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Prior use of antibiotics and immunosuppression are risk factors for fracture-related infection during the COVID-19 pandemic period: a Brazilian prospective cohort study

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Abstract

Background: Little is known about the role of COVID-19 pandemic period on the epidemiology of fracture-related infection (FRI). The present study summarizes the changes in the prevalence, microbiology, and risk factors of FRI during this period.

Methods: A prospective single-center cohort study assessed in the setting of COVID-19 pandemic (2020–2021), clinical, microbiological aspects, and independent risk factors (RF) of FRI. RFs were estimated by bivariate and multivariable analyses using prevalence ratio (PR) with significance at $P < 0.05$. Kaplan–Meier analysis was performed to evaluate treatment outcomes.

Results: Overall, 132 patients were analyzed, with patients with age over 65 years accounting 65.1%. FRI was diagnosed in 21 (15.9%) patients. Independent RFs for FRI were recent and preoperative use of systemic antibiotics (PR: 7.0, 95% confidence interval (95% CI): 2.2 – 22.4, $p = 0.001$) and cancer (PR: 9.8, 95% CI: 2.0 – 48.8, $p = 0.005$). Cultures yielded Gram-negative bacteria in 77.8%, 33.3% were MDR.

Conclusions: We found higher rates of FRI, predominating in the elderly with closed femoral fractures during the COVID-19 pandemic. Prior use of antibiotics and immunosuppression conditions were independent factor for FRI. Our outcomes provide evidence to avoid the empirical use of antibiotics prior to surgery for fracture stabilization.

Keywords: Fracture-related infection, Elderly, COVID-19 pandemic, Risk factors, Gram-negative bacteria, Multidrug-resistance, Prior use of antibiotic, Cancer

Introduction

Fracture-related infection (FRI) remains one of the main concerns among victims of orthopedic trauma due to the higher frequency of unfavorable outcome, especially among patients with open fractures and extensive soft tissue injuries [1, 2]. The infection rate after open reduction and internal fixation (ORIF) ranges from 0.4 to 16.1%, in open fractures, but it may be higher depending

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on many factors including the degree tissue damage and contamination, and patient's underlying chronic medical condition [3]. Recent studies show that the average cost per FRI-patient can reach US\$108,000 dollars, with a cure rate ranging between 70 and 90% [4].

In the context of the COVID-19 pandemic period, surgical procedures for orthopedic fractures stabilization turned out to be a challenge to accomplish. Due to the overwhelming need to treat SARS-CoV-2 virus severe cases and the consequent readjustment of hospitalization flows, surgeries for open and closed fractures stabilization were frequently postponed, usually prolonging the length of hospital stay [5]. Moreover, with the social mobility lockdown during this period of time, there seems to have been a decrease in road traffic accidents and the consequent increase in domestic trauma, such as hip and femur closed fractures in the elderly [6]. Additionally, it is known that SARS-CoV-2 virus infection triggers a pro-inflammatory cytokines storm that in conjunction with the inflammatory process following bone fractures, is likely to influence the morbidity and mortality among these patients [7]. This risk could be mitigated among those undergoing elective surgeries in which a minimum period of 6 weeks was recommended between the COVID-19 diagnosis to the surgical procedure [8]. Nevertheless, for patients undergoing fracture correction in emergencies, co-infection with SARS-CoV-2 virus may be difficult to be ruled out and prevent [9].

Despite the well-known poor outcome of infection following orthopedic fractures on the quality of life of individuals and the higher impact on the socioeconomic status of public or private health care systems, the role of COVID-19 pandemic period (2020–2021) on the epidemiology and management of FRI has yet to be well understood [10]. Therefore, the present study aims at describing the changing epidemiology of patients treated for closed and open fracture stabilization during the SARS-COV-2 pandemic period, the FRI rates with at least one-year of follow up, the microbiological profile and to analyze independent risk factors for FRI.

