Accuracy of Serological Markers, Synovial Fluid, Microbiological Culture, and Histopathological Examination for Diagnosing Periprosthetic Knee Infection

Acurácia dos marcadores sorológicos, do líquido sinovial, da cultura microbiológica e do exame histopatológico para o diagnóstico de infecção periprotética do joelho

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Abstract

Objective This study assessed the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of serological tests, synovial fluid markers, microbiological tissue culture, and histopathological examination of the periprosthetic membrane in diagnosing periprosthetic knee infection.

Methods This study is prospective, and it includes patients undergoing total knee arthroplasty revision surgery from November 2019 to December 2021. The analysis consisted of serological tests (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], and D-dimer), synovial fluid markers (leukocyte and polymorphonuclear cell counts), periprosthetic tissue culture, and histopathological examination of the periprosthetic membrane of all patients.

Results Sixty-two patients had periprosthetic joint infection (PJI) according to the 2018 International Consensus Meeting criteria (infection group), while 22 subjects had no infection. ESR sensitivity and specificity were 83.6% and 45.4%, respectively. CRP sensitivity and specificity were 64.5% and 100%, whereas D-dimer sensitivity and specificity were 78.9% and 25%, respectively. Leukocyte count sensitivity and

Keywords
- arthroplasty, replacement, knee
- postoperative complications
- periprosthetic infection
- biomarkers

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specificity were 75.6% and 100%, polymorphonuclear cell count sensitivity and specificity were 33% and 100%, respectively. Periprosthetic tissue culture sensitivity and specificity culture were, respectively, 77.4% and 100%. Histopathological examination sensitivity and specificity were 43.7% and 100%, respectively.

Conclusions In our study, the total blood cell count in synovial fluid and microbiological cultures of periprosthetic tissues were the most accurate tests for PJI diagnosis. In contrast, polymorphonuclear cell percentage was the least accurate test for PJI diagnosis.

Resumo

Objetivo avaliar a sensibilidade, especificidade, valor preditivo positivo, valor preditivo negativo e acurácia dos testes sorológicos, dos marcadores do líquido sinovial, da cultura microbiológica de tecidos e do exame histopatológico da membrana periprotética para o diagnóstico de infecção periprotética do joelho.

Métodos estudo prospectivo, com pacientes submetidos à cirurgia de revisão de artroplastia total do joelho no período entre novembro de 2019 e dezembro de 2021. Foi realizado análise do marcadores sorológicos (VHS, PCR e D-dímero), do líquido sinovial (contagem de leucócitos e percentual de polimorfonucleares), cultura de tecidos periprotéticos e exame histopatológico da membrana periprotética de todos os pacientes.

Resultados 62 pacientes foram diagnosticados com infecção periprotética do joelho, pelos critérios do *International Consensus Meeting* 2018 (grupo infecção) e 22 pacientes integraram o grupo não infecção. A sensibilidade e especificidade da VHS foram de 83,6% e 45,4%, respectivamente. Os valores de sensibilidade e especificidade da PCR foram de 64,5% e 100% e as do D-dímero foram de 78,9%% e 25%, respectivamente. A sensibilidade e especificidade da contagem de leucócitos foi de 75,6% e 100%, e a do percentual de polimorfonucleares foi de 33% e 100%, respectivamente. A sensibilidade e especificidade das culturas de tecidos periprotéticos foi de, respectivamente, 77,4% e 100% A sensibilidade do exame histopatológico foi de 43,7% e a especificidade de 100%.

Conclusões A contagem total de leucócitos no líquido sinovial e as culturas microbiológicas dos tecidos periprotéticos foram os testes de maior acurácia para o diagnóstico de infecção periprotética em nossa série. O percentual de polimorfonucleares foi o teste de menor acurácia, em nosso estudo, para o diagnóstico de infecção periprotética.

