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Fracture-related infection in Open Long-bone Fractures

A Bicenter Case-control Study in a Limited Resource Country

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Background: Fracture-related infections (FRI) are estimated to complicate approximately 1% of closed fractures and 30% of open fractures globally. These statistics, however, can vary significantly by region, with low-income and middle-income countries experiencing a disproportionately high burden. The studies in these regions are often underpowered to evaluate the local prevalence and contributing factors of FRI. The objectives of this study were (1) to assess the prevalence of FRI in open long-bone injuries and (2) investigate the association between FRI and various risk factors identified in previous research.

Methods: A 5-year age-matched and sex-matched case-control study was conducted at 2 high-volume trauma centers in a limited-resource country. Independent variables included demographics (age and sex), anatomical region, injury mechanism, Gustilo-Anderson grade (GA 2 or higher), smoking status, history of blood transfusion, and timing of antibiotic administration, debridement, and soft tissue coverage. The primary outcome was the presence of FRI, as defined by Metsemakers et al., which required direct observation of pus during surgery or additional confirmatory criteria. Data analysis was conducted using the R package vcd.

Results: Seven hundred six cases were reviewed, showing a 13.2% prevalence of FRI. The 84 infected cases and 168 matched controls were analyzed. Most patients experienced delays in antibiotics (77.4%) and debridement (76.6%) beyond 3 hours and 24 hours, respectively. Multivariate logistic regression revealed statistical significance only for a delay in antibiotic administration exceeding 12 hours ($p = 0.007$), presence of polytrauma ($p = 0.008$), and non-intramedullary nail (IMN) mode of fixation ($p < 0.001$). Delays in debridement (>24 hours), soft tissue coverage (>7 days), and antibiotic administration (3-12 hours) did not show statistically significant associations with an increased risk of infection.

Conclusions: Our study highlights the critical importance of prompt antibiotic administration, especially for high-energy wounds such as polytrauma, in reducing infection risk.

Levels of Evidence: Level III. See Instructions for Authors for a complete description of levels of evidence.

Introduction

Fracture-related infections (FRIs) are estimated to complicate approximately 1% to 30% of fractures worldwide[1]. The incidence varies based on the degree of energy transfer, with closed and Gustilo I types having a lower rate of infection[1]. These statistics, however, vary from region to region, with low-income and middle-income countries (LMICs) bearing a disproportionately high burden[2]. Furthermore, LMICs frequently lack the necessary equipment and personnel to manage FRIs effectively once they occur, resulting in the high prevalence of post-traumatic chronic osteomyelitis[2]. The presence of infection in open fractures has also been shown to increase treatment costs by up to 60%, as noted by Olesen et al., further straining the limited resources available in these regions[3]. Several high-

Disclosure: The **Disclosure of Potential Conflicts of Interest** forms are provided with the online version of the article (http://links.lww.com/JBJSOA/A843).

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quality studies from well-resourced facilities suggest that early administration of antibiotics, timely debridement, and prompt soft tissue coverage can significantly reduce infection rates[4-8]. Patzakis and Wilkins demonstrated that antibiotic administration within 3 hours reduces the risk of infection by almost half[4]. More recently, Lack et al. showed that failure to administer antibiotics within 66 minutes postinjury can increase the odds of infection by a factor of 4[5]. Regarding the time to debridement, Friedrich established the "6-hour rule" after he showed an increased rate of bacteria replication past this mark[9]. Subsequent research, however, has shown that the quality of debridement is more important than the timing, which has extended the recommended optimal time frame up to 24 hours[7]. The GOLIATH meta-analysis of 84 studies showed that debridement within 12 to 24 hours is the critical time threshold beyond which the infection risk is unacceptably high[8]. However, meeting the recommended time frames for these interventions is often challenging in resource-limited settings due to delays in patient presentation and the shortage of operating rooms[10,11]. It is worth noting that studies conducted in these regions are often underpowered, making it difficult to assess the local prevalence, contributing factors, and challenges associated with the prevention and treatment of FRIs[2]. This study explores how these factors influence infection rates in LMIC settings to inform context-specific recommendations. The study's objectives were the following: 1. to measure the prevalence of FRI among open long-bone fractures resulting from moderate to high energy transfer and 2. investigate the strength of association between FRI and several variables that have been shown to increase the risk of infection in previous studies.

