130

Table 7 Score evaluation performance metrics

Score	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	F-measure (%)
FRACTING	63.41	86.52	68.42	83.70	67.00
NURD	14.63	96.63	/	70	18
LEG-NUI	58.54	91.07	75.31	83.27	58.06

FRACTING: FRACTure prediction healING days; NURD: Nonunion Risk Determination; LEG-NUI: Leeds-Genoa Nonunion Index.

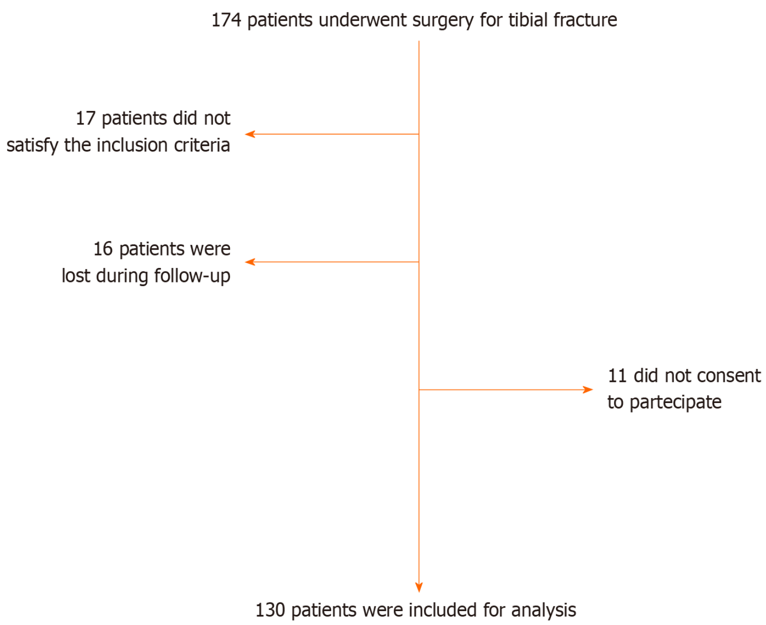

Figure 1 Case selection flow chart.

treatment of tibial shaft fractures. The presence of a large fracture gap and lack of cortical continuity after reduction has been postulated as the best risk factors of delayed healing and nonunion[22]. For example, while developing the NURD score, the authors excluded fractures that have 0% cortical contact because the attending surgeon was already anticipating nonunion[9]. This might affect the power of this score to predict nonunion.

The vascular anatomy and blood supply of the fracture affects fracture healing. Santolini *et al*[23] divided the femur and tibial shaft into three zones, defined as zones of high, moderate, and poor vascularization. They argued that the tibial shaft vascularization is divisible into sections of thirds. The upper third has a high degree of vascularization, the middle third has a moderate degree of vascularization, and the lower third has a poor degree of vascularization. Among the three scores, only the FRACTING score accounted for the location of the fracture.

Deep or superficial infections are significantly associated with tibial nonunion[24,25]. The LEG-NUI score is the only score to account for infections. However, infections may not be present immediately after surgical treatment when the FRACTING and NURD scores are calculated. It should be noted that the developers of the NURD score have also proposed a nonunion prediction score at 6 wk after surgery that does include infection[26].

Our results indicated that male sex is a nonunion risk factor. In addition, the literature also shows that male sex is a risk factor[4], possible due to more males suffering high-energy trauma during sporting activities[27,28]. In a recent systematic review, 11 studies were analyzed for determining the role of male sex as a risk factor[29]. Moreover, male sex seems to increase nonunion risk in fractures unrelated to trauma, such as proximal interphalangeal joint arthrodesis[30].