Materials and methods

Study design

This is a prospective observational single-center cohort study conducted during the 2020–2021 COVID-19 pandemic (March 2020 to March 2021), carried out at a specialized orthopedic trauma center in São Paulo/Brazil, among patients undergoing any surgical treatment of open and closed fractures, in which the diagnosis of FRI had been performed. The primary purpose was to assess in the setting of COVID-19 pandemic period, the outcome of patients treated for fracture stabilization, including the prevalence of fracture-related infection

(FRI), the microbiological epidemiology and to analyze independent risk factors for FRI. The study was previously approved, with the waiver of the free and informed consent form, by the Ethics and Research Committee of the Federal University of São Paulo (UNIFESP) under the number: 0846P/2021.

Inclusion criteria were patients aged 18 years old or over, trauma victims with open and/or closed fractures who underwent any type of surgery for bone fracture stabilization using plate and screw, intramedullary nail (IMN) and Kirschner wires. Patients undergoing arthroplasties or spine instrumentation, severe cases likely to progressed to death within the first 7 days of hospitalization, and patients unable to undergo outpatient follow-up during the study period, and those who did not undergo any type of surgical intervention were excluded. Fracture-related infection (FRI) was defined according to criteria published by Metsemakers et al. [11]. Multidrug-resistant microorganism (MDR) was defined as the non-susceptibility of the identified pathogen to at least one antimicrobial agent from 3 or more different antimicrobial classes [12, 13].

Data collection and variables analyzed

Data were prospectively collected and recorded in data collection forms by the specialists in the musculoskeletal infection group (ECS, SP) based on information from electronic medical records filled out during hospitalization and outpatient follow-up for up to one year after index surgery. The variables were divided as follows: variables related to the patient (1), related to the surgical and perioperative procedure (2). The variables related to the patient were (1): demographics, comorbidities, alcoholism, smoking, ASA (American Society of Anesthesiologists) physical status classification, Charlson comorbidity index, previous use of antimicrobials in the last three months and previous orthopedic infections. Surgical and perioperative procedure were (2): location and classification of the fracture, type of fracture, time between fracture and surgical treatment, prophylactic antimicrobial therapy, COVID-19 symptomatic infection, time of antimicrobial therapy, concomitant infection in the same period of hospitalization, presence of postoperative hematoma, presence of sepsis at the time of infectious diagnosis and early or late infection, result of blood culture sample and microbiological profile.

Microbiological analysis

During the surgical procedure for diagnosis and treatment of FRI, between 3 to 5 samples of peri-implant tissue and bone were collected aseptically, placed in properly labeled sterile containers and sent to the microbiology and histopathology laboratory. In the laboratory,

tissue samples were homogenized in 3 ml of Brain Heart Infusion (BHI) agar for 1 min and inoculated on aerobic blood agar, chocolate agar and anaerobic blood agar in a flask at 35°C, and also in Thioglycolate (TG) medium (BD Diagnostic Systems, Sparks, MD). Blood agar and chocolate agar plates were then incubated at 35–37 °C for 5 days for aerobic cultures and 14 days for anaerobic cultures. TG broth was incubated for 14 days, and in case of bacterial growth (turbidity), the liquid was seeded on blood agar plates (aerobic and anaerobic cultures). Microbiological methods for synovial fluids were similar, inoculating 0.1 mL on agar and liquid broth plates and evaluating aerobically and anaerobically. Isolated bacterial colonies were identified by matrix-assisted laser ionization-desorption-time-of-flight (MALDI-TOF MS) (Bruker Daltonics, Germany). The sensitivity profile was determined for all identified strains according to the prevailing standards of the Clinical Laboratory Standards Institute (CLSI) (Standardization of Antimicrobial Disk Diffusion Susceptibility Testing: Approved Standard—8th Edition, 2010, Vol. 23 No 1) [14]. Low virulence microorganisms (*Staphylococcus epidermidis*) were considered pathogenic when the organism was found in at least 2 different tissue culture samples [14, 15].