Materials and Methods

Study Design

A 5-year age-matched and sex-matched case-control study was conducted at 2 high-volume trauma centers in Addis Ababa, the capital city of Ethiopia. After obtaining ethical approval from both institutions (MF/ORTH/322/2023 and AR/65/2017), we used the Cleveland Clinic Department of Quantitative Health Sciences sample size calculator to determine the sample size, with a significance level of 5% and a power of 80%[12]. The primary exposure variable we considered was a delay to debridement, with a cutoff of greater than 24 hours. This variable resulted in the largest sample size compared with other exposure variables, as shown by previous studies conducted in similar resource-limited settings[13]. According to the reference study, the prevalence of delayed debridement was 96% among infected cases, compared with 87% among noninfected controls[13]. A 1:2 allocation ratio between cases and controls was used due to the limited number of cases. Based on these assumptions, it was determined that a sample size of 279 participants was necessary, which included 93 infected cases and 186 noninfected controls.

The inclusion criteria were open long-bone (femur, tibia, humerus) fractures with Gustilo-Anderson (GA) type II and above. Exclusion criteria included closed or GA I fractures, GA IIIC fractures, fractures infected at the time of presentation, cases with incomplete documentation of study variables, follow-up of less than 6 months, un-united fractures at the time of assessment, and superficial infections that did not require debridement. Closed and GA type I fractures were excluded because the infection rates in this group have been shown to be low[14]. GA IIIC were excluded due to the limited number of cases for meaningful statistical analysis after matching.

The independent variables in the study were patient demographics including age, sex, anatomical region affected, the mechanism of injury, GA type, smoking status, history of transfusion, time to initial antibiotic administration, time to first debridement, time to soft tissue cover, associated nerve injuries, and history of polytrauma (defined as 2 or more injuries, with at least one being life-threatening). The definitive fixation method was classified into 2 main categories: intramedullary nail fixation and nonintramedullary nail fixation, which included only external fixators and nonoperative methods. Internal fixation methods were excluded from the comparison. The time to initial antibiotic was grouped into 3 categories: less than 3 hours, between 3 to 12 hours, and more than 12 hours. This classification is based on a study by Patzakis and Wilkins, which found that a delay of more than 3 hours doubles the risk of infection.[4] The 12-hour upper limit was based on a 2007 study by Al-Arabi et al., which demonstrated that a delay beyond this 12-hour time frame resulted in an infection rate of 100%[15]. The time to first debridement was grouped as less than 24 hours or more than 24 hours, based on the GOLIATH meta-analysis, which showed that a debridement time exceeding 24 hours resulted in an unacceptably high rate of infection[8]. The time to soft tissue coverage was classified into 3 categories: less than 3 days, 3 to 7 days, and more than 7 days based on recommendations from the American College of Surgeons Trauma Quality Improvement Program, which advises achieving a soft tissue coverage within 7 days, and the BOAST 4 guidelines, which recommend coverage within 72 hours[16,17]. The primary outcome examined was the presence or absence of FRI, which was defined according to the criteria established by Metsemakers et al.[18] The documented presence of visible pus during surgery was used to establish the diagnosis as a confirmatory clinical criterion.

A structured questionnaire was used to collect data. To ensure the internal consistency and reliability of the tool, the questionnaire underwent pilot testing with 20 cases, resulting in a Cronbach alpha of 0.71, which was considered acceptable[19]. Data were collected from various sources, including written and electronic medical records, the SIGN intramedullary nail database, elective and emergency surgery logbooks, triage registries, and morning reports. Trained residents gathered this information under the supervision of the first author. Following data collection, the information was reviewed for completeness and consistency, then coded and entered into Microsoft Excel.

Statistical Analysis

To mitigate potential confounders such as age and sex, cardinality matching was performed using the MatchIt package in R. After matching, the balance was evaluated using standardized mean differences (SMD), aiming for an SMD threshold of less

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than 0.1 for age and exact equivalence for sex. The independent variables were organized into 3 categories: patient, injury, and treatment factors. A descriptive analysis was conducted for each variable, by the outcome variable and hospital of admission. Continuous variables were described using medians and interquartile ranges, while categorical variables were expressed in terms of frequencies and proportions. Univariate logistic regression was performed to determine the relationship between all independent variables and the outcome variable, which helped identify candidate variables for the multivariate model. All independent variables with p-values less than 0.25 were included in the multivariate model[20]. To assess multiple collinearity among the independent variables, the variance inflation factor (VIF) was assessed, and the VIF for all candidate variables was found to be below 5. All analyses were performed using R Statistical Software[21]. The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines were used in producing this article[22].