Palavras-chave
- artroplastia do joelho
- complicações pós-operatórias
- infecção periprotética
- biomarcadores

Introduction

Periprosthetic joint infection (PJI) accurate diagnosis is critical for defining treatment and, as a result, clinical outcomes. However, even today, diagnostic confirmation has no single effective test or biomarker,[1,2] relying on laboratory parameters and surgically obtained clinical specimen assessment.[2,3]

Systemic serological markers, such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and D-dimer are the first line of diagnostic assessment in patients with suspected periprosthetic infection. Nevertheless, the 2018 International Consensus (ICM 2018) determined that negative results in these serological tests do not rule out a potential PJI.[4–7]

The leukocyte counts and polymorphonuclear cell percentage in the synovial fluid have been identified as the most significant tests for diagnosing PJI.[8,9] However, other inflammatory causes can influence these parameters, reducing the accuracy of these parameters.[10,11]

Therefore, the objective of this study was to evaluate the accuracy of serological markers, synovial fluid parameters, microbiological cultures, and histopathological examination for periprosthetic knee infection diagnosis per ICM 2018 criteria.

Material and Methods

This study is prospective, and it included all patients undergoing total knee arthroplasty revision surgery in a single tertiary hospital from November 2019 to December 2021. After approval by the Research Ethics Committee (CEP no. 20309419.0 .0000.5273), the volunteers confirmed their

Table 1 Exclusion criteria

EXCLUSION CRITERIA
- Refusal to sign the informed consent form
- Revision of unicompartmental arthroplasty
- Insufficient information to confirm or exclude infection diagnosis
- Use of antibiotic agents within the last 15 days
- Subjects with active bacterial diseases

participation in the study by signing an informed consent form.

►**Table 1** shows the exclusion criteria.

After applying the exclusion criteria, 84 patients from both genders, aged 57 to 87, remained in the study.

The day before surgery, all patients underwent a peripheral blood sample collection for serological tests, including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and D-dimer.

All patients underwent spinal anesthesia with peripheral nerve block. After limb exsanguination and surgical drape placement, an arthrocentesis with a 20G needle collected the synovial fluid (SF) immediately before the surgical incision. A second attempt for SF collection occurred by direct visualization after surgical access if the first procedure was not feasible.

Aliquots of 1 to 2 mL of SF were placed in a vacuum blood collection tube containing EDTA to perform the total leukocyte count and determine the percentage of polymorphonuclear cells. Global and SF-specific automated cytometry employed a Cell Dyn 3700 SL device (Abbott).

An aerobic blood culture tube received 3 to 5 mL of SF for a 14-day microbiological culture.

After prosthetic component removal, we collected the following for microbiological analysis: three femoral bone tissue samples, three tibial bone tissue samples, and a periprosthetic membrane fragment. For histopathological analysis, we collected a periprosthetic femoral membrane sample and a tibial periprosthetic membrane sample. The histopathological examination was positive for infection when five or more leukocytes were present in five high-power fields (400x) per the ICM 2018 criteria.

The bone fragments were placed in sterile tubes with 1 mL of 0.9% saline solution and sent to the microbiology laboratory for microbiological cultures for 14 days.

For histopathological examination, we collected one or two fragments of the periprosthetic membrane and stored them in a vial containing 10% formaldehyde.

Diagnostic confirmation for the infection group relied on i) the growth of the same pathogen in two or more periprosthetic tissue cultures, ii) the presence of fistula, and iii) a score equal to or greater than six per the 2018 ICM algorithm. This score consisted of the following diagnostic parameters: an ESR higher than 30 mm/h, CRP levels higher than 1 mg/dL, leukocyte count higher than 3.000 cells/µL, polymorphonuclear cell percentage higher than 80%, and leukocyte esterase ++.

We analyzed descriptively quantitative data and presented them as mean values, standard deviations (SD), medians, and minimum and maximum values. Categorical variables were presented as frequencies and percentages. The Student's t-test compared parameters with a normal distribution, while the non-parametric Mann-Whitney test compared variables with no normal distribution. The chi-square or Fisher's exact test analyzed categorical variables when necessary. All analyses occurred in Med Calc and GraphPad Prism software. The p-value significance was lower than 0.05.

Results

Using the 2018 ICM criteria, we assessed clinical and laboratory data from 84 patients who underwent total knee arthroplasty revision surgery or total knee arthroplasty failure investigation. Sixty-two patients were diagnosed with PJI and comprised the infection group, while 22 subjects were part of the non-infection group. ►**Table 2** summarizes the demographics of both groups.

