*Acta Orthop. Belg.*, 2020, **86**, 313-319

ORIGINAL STUDY

# Can infection be predicted after intramedullary nailing of tibial shaft fractures?

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**Despite the progress in tibial fracture care, some patients contract infection following intramedullary nailing. We analyzed which risk factors could predict infection in 171 tibial fractures. The independent variables included age, gender, body mass index, and comorbidities, along with external factors of fracture pattern, nailing settings, and treatment processing time. A multiple logistic regression was used to identify infection risk factors.**

**The risk of infection significantly increased according to the open grading, the fractures' classification, time until antibiotic administration, and time until nailing. Gustilo type I fractures presented a higher rate of infection than expected, explained by a longer delay before surgery. The probabilistic equation allows infection prediction with high sensitivity and specificity. In total, we showed that no antibiotics' prescription in emergency service and a transverse fracture pattern were predictors of infection. An infection risk score can be computed, aiding surgeons in decision making. Outcomes could improve keeping these observations in mind.**

**Level of evidence:** Retrospective cohort study. Level iii.

**Keywords :** Infection ; intramedullary nailing ; risk factor ; tibial fracture.

## INTRODUCTION

In open long-bone fractures, because of its limited soft-tissue coverage and high energy pattern, the tibia is the most frequently affected site in numerous trauma events (44%) *(24)*. These fractures are more exposed to external germs, increasing the risk of infection, and their management proves more complex *(13)*. Infections occur in 1-30% of cases, depending on Gustilo classification *(24,29,31)*. A deep infection likely increases hospitalization duration, doubles the re-admission rate, and impairs the physical capacities and quality of life of patients *(3)*. Infection increases costs for both patients and healthcare by 2 to 20 times *(2)*.

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*Conflict of interest: All authors declare that they have not received any funding or other benefits in support of this study. No relevant financial relationships to disclose.*

Identifying risk factors able to predict infection can help develop a preventive approach. Infection risk scores (IRS) can be created using predictors so as to identify which patients require closer attention. The National Nosocomial Infections Surveillance (NNIS) System and the Study on the Efficacy of Nosocomial Infection Control (SENIC) scores were shown not to be useful in predicting the risk of infection following fracture fixation *(25)*. The time elapsed since the accident, type of open fracture according to Gustilo criteria, and type of soft tissue damage according to Tscherne classification were employed to build an IRS for use at a patient's first evaluation for open fracture *(20)*. However, the sensitivity of this IRS proved poor. We thus aimed to identify predictive factors and create a more sensitive and useful IRS for daily practice.

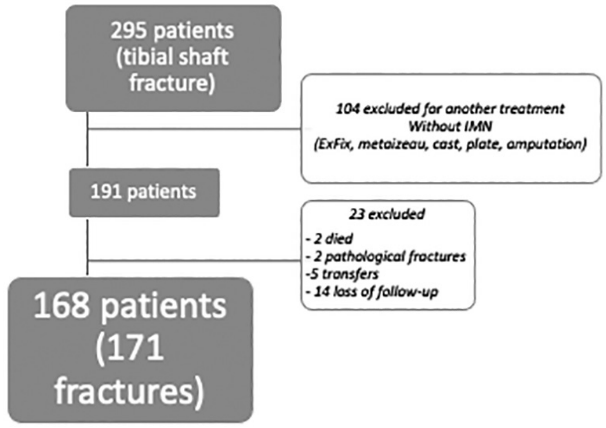


***Figure 1.*** – Flow diagram illustrating patient enrolment and exclusion criteria.

## MATERIAL AND METHODS

The study protocol was approved by the university's ethics committee (reference N° B403201523492). Based on the hospital medical database, 295 patients were selected, each one treated for at least one tibial diaphyseal fracture at the Cliniques Universitaires Saint-Luc in Brussels between 2005 and 2015. All patients were afforded treatment in accordance with good clinical practice guidelines, with standard follow-up performed after each surgery. We excluded 104 patients who underwent another fixation treatment (plate, External Fixation [ExFix], cast etc.) without intramedullary nail (IMN). A total of 191 patients received IMN, of which 23 were likewise excluded due to missing follow-up, transfer to another institution, and pathological fractures or death within two months of the trauma. Finally, 168 patients were selected, three presenting bilateral tibial fractures, resulting in a total of 171 fractures for analysis.