Statistical analysis

Data analysis included mean, median, standard deviation, interquartile range, variance for continuous variables and frequencies and proportion for categorical variables. The association between two categorical variables was performed using Pearson's Chi-square test or Fisher's exact test for categorical variables. The Kaplan–Meier test and the log-rank test were used to assess the influence of the variables of interest on survival time, that is, the time until infection occurs. A Cox regression model was fitted to identify factors related to time to infection. Risk estimates were calculated on the variables associated with risk factors for FRI and reported as a prevalence ratio (PR) with respect to the 95% confidence interval (CI). Variables with $p \leq 0.25$ were selected for multivariable analysis. All results were considered significant for a probability of significance lower than 5% ($p < 0.05$), therefore having at least 95% confidence in the conclusions presented.

Results

Overall, 189 patients with orthopedic fractures were evaluated for inclusion in the study. Of these, 57 (30.1%) were excluded: spine fracture (16), femoral neck fracture undergoing arthroplasty (30), two patients excluded for age under 18 years, 05 did not undergo surgical correction and 04 patients lost prospective outpatient follow-up. A total of 132 patients

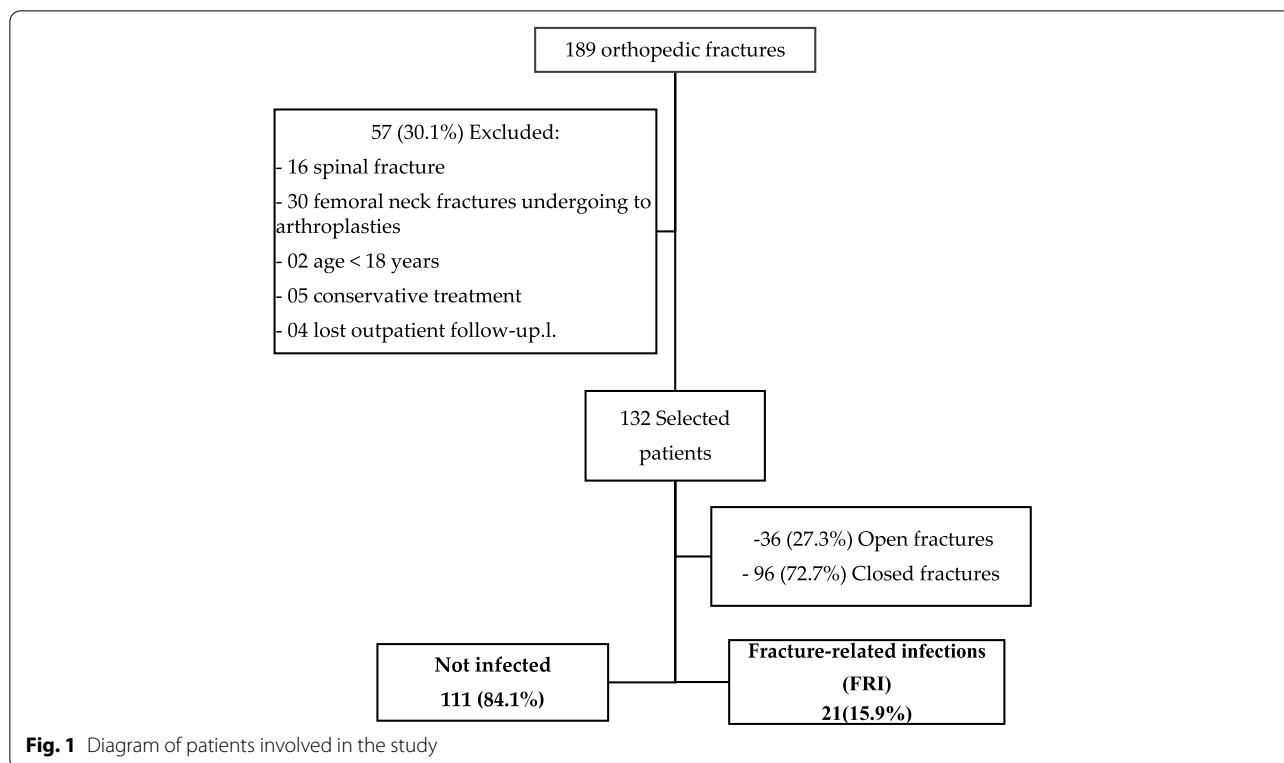
who underwent surgical correction of fractures were selected for analysis and prospective followed, of which male sex was 75%, with mean age of 50.4 years ($SD \pm 22.9$ years). Patients with age over 65 years accounted 65.1%. Charlson comorbidity index with a low score (up to 4 points) was diagnosed in 80.9% of patients. Fractures due to road traffic accidents (motorcycle/car) and falls from standing height occurred in 42.4% and 30.3%, respectively. Lower limbs fractures accounted for the majority of cases (80.3%). Closed and open fractures were 72.7% (96/132) and 27.3% (36/132), respectively. Out of 36 open fractures, 69.4% were classified as Gustilo–Anderson III or higher. Fracture-related infections (FRI) were diagnosed in 21 (15.9%) patients, of which 13 (9.8%) and 8 (6.1%) were open and closed fractures, respectively. (Fig. 1).