Results

The study analyzed 706 cases of open long-bone fractures. Of these, 50 cases were excluded due to incomplete documentation, and an additional 19 cases were excluded because the fractures were already infected at the time of presentation. The analysis revealed an overall prevalence of FRI of 13.2% among the eligible cohort. Of the 637 cases, infections were distributed across GA types as follows: 9 cases (5% of the eligible cohort) were GA type II, 65 cases (16%) were GA type IIIA, and 10 cases (30%) were GA type IIIB. These 84 infection cases were included for further analysis. For comparison, 168 matched controls were selected from the remaining pool. The median age for the cases was 28 years (IQR = 16), compared with 26 years (IQR = 15) for the controls (Table I). A majority of participants were male, representing 95% (n = 240) of the total patient cohort. The primary causes of injury were gunshot wounds, which accounted for 45% (n = 114) of cases, and road traffic accidents, which made up 39% (n = 97). Overall, the study included 127 femur fractures (51%), 119 tibia fractures (47%), and 6 humerus fractures (0.02%). The distribution of cases varied by hospital, with BLH treating 80% (n = 101) of the femur fractures and ALERT managing 66% (n = 79) of the tibia fractures. Only 14% (n = 21) of the patients from Black Lion Hospital and 34% (n = 36) of patients from ALERT Hospital received their initial antibiotics within 3 hours (Fig. 1). Twenty-three percent (n = 34) of patients from Black Lion Hospital and 24% (n = 34) of patients from ALERT Hospital had their first debridement done within the first 24 hours (Fig. 2). Sixty-eight percent (n = 99) of the patients from Black Lion Hospital and 88% (n = 93) from ALERT Hospital had soft tissue coverage within 7 days (Fig. 3).

The infection rates were higher for gunshot wounds compared with road traffic accidents when debridement was delayed by more than 24 hours, with rates of 42.3% for gunshot wounds and 36.9% for road traffic accidents. When examining treatment methods, it was found that intramedullary nails had the lowest infection rate at 15.3%, while non-IMN methods exhibited a higher infection rate at 75% (Table II). Infection rates across other variables, including anatomical site, transfusion status, polytrauma, smoking history, associated nerve injury, and comorbidities, are summarized in Tables I and II

TABLE I Infection Rates By Patient and Injury Factors

Variables	FRI	
	No N = 168*	Yes N = 84*
Age	28 (22, 38)	26 (22, 37)
Sex (%)		
M	160 (95)	80 (95)
F	8 (4.8)	4 (4.8)
Anatomical region (%)		
Femur	80 (48)	47 (56)
Tibia	85 (51)	34 (40)
Humerus	3 (1.8)	3 (3.6)
GA classification (%)		
II	69 (41)	9 (11)
IIIA	96 (57)	65 (77)
IIIB	3 (1.8)	10 (12)
Polytrauma	20 (12)	21 (25)
Associated nerve injury	7 (4.2)	4 (4.8)
Smoker	5 (3.0%)	4 (4.8%)
Comorbidities (DM/HIV)	0 (0%)	5 (5.9%)

FRI = fracture-related infection. *Median (Q1, Q3); n (%)

Univariate logistic regression showed that a higher GA grade ($p < 0.001$), antibiotic delay >12 hours ($p < 0.001$), debridement delay >24 hours ($p < 0.001$), soft tissue coverage >7 days ($p < 0.001$), non-IMN mode of fixation ($p < 0.001$), presence of polytrauma ($p = 0.009$), and history of blood transfusion ($p = 0.017$) are significantly associated with the presence of infection (Table III). The mode of injury, additional nerve injury, and smoking status were not found to be statistically significant. On the multivariate logistic regression, delay of antibiotics >12 hours (aOR = 4.92, 95% CI 1.63-16.9; $p = 0.007$), presence of polytrauma (aOR = 3.84, 95% CI 1.44-10.5; $p = 0.008$), and non-IMN mode of fixation (aOR = 13.2, 95% CI 6.17-30.4; $p < 0.001$) showed statistical significance (Table III). Delays in debridement >24 hours ($p = 0.09$), soft tissue coverage >7 days ($p = 0.06$), and antibiotic delays 3 to 12 hours ($p = 0.8$) did not show statistical significance. Post hoc logistic regression comparing delays in antibiotic delivery <3 hours versus ≥3 hours (collapsing 3-12 and >12-hour groups) revealed no statistically significant association with infection risk (aOR = 2.61, 95% CI 0.94-8.14; $p = 0.078$).