The factors analyzed in this study included both internal and external factors. The former comprised age, gender, body mass index (BMI), and comorbidities like smoking, diabetes, alcohol intake, as well as chronic use of corticosteroids or drug addiction. The external factors were also the pattern and classification of the fracture (AO classification), level of trauma energy, and associated lesions on the same limb. The Gustilo-Anderson classification was likewise employed for open fractures. Trauma energy was classified into two groups: low and high. Low energy was defined as when a patient fell from standing; high energy when a patient was injured in a motor vehicle accident. The external factors were the time between injury and treatment, type of initial treatment, antibiotic (AB) delay (i.e. during emergency admission or in the per-operative period), closed vs. open fracture reduction, type of nailing (nail and reamer diameters, number of screws), and the delay prior to nailing.

Patients were followed up until there was evidence of fracture union and healing. Fracture healing was defined clinically by absence of pain, stable walking pattern, and x-ray of three solid bridging callus ridges connecting the fracture fragments on both the anteroposterior and lateral views *(21)*. Only deep infections were selected. Following CDC guidelines *(16)*, deep infection involves deep tissues, such as fascial and muscle layers; this also includes infection involving both superficial and deep incision sites and organ/space surgical site infection draining through the incision *(21,32)*.

## STATISTICAL ANALYSIS

A descriptive analysis and univariate analysis (odds ratios) was first conducted. Secondly, a multiple logistic regression model was employed to determine the risk factors of infection. The Sigmaplot 13 SPSS software was used. Continuous variables were subdivided into binomial variables (0 or 1) based on median values: 0=inferior, 1=superior or equal to median.

Several variables had to be excluded due to an aberrant standard error or VIF (Variance Inflation Factor) >5 to avoid multicollinearity. All outcomes with p-values <0.05 were considered statistically significant. The risk of infection was computed according to the set of variables, with an IRS established. We further determined the sensibility/specificity, the area under the receiver operating characteristics (ROC) curve, and the IRS cut-off.

## RESULTS

The mean age of the population was 45.6 years old (14-95 years). In total, 61.4% (105/171) of the fractures were observed in men, and 67.3% (115/171) were closed fractures. Comorbidities are summarized in table I.

Table I. – Prevalence of comorbidities

| Comorbidity | Prevalence (%) |
|---|---|
| Smokers | 23.4 |
| Daily alcohol consumers | 12.3 |
| Diabetics | 5.3 |
| Drug addicts | 5.3 |
| Chronic corticotherapy | 2.9 |

Initial stabilization was performed in 80.7% (138/171) by IMN, in 5.8% (10/171) by cast, and in 13.5% (23/171) by external fixation. The final osteosynthesis by IMN was performed within one day following the trauma in 78%.

In our population, the infection rate was 7.6% (13/171), with its incidence according to the Gustilo classification presented in table II.

The delay until nailing was assessed for each Gustilo classification grade using univariate analysis (odds ratios). The rate of infection did not significantly differ when the IMN was delayed for open fractures, which were primarily fixed with an ExFix. It should also be noted that the rate of infection proved higher when IMN was delayed in closed fractures.

Table II. – Prevalence of comorbidities

| Gustilo classification | Incidence of infection (%) |
|---|---|
| 0 (closed fracture) | 3 |
| I | 15 |
| II | 18 |
| III | 20 |

Factors that were significant upon multiple logistic regression analysis and their respective odds ratios are presented in table III, with the multiple logistic regression shown in equation, as follows (eq 1):

The risk of infection was shown to be significantly increased in cases involving open fracture, transversal fracture, long delay before nailing (after the first 24 hours), and absence of antibiotic prophylaxis during emergency admission. This IRS had a sensitivity of 0.92 and specificity of 0.91, with a cut-off of -1.27 logits and an area under the curve of 0.932 (Figure 2)..