Temporary external fixator insertion for the first surgical fracture stabilization was placed in 20.6% of patients. Definitive surgical correction of the fracture within 72 h of the trauma occurred in 66.7%. Importantly, during the study period 3.8% (5/132) of patients evolved with symptomatic Covid-19 infection after surgery, requiring specific respiratory assistance in the intensive care unit. In addition, 3.8% (5/132) of patients described a recent preoperative use of systemic antibiotics for any cause. Demographic, pre- and post-surgical findings can be found in Table 1.

The risk variables showing statistical significance of FRI in the univariate analysis were recent use of antibiotics in the preoperative period ($p = 0.002$), type of fracture (open vs. closed, $p < 0.001$), use external fixator (with vs. without, $p = 0.015$), osteosynthesis with plate and screw ($p = 0.006$), mechanism of injury (car accident vs others, $p = 0.023$), infection by COVID ($p = 0.028$) (Table 2).

However, in the multivariable analysis, only recent and preoperative use of systemic antibiotics and the presence of cancer were independent risk factors for FRI (Table 3). Indeed, among those with recent antibiotic intake, the incidence of FRI was 7 times higher (CI 2.2; 22.4) than in the group that did not use antibiotics. While the presence of cancer increased the risk for FRI by approximately 9.8 times (CI 2; 48.8). These two variables were found mainly in elderly patients. In the survival analysis to identify independent risk factors related to time to diagnosis of FRI and death, prior use of antibiotic, habit of smoking and open fractures influenced the time to FRI or death with statistical significance. (Table S1 and Fig. 2).

Regarding microbiological findings among 21 FRI patients, tissue cultures were negative in six (28.5%), and polymicrobial in 4 (19.2%). The most frequent isolated microorganisms were *Klebsiella pneumoniae* (27.8%) and other Enterobacteriaceae (77.7%). Fewer Gram-positive cocci (22.2%) and no *S. aureus* were identified. Overall,



seven patients (33.3%) were infected by multi-resistant microorganisms (Table S2).

Discussion

There are few prospective studies carried out during the COVID-19 pandemic period aiming to describe the current changes in the epidemiology and risk factors of FRI [16]. In our study the overall FRI rate was 15.9%, which is high compared to the 11.6% described by Kamat et al. [17] and similar to the 14.9% described by Singh et al. [18].

Rather than road traffic accidents, domestic trauma seemed to have stood out during the pandemic period especially falls from any height involving the elderly due to the long period of social distancing and domestic confinement [16, 19]. On top of that, the presence of comorbidities and the severe co-infection by SARS-CoV-2 virus also became important risk factors for FRI in this population, according to the multicenter study by McDonald et al. [20]. This study compared injuries and trauma mechanisms before and during the pandemic, depicting a reduction in the number of fractures in general, but an increase of over 30% of hip fractures. Additionally, the author showed an increase in the age range of the population. The present study also identified a similar clinical and epidemiological trend related to patient's demographics, comorbidities, and characteristics of