Discussion

The prevalence of infection in this study was 13.2%, which aligns with global statistical estimates. A recent meta-analysis of 13 randomized trials for open tibia fractures has

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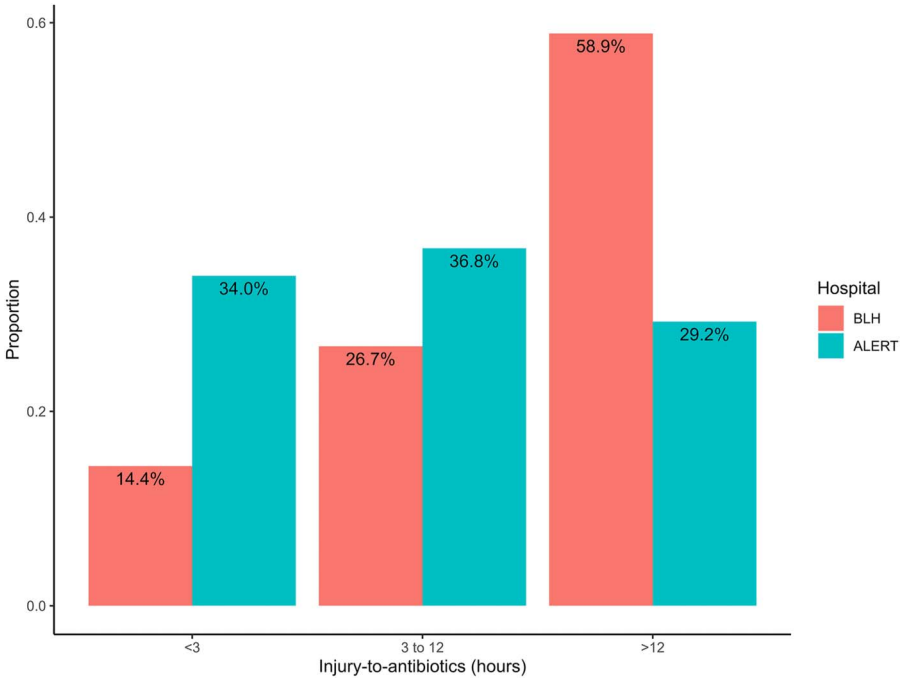


Fig. 1

Proportion of patients receiving timely antibiotic administration within recommended time frames, stratified by hospital.

shown an infection rate of 12.2%.[23] When examining infection rates by GA type, the findings of this study closely align with those of Thakore et al., which reported rates of 8% for GA type II, 14% for GA type IIIA, and 30% for GA type IIIB[24]. Nevertheless, the infection rates observed across all types in this study were higher than the pooled estimates presented by Papakostidis et al., which showed rates of 3.3% for GA type II, 5% for GA type IIIA, and 12.3% for GA type IIIB[14]. Furthermore, the

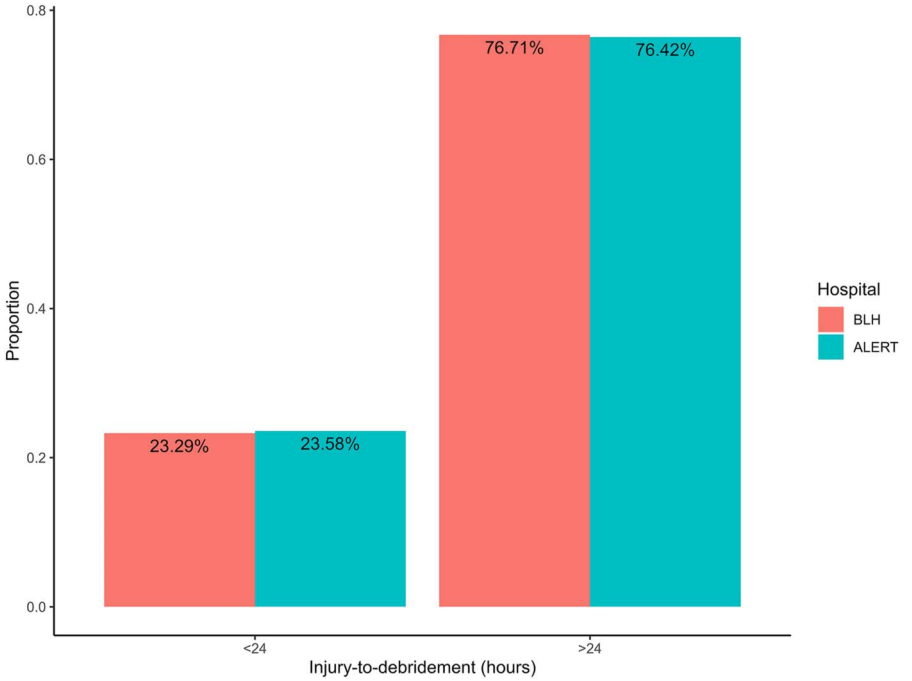


Fig. 2

Proportion of patients receiving timely debridement within recommended time frames, stratified by hospital.