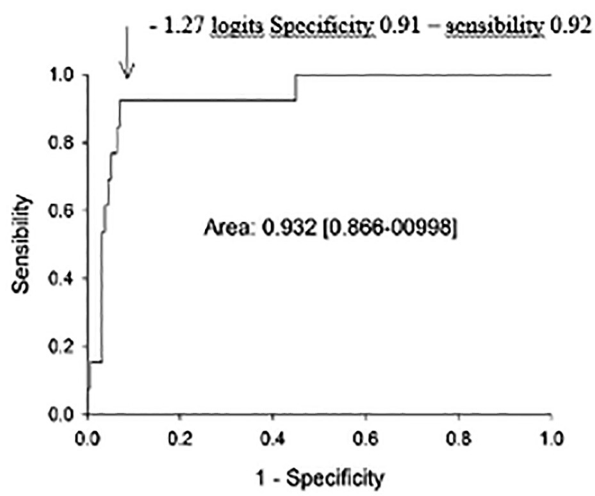


***Figure 2.*** – Phase diagram illustrating specificity vs. sensibility of infection risk score (IRS) results.
The variable to test was the equation results (in logits) for each patient and the state variable was dichotomous state 1=infected vs. 0 not infected. The ROC curve was also calculated.

The frequency histogram in figure 3 illustrates the position of all patients, with infection cases compared to the infection cut-off.

Table III. – Prevalence of comorbidities

| Variables | Odds ratio estimates (95% CI) | p-value |
|---|---|---|
| Open fracture | 102.4 (3.9-2639.7) | 0.005 |
| Class. AO (Transversal) | 65.2 (1.0-4071.3) | 0.048 |
| IMN delay (≥ 24H) | 40.3 (1.9-820.3) | 0.016 |
| AB delay (later than emergency room) | 11.3 (1.1-116.1) | 0.041 |

## DISCUSSION

Our results enabled us to extrapolate IRS prediction to any tibial fracture treated with IMN. Given that this formula includes more factors, it results in increased sensitivity and specificity. The main predictive factors were open fracture, fracture pattern according to AO classification reflecting the energy needed to create the fracture, delay before IMN management, and antibiotic prophylaxis not prescribed during emergency admission. Diabetes and drug addiction were the worst comorbidities in this model.

Open fractures were shown to be significantly associated with infection *(8,11,17,21,31)*. All surgeons expectedly assume Gustilo type of fractures to be associated with the risk of infection *(10,11,21,24,32)*. Thakore et al. (2016) demonstrated that the higher the Gustilo grade was, the more complications (infections or non-unions) occurred *(29)*. However, this is in contradiction with our results that show more infections than expected in Gustilo I fractures (15%), as compared to the results in previous studies (2-9% *(14,18,29)*). The patients in this group had their initial surgery after longer delays (10.9 hours on average) than Gustilo II or III patients (5.03 and 1.9 hours respectively), similar to the delays in closed fracture cases (12.6 hours), which may potentially account for the increased infection rate. The Gustilo classification grade can be revised after surgical debridement, and the classification of the fracture may be biased from the beginning of treatment. Some Gustilo II fractures can thus be wrongly classified as Gustilo I fractures, leading to underestimation. It proves crucial to re-evaluate the severity of the lesion *(30)* in order to design an appropriate treatment corresponding to the fracture severity.