trauma. Moreover, despite having few severe cases (five) of COVID-19 infection, it proved to be a significant factor for FRI in the univariate analysis and likely influenced towards the higher rates of FRI. We also hypothesized that this shift may have been due to the restrictive measures implemented during the lockdown to contain the virus progress. Besides, the SARS-CoV-2 virus infection severity and consequently increased in the length of hospital stay justifies the frequently delay for definitive surgical fracture stabilization which some of our patients experienced during this pandemic period. Among many modified and non-modified factors, delayed definitive fracture stabilization following closed trauma is thought to impact in the rates of FRI in the elderly [21].

An important find in the present study was the role of recent use of preoperative antibiotics which was a strong and independent association with FRI. Patients with a history of previous used antibiotics had 7 times higher risk of FRI than patients who had not. This data is very relevant due to few previous reports in the literature. In their series of 502 patients, Declercq et al. [22] showed that the use of an antimicrobial regimen to treat an infection unrelated to the fracture was statistically significant for the occurrence of FRI. However, there were unclear reasons for this association. Although not analyzed in the study, we argue that an over prescription of empirical antibiotic therapy is likely to have occurred during

Table 1 Demographic and clinical characteristics associated with trauma and treatment of 132 patients evaluated

Variables	Results N(%)
Gender	
Male	99 (75)
Age (years)	
Mean ± Standard Deviation	50.4 ± 22.9
P ₅₀ (P ₂₅ – P ₇₅)	44.0 (31.0; 70.7)
Age group	
up to 21 years old	11 (8.3)
From 22 to 40 years old	44 (33.3)
From 41 to 60 years old	31 (23.5)
> 60 years old	46 (34.9)
Comorbidities	
Arterial Hypertension	30 (22.7)
Diabetes Mellitus	15 (11.3)
Renal KidneyDisease	6 (4.5)
Cancer	4 (3.0)
Others comorbidities	13 (9.8)
Surgical risk classification ASA^b	
1	97 (73.5)
≥ 2	35 (16.5)
Preoperative use of ATB	
Yes	5 (3.8)
Charlson Index^a	
Up to 4	106 (80.9)
Over 4	25 (19.1)
Time between Fracture and surgery (hours)	
Up to 24 h	51 (38.7)
From 25 to 72 h	37 (28.0)
Over 72 h	44 (33.3%)
Type of fracture	
Open fracture	36 (27.3)
Closed fracture	96 (72.7)
Gustilo Anderson Classification (G-A)	
Type I-II	11 (30.6)
III A, B and C	25 (69.4)
Type of implant used	
Plate/Screw	58 (43.9)
intramedullary nail	74 (56.1)
Nail at the proximal end of the femur	
Yes	37 (50.0)
Affected limbs	
Lower	106 (80.3)
Upper	23 (17.4)
Lower / Upper	3 (2.3)
External fixator^a	
Yes	27 (20.6)
Mechanism of injury	
Motorcycle / car accident	56 (42.4)
Fall from one's own height	40 (30.3)
Fall from height	19 (14.4)
Others	17 (12.9)
Infection by COVID	
Yes	5 (3.8)

Table 1 (continued)^a—one undisclosed patient, ASA^b—American Society of Anesthesiologists

the entire COVID-19 pandemic period, including within the orthopaedic in ward of our tertiary hospital where a higher number of elderly patients with closed fractures underwent orthopaedic surgery. Recent published multicenter studies corroborate this argument, showing an overuse of empirical antibiotic therapy among hospitalized patients [23]. Besides, inappropriate prescription of antibiotics increases the selective pressure on patient's bacterial microbiota impacting on the development of drug-resistant bacterial infections [24]. Multidrug-resistant Gram-negative bacteria were the causative agents of 33% of FRI in the present study.

Comorbidities in the elderly population is common, including diabetes, hypertension, chronic heart diseases and cancer which impairs the immune response. In our study the presence of any type of cancer increased the risk for FRI by approximately 9.8 times. Conversely, in a case series study of 480 patients, Metsemakers et al. [25] observed that the healthier patients without immune-depressive comorbidities evolved with lower infection rate.