Twenty-three percent of PJI patients had negative microbiological cultures. Figure 1 shows the microbiological profile of PJI patients with positive cultures. Monomicrobial

Table 2 Demographic distribution

	No infection	Infection
N	22	62
Gender, *n (%)*		
Female	11 (50%)	23 (37%)
Male	11 (50%)	39 (63%)
Age (years), *mean (±standard deviation)*	71.2 (±7.9)	68.9 (±8.7)
Body mass index (kg/m^2), *mean (±standard deviation)*	26.9 (±10.4)	27.4 (±9.9)
Diabetes, *n (%)*	5 (23%)	12 (19%)
Inflammatory disease, *n (%)*	3 (14%)	11 (18%)
Previous implant, *n (%)*		
Primary prosthesis	18 (82%)	38 (61%)
Revision	4 (19%)	18 (29%)
Frequency of infection-characteristic events, *n (%)*		
Fistula ≥ 2 positive cultures Diagnosis per score higher than six points	0 0 0	16 (25%) 46 (74%) 11 (18%)
Time between prosthesis placement and infection, *n (%)*		
≤ 3 months 3–12 months > 12 months	1 (5%) 2 (9%) 19 (86%)	23 (37%) 7 (11%) 32 (52%)

[a]T-test, [b]Fischer's exact test, n: number of patients

infections represented 79% of cases. Gram-negative organisms occurred in 24% of the cultures. The most frequently identified pathogen was *Staphylococcus aureus*, present in 26% of the samples.

ESR assessment occurred on the 22 subjects from the non-infection group and the 55 patients from the infection group. ESR median value was significantly higher in the infection group, at 62 mm/h (interquartile range [IQR]: 39–93) compared to the non-infection group, which presented a median ESR value of 36 mm/h (IQR: 18–50.25) ($p = 0.0021$) (►**Fig. 2A**).

We identified that 54.5% (12/22) of patients in the non-infection group had an ESR value higher than the cutoff point from the ICM 2018 criteria. For the infection group, 16.4% (9/55) of patients had an ESR value below the cutoff value. As such, ESR sensitivity and specificity values were 83.6% and 45.4%, respectively.

Regarding CRP plasma levels, the median value was 2.3 mg/dL (IQR: 0.6–7.5) in the infection group and 0.1 mg/dL (IQR: 0.1–0.12) in the non-infection group, constituting a statistically significant difference ($p = 0.03$) (►**Fig. 2B**).

No subjects from the non-infection group had CRP levels higher than the cutoff point determined by the ICM 2018 criteria. For the infection group, 35.4% (22/62) of patients had CRP levels below the cutoff point. Therefore, CRP sensitivity and specificity were 64.5% and 100%, respectively.

As for plasma D-dimer levels, the median value in the infection group was 2.8 mg/dL (IQR: 0.9–5.4) and 1.3 mg/dL (IQR: 0.7–1.9) in the non-infection group, with a statistically significant difference ($p = 0.03$) (►**Fig. 1C**).

We identified that 75% (12/16) of patients in the non-infection group had D-dimer levels higher than the cutoff point from the ICM 2018 criteria. For the infection group, 21% (8/38) of patients had levels below the cutoff point. D-dimer sensitivity and specificity values were 78.9% and 25%, respectively.

SF leukocyte quantification occurred in 63 patients, including 41 from the infection group and 22 from the non-infection group. The median value for the infection group was 12,275 cells/μL (IQR: 2,350 - 35,050), which was significantly higher than the median value for the non-infection group, which was 355 cells/μL (IQR: 239 - 776) ($p < 0.0001$) (►**Fig. 3A**).

Using the cutoff points suggested by ICM 2018, we observed that no subject from the non-infection group presented a positive result for this test. Meanwhile, 24% (10/41) of patients from the infection group had values below the cutoff point. As such, sensitivity and specificity values were 75.6% and 100%, respectively.

Sixty-one patients underwent an assessment of polymorphonuclear neutrophils (PMN) percentage in the synovial fluid, including 39 from the infection group and 22 from the non-infection group. Following the ICM 2018 recommendation, this evaluation had a 90% cutoff point if surgery occurred within the last 90 days and 80% if the procedure occurred more than 90 days ago.

We identified that no patient from the non-infection group had a percentage of PMN in the synovium higher than the criteria cutoff. However, 66% (26/39) of patients from the infection group had a polymorphonuclear cell percentage lower than the cutoff point for infection diagnosis.

The median polymorphonuclear cell percentage was 40% (IQR: 20–87) in the infection group and 18% (IQR: 8.7–27) in the non-infection group, being significantly higher in the infection group ($p = 0.0001$) (►**Fig. 3B**). The sensitivity and specificity values were 33% and 100%, respectively.