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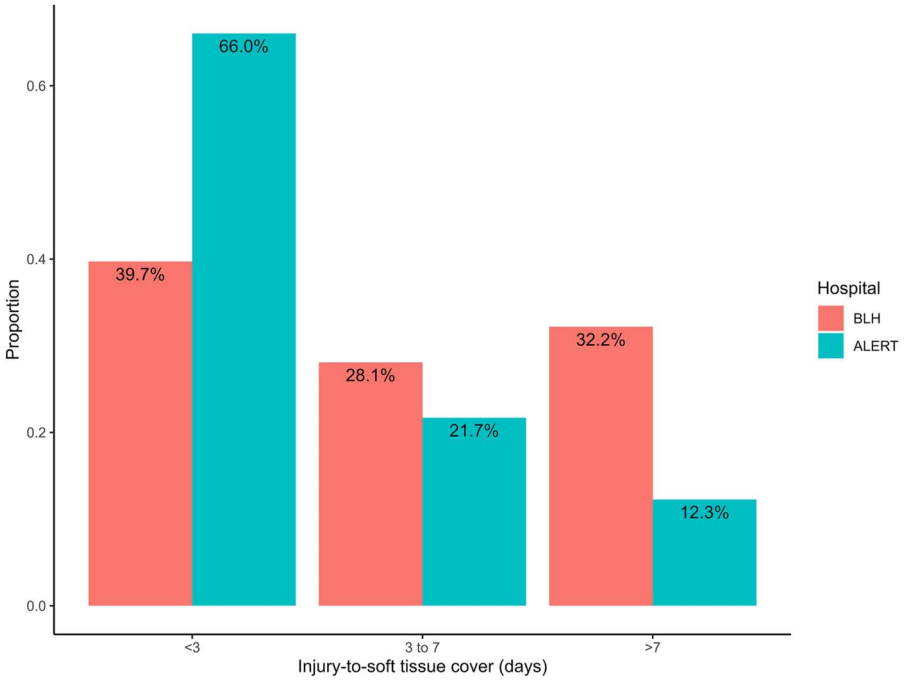


Fig. 3

Proportion of patients receiving timely soft tissue coverage within recommended time frames, stratified by hospital.

results of this study showed that the early initiation of antibiotics is linked with a lower risk of infection. Particularly, a delay of more than 12 hours after an injury increased the odds of developing an infection by 5-fold (OR 4.92, P = 0.007). It is worth noting that the odds of infection associated with a delay of 3 to 12 hours were not statistically significant (p = 0.8). This lack of association was also observed in a post hoc analysis that combined the 3 to 12 hour and > 12-hour groups into a single category of more than 3 hours (aOR = 2.61, p = 0.078). This suggests that the increased risk observed with delays of more than 12 hours may be diluted when aggregated with shorter delays. While our study highlights a disproportionate risk with extreme delays (>12 hours), we emphasize that antibiotics should ideally be administered during the initial contact with the patient, and unnecessary delays should be avoided whenever possible. Regarding time to debridement, after adjusting for covariates (GA type, choice of definitive fixation, polytrauma status, time to antibiotics and soft tissue coverage), no statistically significant association was observed between delayed debridement (>24 hours) and an increased risk of infection (p = 0.09). This is in line with the findings of Mener et al. (2020) and Heckmann et al. (2022), where prolonged time to debridement was not associated with increased infection rates[25,26]. Higher GA types, which may provide insight into the extent of energy transfer, did not demonstrate a statistically significant association with elevated infection rates in the multivariate regression analysis. This finding is in contrast to findings by Wilkinson et al. (2023), which identified Gustilo IIIB or IIIC fractures as the strongest predictor of deep infection (OR 11.8, p < 0.001)[27]. Furthermore, this study showed a significant association between nonintramedullary fixation methods and increased infection rates, with an odds ratio of 13.2 (p < 0.001). The higher incidence of infections associated with the use of external fixators as a definitive fixation choice is supported by