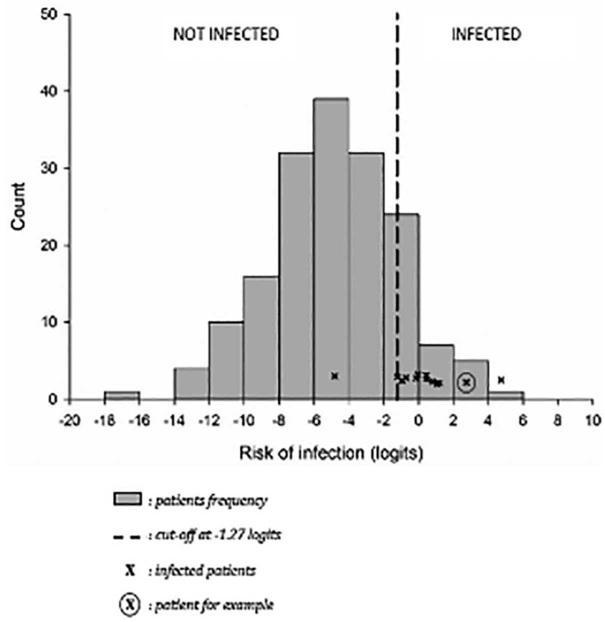


***Figure 3.*** – Frequency histogram of patients compared to infection cut-off.
For example, one of our infected patients was a 67-year-old man with a BMI of 23.7 exhibiting no comorbidity. He suffered an open tibial fracture (Gustilo I, Class. AO. 42 – C2) falling from standing. He received AB upon admission to the emergency room, and the wound was debrided and sutured. The patient was secondarily referred to our center within 96 hours. The injury was initially stabilized with an ExFix. The final osteosynthesis by IMN was performed 16 days post-trauma. The formula applied to this case was: "Logit P = -7,398 - (3.348 * 1 (age >45y)) + (1.124 * 0 (BMI <25)) - (0.819 * 1 (male gender)) - (2.147 * 0 (no tobacco)) + (3.731 * 0 (no diabetes)) + (1.770 * 0 (no alcohol)) + (0.199 * 0 (no corticosteroid use)) + (4.028 * 0 (no drug addiction)) + (4.629 * 1 (open fracture)) - (2.288 * 0 (no Gustilo Type >I)) + (0.792 * 1 (class. AO Type >A)) + (4.178 * 1 (Class. AO Group >1)) - (4.511 * 0 (low energy trauma)) + (1.015 * 1 (ExFix first)) - (0.599 * 0 (no fasciotomy)) + (2.426 * 0 (direct AB)) + (3.699 * 1 (IMN delay ≥24h)) + (1.516 * 0 (no open reduction))". The IRS score was thus 2.748 logits, beyond the cut-off value. We could have predicted beforehand that his infection risk was high. The circle indicates the injury location on the frequency histogram.

While several studies have previously assessed the time delay prior to nailing, they were not associated with definitive conclusions *(14,18)*. When considering all types of fractures, nailing within the first 24 hours resulted in better outcomes in our study and nailing after 24 hours significantly increased the infection risk, yet solely for closed fractures. Long delays before nailing (more than 24 hours) were reported by Metsemakers et al. as being predictive of infection *(21)*. Our sample has been similar to theirs, with 67% closed fractures. In their study, an ExFix before IMN was the only variable that significantly predicted infections on multivariate analysis. This was not observed in our study. A damage control strategy consisting first of external fixation and later IMN of the fracture has been found to provide good clinical results when local complications are prevented through proper reduction, firm fixation, early soft-tissue reconstruction, and early rehabilitation *(26).* Implementing IMN quickly following primary treatment of open tibial shaft fractures with ExFix has been reported as a more effective way to manage these fractures, causing less infection than definitive treatment with external fixation alone *(28)*. Although it has been suggested that primary unreamed nailing in open Gustilo IIIB fractures proves more efficacious for maintaining limb alignment while resulting in less infections/inflammatory problems than half-pin external fixators, these results were achieved when optimal debridement and delayed primary closure, skin grafting, and/or myoplasty were performed between three and ten days following injury *(15)*. Yokoyama et al. published their analysis of open fractures, revealing that immediate nailing for Gustilo IIIB and IIIC fractures led to deep infection compared to performing an ExFix first *(31)*. They also reported that performing IMN after external fixation (especially in cases involving pin-site infection) was associated with a high risk of deep infections, and that debridement within 6 hours and appropriate soft-tissue management were both important determinants in preventing deep infections. The benefit of maintaining external fixation for shorter times for infection prevention has previously been reported *(5)*.