The role of high-energy open fractures in the pathogenesis of FRI is well investigated [26, 27], while in the present study it was independently associated with time to diagnosis of FRI. In fact, more than two-thirds of FRI cases comprised open fractures. In the setting of public healthcare system in developing countries, the management of patients with high energy open fractures of the lower limb due to road traffic accidents may be hampered, increasing the likelihood of FRI [28–30]. Nevertheless, we are in accordance with Morgenstern et al. [31] emphasizing the importance of having a holistic and multidisciplinary approach in the prevention of FRI following trauma. In this regard patient's characteristics including common habits are taken into consideration. Several studies associate smoking with poor surgical treatment outcomes for fractures, although the evidence is still contradictory [32, 33]. In our series, smoking was independently influenced the time to diagnosis of FRI.

The study has limitations for being carried out in a single center of a large tertiary teaching hospital offering special orthopaedic care to a regional population located in a major city in a developing country, which limits the global comparison of the data. Besides, the overall number of FRI was low that may have biased our results, although multivariable analyses were performed to identify independent factors related to time and diagnosis of infection. Importantly, another limitation is related to patient's selection bias as we excluded those

Table 2 Risk factor for the infection outcome according to univariate analysis

Analyzed variable	Not Infected (n = 111)	Infected (n = 21)	p-value
Demography	N (%)	N (%)	
Male	84 (75.8)	15 (71.43)	0.680*
Age (average-years)	50.8	48.5	0.651**
P50(p ₂₅ -p ₇₅)	44.0 (31.0; 72.0)	48.0 (30.5; 64.0)	
Comorbidities			
Habit of smoking	30 (27.0)	5 (23.8)	0.759
Alcoholism	29 (26.1)	4 (19.0)	0.492*
Arterial hypertension	23 (20.7)	7 (33.3)	0.255***
Cancer	3 (2.7)	2 (9.5)	0.179***
Perioperative risk			
Classification ASA ^b			
1	83 (74.7)	14 (66.6)	0.440*
≥ 2	28 (25.2)	7 (33.3)	
Charlson index ^a			
Up to 4	88 (79.2)	18 (85.7)	0.763***
Over 4	22 (19.8)	3 (14.2)	
Associated with trauma			
Mechanism of injury			
Fall from one's own height	38 (3.4)	2 (9.5)	
Motorbike/car accident	47 (42.3)	9 (42.8)	0.023***
Fall from height	4 (3.6)	3 (14.2)	
Open fracture	23 (20.7)	13(61.9)	< 0.001*
Closed fracture	88 (91.7)	8 (8.3)	
Gustilo-Anderson			
I	4 (3.6)	2 (9.5)	
II	4 (3.6)	1 (4.7)	0.688*
III A, B and C	15 (13.5)	10 (47.6)	
External fixator ^a	18 (16.2)	9 (42.8)	0.015***
Low Limber fracture	88 (79.2)	18 (85.7)	0.861***
Time interval Fracture-surgery(h)	87.8 ± 119.8	93.3 ± 118,8	0.847**
Average p ₅₀ (p ₂₅ - p ₇₅)	48 (24; 96)	24 (12; 121.5)	
Perioperative data			
Type of osteosynthesis			
Plate and screw	43 (38.7)	15 (71.4)	0.006*
Locked intramedullary nail (IMN)	68 (61.2)	6 (28.5)	
Recent preoperative use of ATB	1 (0.9)	4 (19.0)	0.002***
Infection by covid	2 (1.8)	3 (14.2)	0,028***