The sensitivity and specificity of two or more periprosthetic tissue cultures were, respectively, 77.4% and 100%.

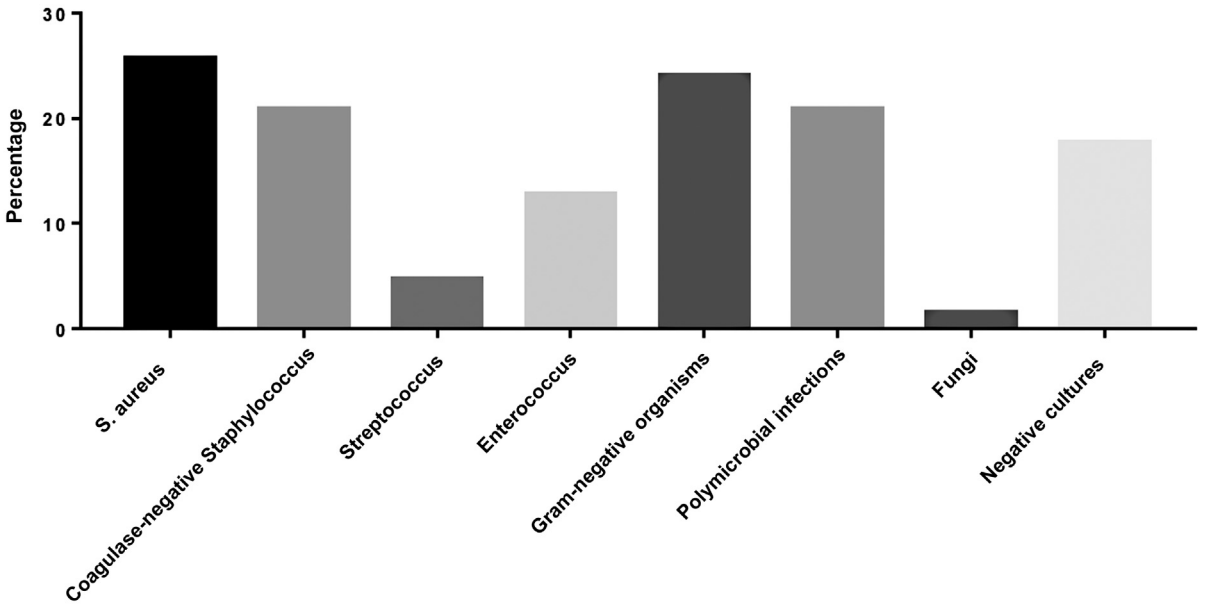

Fig. 1 Microbiological profile from patients with periprosthetic joint infection.

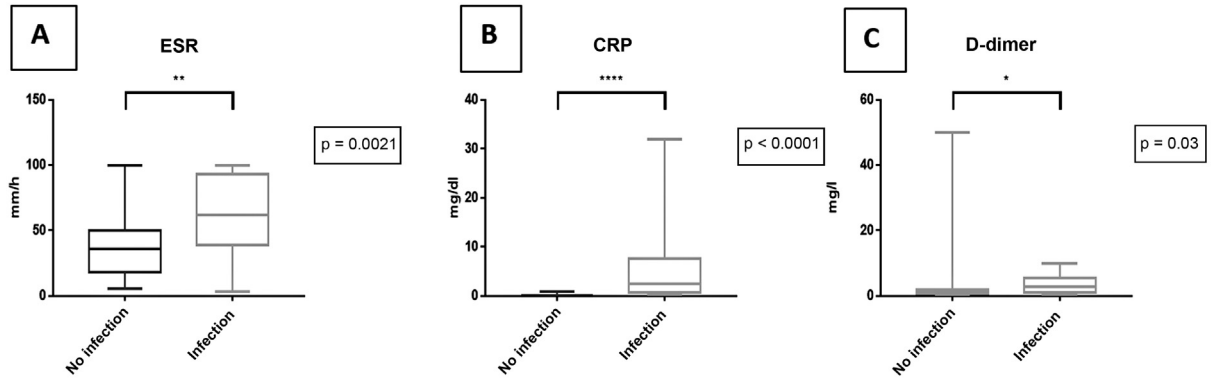

Fig. 2 (A) Erythrocyte sedimentation rate (ESR) from patients from the group infection or no infection. $^{**}p = 0.0021$. **(B) C-reactive protein** (CRP) from patients from the group infection or no infection. $^{*}p < 0.0001$. **(C) D-dimer** from patients from the group infection or no infection. $^{*}p = 0.03$. Mann-Whitney test.