Previous studies evaluated the benefit of antibiotic prophylaxis. According to Young et al. (2013), prophylactic antibiotics for long-bone fracture nailing reduced the risk of infection by 29% *(33)*. No evidence was reported, however, regarding whether patients with closed fractures had no other risk factors for deep infection *(4)*. Several reports discussed antibiotic protocols and their efficacy. In our study, commencing antibiotic prophylaxis as soon as the patient was admitted to the emergency room significantly prevented infection. Patzakis and Wilkins reported an infection rate of 4.7% when antibiotics were administered within 3 hours of injury, compared to 7.4% when the treatment was delayed for more than 3 hours, although significance was not mentioned *(27)*. We thus agree with the Gosselin et al. recommendation according to which antibiotics should be administered as soon as possible in open fractures *(12)* but also in closed fractures.

In our study, transverse fractures (fractures classified in AO classification Group 2 or 3) were more prone to infections. As the energy needed to provoke this fracture pattern is higher, this most probably increases secondary soft-tissue damage *(9)*. While open fractures often receive closer attention from surgeons, closed fractures with soft-tissue damage classified as Tscherne II or III were, however, likewise associated with an increased infection risk *(20)*.

In our study, current smokers were not shown to be at high risk on multivariate model. This is not in line with the scientific literature, which reports active smokers to be more than twice as likely to develop an infection and osteomyelitis, with previous smokers being equally and similarly at risk *(7)*. In a meta-analysis involving the last 30 years of scientific literature on open tibial fractures, Kortram et al. identified smoking as a statistically-significant risk factor for infectious complications *(19)*. Nevertheless, there is still debate surrounding this issue, as all factors should be tested for independence in a multivariable model and prospective studies.

Our study had some limitations. Comparing different authors can prove difficult, and care must thus be taken before drawing definite conclusions, as 70% of them did not provide any valid definitions of complications in their articles *(22)*. In addition, although some variables had to be excluded from multiple analyses due to aberrant or wrong outcomes, we cannot be sure that these variables were without impact. Finally, some of the subgroups were small sample-sized.

Our study strength included the high number of criteria taken into account in the multivariate analysis. Only few studies had carried out multivariate analysis in this field, and their depth of the investigations was limited due to a small variable set. For example, only few studies took into account the confounding effects of patient comorbidities. Nevertheless, there is currently substantial evidence indicating that individual factors like obesity, diabetes, tobacco smoking, alcohol consumption, and drug use can influence outcomes *(1,3,6,23)*. In our study, the number of comorbidities prior to trauma was directly associated with the number of complications, including infection. Nevertheless, upon multiple analyses, comorbidities had no individual effect on infection rates. The advantage of this study was that it took into account each patient-dependent factor in addition to those related to both the fracture and surgery performed.

In conclusion, in this research, we developed an infection risk score that proves both sensitive and specific. This could help surgeons to better inform patients and to develop treatment protocols to prevent this complication. Gustilo I fractures should not be overlooked, given that they are prone to delayed treatment and infection. Soft-tissue debridement should be performed early, and the Gustilo classification revised accordingly. All fractures should receive adapted antibiotic prophylaxis upon patient arrival in the emergency room. Transverse fractures are likewise more at risk and must thus receive greater attention. If the fracture is closed, the gold standard consists of performing nailing within the first 24 hours in order to prevent infection. For open fractures, there is still debate regarding the Gustilo grade. External fixation likely performs better for Gustilo Type III fractures, although it should preferably be kept as brief as possible and quickly be replaced by IMN.

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