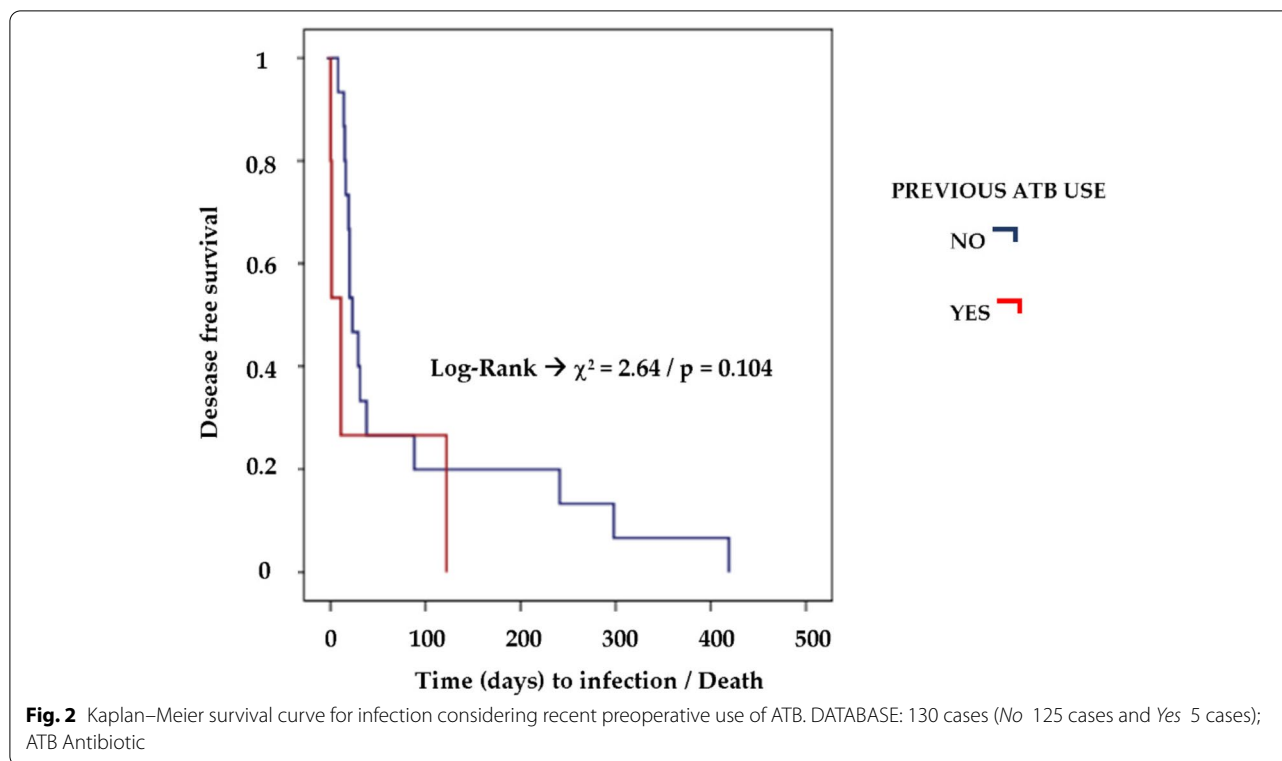
The probability of significance refers to the Chi-square test (*), Student's t test (**), Fisher's exact test (***), ^a—one undisclosed patient, ASA^b American Society of Anesthesiologists, ATB Antibiotic

Table 3 Risk factors independently associated to infection outcome—multivariable analysis

Analyzed Variable	PR (95% IC)	p-value
Recent preoperative use of ATB	7.0 (2.2; 22.4)	0.001
Cancer	9.8 (2; 48.8)	0.005

Significance probabilities in multivariable analysis refers to Poisson regression, PR prevalence ratio, ATB – antibiotics

with extreme ill conditions with greater immunological susceptibility to infections and likely to progress to death within the first 7 days of hospitalization. Nevertheless, we included in the analysis patients with severe comorbidities such as neoplasia and those with extreme advanced ages. A challenging factor was carrying out the study during the lockdown period, which made it difficult to diagnose and treat FRI. However, the patients were followed prospectively, for a period of at least 12 months,



and most importantly the definitions of FRI used were standardized and well-defined according to Metsemakers et al. [12], decreasing the chance of bias. Moreover, the robust statistical analysis of the data contributes relevant information for planning higher impact study designs.