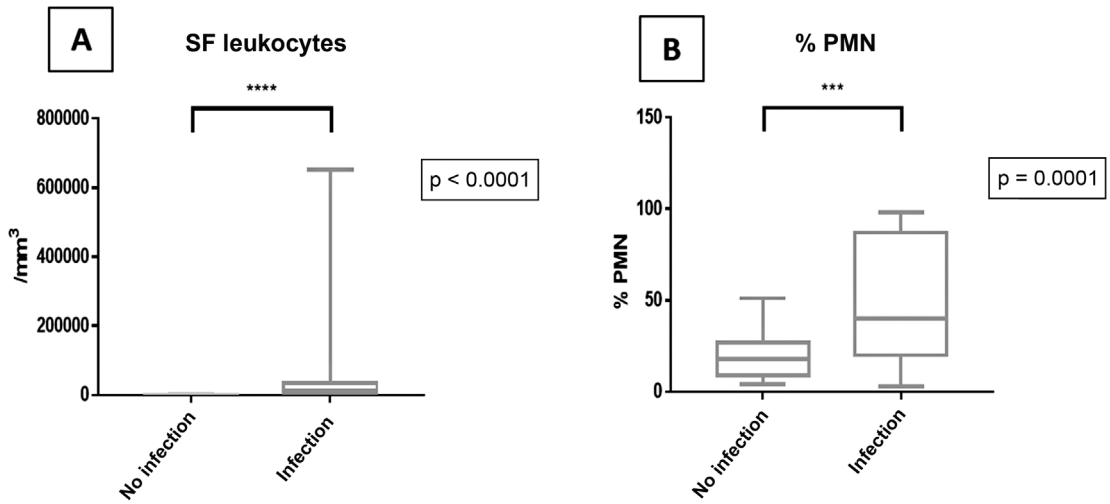

Fig. 3 (A) Leukocyte count in the synovial fluid (SF) from patients from the group infection or no infection. **(B) Percentage of polymorphonuclear neutrophils** (PMN) from patients from the group infection or no infection. $^{*}p < 0.0001$. Mann-Whitney test.

The histopathological examination for PJI diagnosis presented 43.7% of sensitivity and 100% of specificity.

►**Table 3** describes the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of serological tests, synovial fluid markers, microbiological tissue culture, and histopathological examination of the periprosthetic membrane for periprosthetic infection diagnosis.

Table 3 Diagnostic performance of knee periprosthetic infection markers

	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
C-reactive protein	64.5%	100%	100%	50%	73.8%
Erythrocyte sedimentation rate	83.6%	45.4%	79.3%	52.6%	72.7%
D-dimer	78.9%	25%	71.4%	33.3%	62.9%
Leukocyte count in the synovial fluid	75.6%	100%	100%	68.7%	84.1%
% Neutrophils in the synovial fluid	33%	100%	100%	45.8%	57.3%
Histopathologic analysis	43.7%	100%	100%	43.7%	60.8%
Microbiological culture (>2)	77.4%	100%	100%	61.1%	83.3%

Discussion

The importance of this study consists in identifying the sensitivity and specificity of each diagnostic test for periprosthetic knee infection in the Brazilian population. The 2018 ICM for periprosthetic infection diagnosis delimited the role of ESR, CRP, and D-dimer in PJI. However, negative serological results do not exclude a potential PJI[4–7] since any inflammation and infection increase the levels of these markers, compromising their sensitivity and specificity for PJI diagnosis. Therefore, values within the normal range cannot rule out a periprosthetic infection.[10,12–15] As such, it is critical to analyze these diagnostic parameters in the Brazilian population.