TABLE II Infection Rates By Treatment Factors

Variables	FRI	
	No N = 168*	Yes N = 84*
Injury-to-antibiotic (hours) (%)		
<3	50 (88)	7 (12)
3 to 12	64 (82)	14 (18)
>12	54 (46)	63 (54)
Injury-to-debridement (hours) (%)		
<24	51 (86)	8 (14)
>24	117 (61)	76 (39)
Injury-to-soft tissue cover (days) (%)		
<3	100 (78)	28 (22)
3 to 7	44 (69)	20 (31)
>7	24 (40)	36 (60)
Definitive fixation (%)		
IMN	149 (85)	27 (15)
Non-IMN	19 (25)	57 (75)
Transfusion history	10 (43)	13 (57)

IMN = intramedullary nail, FRI = fracture-related infection. *n (%).

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TABLE III Univariate and Multivariate Logistic Regression Analysis of Factors Associated With Infection

		Unadjusted			Adjusted		
Variables	N	OR*	95% CI*	p	OR*	95% CI*	p
GA classification	252						
II		—	—		—	—	
IIIA		5.19	2.53-11.8	**<0.001**	1.27	0.47-3.56	0.641
IIIB		25.6	6.51-132	**<0.001**	3.71	0.52-32.8	0.211
Injury-to-antibiotics (hours)	252						
<3		—	—		—	—	
3 to 12		1.56	0.60-4.39	0.372	1.16	0.35-4.13	0.807
>12		8.33	3.69-21.5	**<0.001**	4.92	1.63-16.9	**0.007**
Injury-to-debridement (hours)	252						
<24		—	—		—	—	
>24		4.14	1.96-9.87	**<0.001**	2.90	0.89-10.5	0.088
Injury-to-soft tissue cover (days)	252						
<3		—	—		—	—	
3 to 7		1.62	0.82-3.18	0.159	0.86	0.31-2.34	0.772
>7		5.36	2.78-10.6	**<0.001**	2.67	0.95-7.66	0.064
Transfusion history	252						
No		—	—		—	—	
Yes		2.89	1.22-7.08	**0.017**	0.98	0.28-3.46	0.970
Polytrauma	252						
No		—	—		—	—	
Yes		2.47	1.25-4.90	**0.009**	3.84	1.44-10.5	**0.008**
Definitive fixation	252						
IMN		—	—		—	—	
Non-IMN		16.6	8.71-32.8	**<0.001**	13.2	6.17-30.4	**<0.001**

*IMN = intramedullary nail, OR = odds ratio, and CI = confidence interval.
Bold entries indicate statistical significance at $p < 0.05$.

the research conducted by Tesso et al. (2024), which documented an infection rate of 42%[13]. Finally, in contrast to the delay to antibiotics and debridement, most of the patients at both institutions had a soft tissue cover within the recommended time frame of 7 days. This study found that a delay beyond this time showed a 3-fold increase in the odds of infection (OR 2.67, $p = 0.064$); however, the finding was not statistically significant. UK literature, including the BOAST4 guidelines, stresses early intervention, advocating soft tissue reconstruction within 72 hours[17]. Earlier studies have also shown an association between blood transfusion during surgery and an increased risk of infection. A meta-analysis by Teng et al. (2015) showed that restrictive blood transfusion strategies were associated with a 35% decrease in infection risk.[28] Our multivariate analysis, adjusted for confounders, revealed that the association between transfusions, and infection risk was not statistically significant ($p = 0.97$). A systematic review and meta-analysis by Kortram et al. (2017) showed an increased risk of infection in polytrauma patients (RR 1.49, $p = 0.03$)[29]. This finding aligns with our study, which demonstrated that the presence of polytrauma raises the infection risk nearly 4-fold (OR 3.84, $p = 0.008$). Diabetes and HIV were assessed, however, were found to be insufficient for analysis, as the majority of the patients were young adults with no comorbidities.

In conclusion, this study supports previous works on FRI. Despite the broader safety time ranges in our findings, we underscore the critical importance of early antibiotics administration, early debridement, and timely soft tissue cover. The limitation of the study lies in its retrospective design, which may introduce potential selection bias. Another limitation is that the study involved only 2 centers, which may limit the generalizability of the findings. We also used the GA classification as it was the one referenced in the charts we examined. However, this system has only moderate reliability, as indicated by Horn and Retting[30]. We recommend that future prospective studies adopt the OTA Open Fracture Classification (OTA-OFC), which is more comprehensive and demonstrates moderate to good interobserver agreement.[31] ■

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