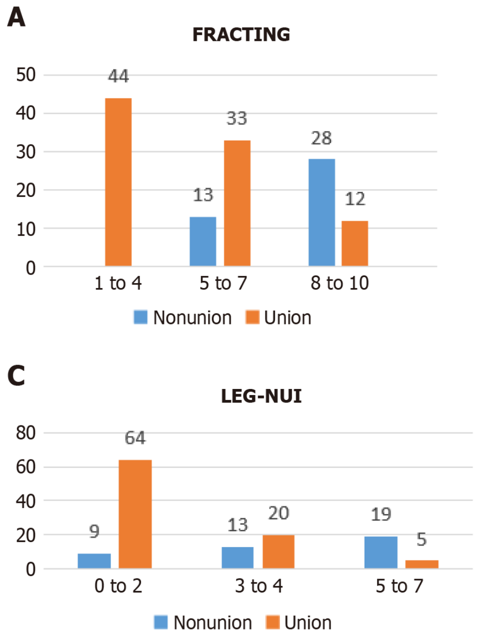

Figure 2 Histograms of score distribution. A: Scores for Tibia FRACTure prediction healING days; B: Scores for Nonunion Risk Determination; C: Scores for Leeds-Genoa Nonunion Index. FRACTING: FRACTure prediction healING days; NURD: Nonunion Risk Determination; LEG-NUI: Leeds-Genoa Nonunion Index.

Increased age is another risk factor affecting fracture healing, although in our patient cohort older age does not increase the risk of nonunion. Many studies have demonstrated the effect of age on delayed union or nonunion[31-36]. It is believed that increased age is a risk factor because of poor bone stock as well as incompliance with postoperative instructions about weight bearing[37].

Smoking is also associated with nonunion in several studies[38-40]. Only the FRACTING score accounts for smoking. The studies that developed NURD and LEG-NUI did not find a statistical significance in the relationship between smoking and fracture healing. Some drugs can affect fracture healing, including NSAIDs[41,42], corticosteroids[43,44], anticoagulants[45], and anticonvulsants[46]. Again, only the FRACTING score accounts for NSAID use. The LEG-NUI study had removed this parameter because NSAIDs were no longer given as postoperative analgesia.

Chloros *et al*[47] analyzed and compared scores for early prediction of tibial fracture nonunion. They included the Tibial Fracture Healing score as well. They demonstrated that the LEG-NUI score was associated with better accuracy and reliability. We demonstrated that the NURD score showed the worst accuracy, and the FRACTING and LEG-NUI scores showed the same accuracy (79.2%). The FRACTING score showed better positive predictive value (83.7%) and specificity (86.5%), while the LEG-NUI score showed better negative predictive value (85.3%) and sensitivity (68.3%). The diagnostic accuracy demonstrated greater accuracy by the FRACTING score in low score values, which could be explained by the wider range score and that nail fixation naturally has a low score (the FRACTING score assigns 3 points for external fixation, 2 point for plate and screw, and 1 point for nailing).

The limitations of our study included the retrospective and the multicentric nature. When a multicenter study is conducted, especially in the surgical field, it is easy to have bias related to the surgeon's experience, surgical technique, postoperative treatment, and definition of healing. For example, there is no consensus for the use of skeletal traction while waiting for surgery and allowing full or partial weight bearing after the surgery[48,49]. In addition, none of the scores consider this factor. Radiographic healing of the fracture was determined by the investigator based on clinician experience, clinical well-being, and evidence of 3 out of 4 welded cortices. Moreover, there is no objective radiographic scoring to ensure fracture healing.

There are several variables that prevent the standardization of leg fracture surgery including intramedullary canal reaming[50], fibular osteotomy vs fibular fixation vs no touch fibular fracture focus[51], the use of a poller screw, and the time of wound closure. The use of local prophylactic antibiotics[52], like antibiotic-coated nails[53], in open fractures could be a solution to prevent septic nonunion. Therefore, any intraoperative or postoperative treatments (like biophysical stimulation with pulsed electromagnetic fields) that promote bone healing should be used[54].

CONCLUSION

Our multicenter study compared the value of three scores predicting tibial shaft fracture nonunion. The FRACTING and LEG-NUI scores showed the best reliability. For this reason, we recommend the use of these predictive scores in clinical practice because they can help guide the surgical approach and choice of adjuvant therapy (ultrasound, pulsed electromagnetic fields, coated nails, or application of growth factor). Moreover, the awareness of nonunion risk could be reported to the patient and be included in the informed consent, protecting the surgeon in the treatment pathway.

FOOTNOTES

Author contributions: Gigante AP and Quarta D designed the study; Quarta D, Lattanzi G, and Grassi M collected the patients' clinical data; Quarta D and Grassi M analyzed the data; Quarta D wrote the paper; Potena D and D'Anca A contributed to the statistical analysis; all authors read and approved the final manuscript.

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