Pérez-Prieto et al.[16] demonstrated that one-third of periprosthetic infections had CRP levels within the normal range, and two-thirds presented ESR values within the normal range. In our study, 16% of patients with periprosthetic infections had ESR levels within normal limits; in addition, among patients with aseptic prosthesis failures, 54% had ESR levels higher than those required for PJI diagnosis. In a recent meta-analysis, Carli et al.[10] showed a 79% sensitivity and an 81.6% specificity for ESR, with respective values of 81.3% and 84.5% for CRP.[10,14] In our study, ESR was drastically lower compared to Carli et al.[10] As for CRP, our series presented a sensitivity consistent with the meta-analysis by Carli et al.,[10] but specificity was significantly higher (84.5% versus 100%). We believe such differences derive, at least in part, from differences in the microbiological profile of infections in the several series since the pathogen's virulence profile may relate to the host's inflammatory response pattern.

D-dimer levels have been investigated as a potential diagnostic biomarker.

D-dimer levels have been investigated as a potential diagnostic biomarker.[9,17] However, D-dimer is not a specific infection marker.[9] Shahi et al.[18] showed that D-dimer sensitivity and specificity of D-dimer were, respectively, 89.4% and 92.7%. Other authors, however, reported a sensitivity of 64.5% to 68% and a specificity of 50.7% to 65%.[19–21] In our study, although D-dimer sensitivity was within the described range, we identified a significantly lower specificity compared with the literature. Therefore, the accuracy of this serological test was only higher than the accuracy of polymorphonuclear cell percentage and the histopathological examination in our series.

Similarly, the host's immune response and the previous use of antibiotic agents can influence SF markers.[9,10,22] Leukocyte counts in SF may be higher in patients with rheumatoid arthritis, periprosthetic fracture, and soon after total knee replacement.[3,10,22–24] Therefore, we suppose these SF tests may have variable sensitivity and specificity for diagnostic confirmation in different populations.

A recent meta-analysis showed that leukocyte count has 92.5% sensitivity and 90.1% specificity for diagnosing a chronic periprosthetic infection.[10] Other authors reported sensitivity and specificity of, respectively, 83% and 94%.[14] Thus, our results regarding leukocyte counts are consistent with the literature.[10,14,23,24] Therefore, this test had good sensitivity and specificity for PJI diagnosis.

The sensitivity of the polymorphonuclear cell percentage for PJI diagnosis ranges from 78% to 87.8%, while the specificity ranges from 90.7 to 93%.[10,14] Our results confirm that this test has a high specificity of 100%. However, our series identified a significantly lower sensitivity (33%) compared with the literature. Several studies have identified intrinsic functional heterogeneity in the human neutrophil pool in physiological and pathological conditions.[25,26] Therefore, we believe that the epidemiology and virulence of pathogens can influence the recruitment and activation of these cells, resulting in the variability of this parameter.

Recent studies have demonstrated a wide sensitivity range in microbiological cultures for PJI diagnosing, from 44.6% to 97.5%. In our study, sensitivity was 77.4%.[10,27] We believe such variation in microbiological culture results comes, at least partially, from the lack of standardization of laboratory processes and culture media. Moreover, there is no consensus on which peri-implant tissue is more sensitive and, as such, more suitable for cultures.

A recent meta-analysis evaluating the accuracy of diagnostic tests for chronic periprosthetic infection showed that the sensitivity and specificity of histopathology considering five polymorphonuclear cells per high-power field were 95.6% and 76.6%, with a sensitivity of 72%. Considering the cutoff point of 10 polymorphonuclear cells per high-power field, sensitivity was 94.2%, specificity was 73.9%, and accuracy was 68%.[10] In our study, the sensitivity of this test was significantly lower, and we believe these differences arise from observer training-related variations.

This study has some limitations. The low number of patients with aseptic failures included in the study was because part of the analysis occurred during the COVID-19 pandemic, which had fewer surgeries, particularly elective procedures. Another limitation refers to losses in analyzing some markers. At least partially, this occurred because of the disruption in care processes during the COVID-19 pandemic and the need for urgent treatment for some patients. Lastly, although only 17% of the patients from our sample had chronic inflammatory diseases, we did not evaluate the influence of these conditions on the diagnostic parameters of periprosthetic infection. Therefore, further studies with more patients, subpopulational assessments, and correlating pathogens and infection chronicity are required.

Conclusion

The total leukocyte count in synovial fluid and microbiological cultures of periprosthetic tissues were the most accurate tests for diagnosing periprosthetic infection. Polymorphonuclear cell percentage and histopathological examination were the least accurate tests for diagnosing periprosthetic infections in our study.

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Conflict of Interests
The authors have no conflicts of interest to declare.

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