Conclusion

In conclusion, in this single-center prospective study we found higher rates of FRI, predominating in the elderly with closed lower limb fractures during the COVID-19 pandemic period. Prior use of antibiotics and presence of cancer were independent factor for FRI. The majority of infection were due Gram-negative bacteria with higher rates of MDR. Our outcomes provide evidence to avoid the empirical use of antibiotics prior to surgery for fracture stabilization. Further analysis during the lockdown period may be needed to confirm these results.

Abbreviations

ASA: American Society of Anesthesiologists; ATB: Antibiotic; BHI: Brain-heart-infusion; CI: Confidence interval; COVID: Coronavirus infection diseases; CLSI: Clinical Laboratory Standards Institute; DAIR: (Debridement, antibiotics, and implant retention); FRI: Fracture related infection; G-A: Gustillo & Anderson; IMN: Intramedullary Nail; MALDI-TOFMS: Matrix-assisted laser ionization-desorption-time-of-flight; MDR: Multidrug-resistant; OR: Odds ratio; PR: Prevalence Ratio; RF: Risk factors; SD: Standard deviation; TG: Thioglycolate; UNIFESP: Federal University of São Paulo.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12891-022-05493-5>.

Additional file 1: Table S1. Assessment of the influence of variables in time until infection diagnosis. **Table S2.** Frequency of microorganisms isolated in tissue cultures.

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Authors' contributions

ECS, SP, ADA and MJS; Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND Drafting the work or revising it critically for important intellectual content; AND Final approval of the version to be published; AND Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. CF, FBR, INS and MNK; Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND Drafting the work or revising it critically for important intellectual content; AND Final approval of the version to be published.

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Availability of data and materials

Epm, Ortoinfecto (2022), "MUSCULOSKELETAL INFECTION", Mendeley Data, V1, <https://doi.org/10.17632/grxjspb29.1>.

Declarations

Ethics approval and consent to participate

The study was previously approved, with the waiver of the free and informed consent form, by the Ethics and Research Committee of the Federal University of São Paulo (UNIFESP) under the number: 0846P/2021. In addition, we confirm that all methods were performed in accordance with the relevant guidelines and regulations currently available.

Waiver of consent justification Patient consent was waived by the local IRB for this observational study because involved in minimal risk to the subject due to the anonymization of patients' data and meets specific criteria during the COVID-19 pandemic period. The reasonable rationale for why the research would not be possible without the waiver is stated below:

1. The need to carry out only online consultation follow-up, made it difficult to obtain many patients' consents, as social distance was mandatory during this period.
 2. Fracture-related infection diagnosis is usually performed months after surgery, and many patients were contacted online or even by telephone, hindering the possibility to obtain a signed informed consent.
 3. The research could not practicably be carried out without waiver, as involved more than 100 non-infected patients.
 4. Part of this cohort study is retrospective because existing data, specimens and medical records were available and analysed as of the date of IRB submission.
 5. The research could not practicably be carried out without using identifiable private information and biospecimens in an identifiable format.
 6. The waiver will not adversely affect the rights and welfare of the subjects.
 7. Inability to identify subjects that is likely to evolve to fracture-related infection, which may occur from the emergency admission to months after the surgical procedure. Therefore, the study staff can't plan for coverage to obtain consent.
 8. The study involved more than 100 patients undergoing any type of surgery for fracture stabilization, which has been physically impossible to obtain consent from them all.
 9. The number of patients with FRI was small (21) and removing any subject due to the impossibility to obtain the consent or even those refusing to participate in the study would largely bias our results.
 10. FRI is a relatively rare disease and loss of a few subjects would affect the power of the study.
 11. During the COVID-19 pandemic period, there were subjects, especially older patients, with severe medical condition and co-infected with SARS-CoV2 virus infection, which was not appropriate to approach families during the course of hospitalization.
- Not applicable.

Competing interests

The authors declare no conflict of interest.

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