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Diagnostic accuracy of synovial fluid, blood markers, and microbiological testing in chronic knee prosthetic infections

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Abstract
Introduction This retrospective study was undertaken to define cut-off values for synovial fluid (SF) leukocyte count and neutrophil percentage for differentiating aseptic failure and periprosthetic joint infection (PJI) and to evaluate the diagnostic accuracy of blood inflammatory markers, and microbiological testing according to the criteria proposed by the International Consensus Meeting (ICM) of Philadelphia.
Methods All patients who underwent revision total knee arthroplasty from January 2010 to July 2015 were included: we identified and classified 31 PJIs and 136 aseptic joints. The diagnostic performance of single test was assessed by receiver operating characteristic curve analyses. The sensitivity and specificity were calculated for each of the cut-off values and the area under the curve (AUC) was calculated.
Results The median SF leukocyte count as well as the neutrophil percentage and inflammatory markers were significantly higher in patients with PJI than in those with aseptic failure ($p < 0.001$). A leukocyte count of $> 2.8 \times 10^3$/μL had a sensitivity of 83.8% and a specificity of 89.7% whereas a neutrophil percentage of > 72% yielded a marginally higher sensitivity of 84% and a specificity of 91%. Applying the ICM criteria we found a significant correlation between all these diagnostic measures and PJI ($p < 0.001$) except for a single positive culture. The most accurate criterion of the ICM was the synovial neutrophil differential (AUC = 0.89; 95% CI 0.81–0.97), followed by SF leukocyte count (AUC = 0.86; 95% CI 0.78–0.94), increased inflammatory markers (AUC = 0.85; 95% CI 0.76–0.93), and two positive periprosthetic cultures (AUC = 0.84; 95% CI 0.73–0.94). The presence of sinus tract communicating with the joint and a single positive culture showed unfavourable diagnostic accuracy (AUC = 0.60, 95% CI 0.47–0.72; AUC = 0.49, 95% CI 0.38–0.61, respectively)
Conclusions The present study highlights the adequate ability of fluid cell count and neutrophil differential to distinguish between PJI and aseptic loosening. The clinical utility of fluid analysis in diagnosing infection can be improved by evaluation of other diagnostic criteria.
Level of evidence Level I Diagnostic Study.

Keywords Synovial leukocyte count · Periprosthetic joint infection · Diagnosis · Total knee arthroplasty

Introduction

Periprosthetic joint infection (PJI) is one of the most feared complications after total joint arthroplasty, as it is associated with very high morbidity and mortality rates and along with considerable economic implications [1–7]. PJI is currently the most common indication for revision total knee arthroplasty (TKA) (16.8% of all knee revisions) and the third most common indication for revision total hip arthroplasty (14.8% of all hip revisions) worldwide [1, 4, 5, 8]. Although a definite preoperative diagnosis of septic failure is imperative for proper treatment and management, the diagnosis of PJI still remains a serious clinical challenge [9–11]. Unfortunately, no 'gold standard' exists and no

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single test is available with 100% of diagnostic accuracy to detect an infection. In an effort to standardize the definition of PJI, several orthopaedic and infection associations have issued guidelines and expert opinions. The Musculoskeletal Infection Society proposed in 2011 a multi-criteria definition of PJI that was later modified during the International Consensus Meeting (ICM) of Philadelphia in 2013 [12, 13]. According to the ICM criteria, the definition of PJI is based on the combination of clinical features (sinus tract); SF tests (leukocyte count, neutrophil percentage, fluid culture, and leukocyte esterase); blood tests [erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)]; and histological and microbiological tissue analysis [13]. The synovial fluid (SF) leukocyte count and neutrophil differential of the aspirated joint have become important tools during the preoperative assessment. Although previous investigators have attempted to determine the cut-off value for the cell count and neutrophil percentage, the pre-diagnostic and analytic modalities are not well documented and the exact values are wide-ranging [3, 14–20]. Therefore, the diagnostic accuracy values seem questionable.

The aim of this retrospective study was therefore to define the cut-off values for SF leukocyte count and neutrophil percentage in order to differentiate aseptic failure from PJI, and to evaluate the diagnostic accuracy of blood markers, and microbiological testing according to the ICM criteria for diagnosing a PJI.

Patients and methods

We retrospectively reviewed 250 consecutive revision TKR performed at our institution between January 2010 to July 2015. Approval was obtained from the Internal Review Board (IRB) of Istituto Fiorentino di Cura e Assistenza, Florence, Italy (ID 166bis/13-10-2015), in accordance with the Declaration of Helsinki. Patients gave their informed consent prior to be included in the study.

When the study was planned, diagnosis of PJI had to be defined by at least three of the following criteria: (1) characteristic clinical signs and symptoms with presence of a sinus tract, (2) two positive microbiological cultures with phenotypically identical organisms obtained from intraoperative specimens or joint aspirates, (3) the presence of acute inflammation on histopathological examination (as determined by the pathologist), (4) elevated synovial fluid leukocyte count ($\geq$ 1700 per cubic millimeter) or a finding of more than 65% neutrophils, (5) elevated ERS or CRP. After ICM criteria were released, case-definition was based on these criteria, and all the cases previously enrolled were considered in the definitive analysis only if they also fulfilled ICM criteria [13].

Chronic inflammatory joint diseases (e.g., rheumatoid arthritis, psoriatic arthritis); acute (< 90 days after the index procedure) and late hematogenous (symptoms of less than 3 weeks duration) infection; and an inadequate amount of synovial fluid ($\leq$ 10 mL) for culture, WBC, and PMN (neutrophil) percentage determinations were considered as exclusion criteria. Patients included in the study had to withdraw any antibiotic treatment at least 2 weeks before the diagnostic procedure.

For all included patients, we collected the following data: demographic data (age and sex), medical history, initial clinical presentation, laboratory investigations (ESR and CRP levels), SF white blood cell count and neutrophil percentage, and microbiologic studies (cultures obtained from SF sample and intraoperative tissue).

A preoperative joint aspiration, after a 2-week antibiotic-free period, for SF fluid cell count and microbiological analysis was performed under sterile conditions in order to establish the diagnosis of PJI before surgery. The aspirate was transferred into two different vials: one for cell counting containing EDTA (either K2 or K3) and the other (at least 4 mL of aspirate) for inoculation in aerobic and anaerobic blood culture bottles (Bact-Alert FA, FN; bioMerieux, Marcy l'Etoile, France) for 14-day incubation. Synovial fluid samples collected in EDTA-coated tubes were transported at room temperature to the laboratory and stored at room temperature. The specimens were analysed within 3 h from sampling. Leukocyte and differential counts were determined by microscopic examination. The cell counts were performed at 400× magnification in Burker chambers using Stromatolitic Agent (Stromatol). The dilution with Stromatol was performed taking into account the number of cells obtained from automated cell count on a haematological analyser. The dilution ranged from 1:2 to 1:200. The synovial smear was stained with May Grunwald–Giemsa stain in order to accurately calculate the differential count. Additionally, at least five samples for peri-prosthetic tissue were also collected into different sterile universal receptacles in all patients for microbiological analysis. Brain–heart infusion broth (bioMerieux, Marcy l'Etoile, France) was added to the specimens within 1 h of collection and incubated for 24 h at 37 °C before terminal subculture.

Statistical analysis

Descriptive statistics were used for continuous variables, and proportions for categorical variables. Continuous variables were compared using the Mann–Whitney *U* test and categorical variables by the Fisher's exact or Chi-squared test.

Receiver operating characteristic (ROC) curves, which depict the relationship between true-positive results (sensitivity) and false-negative results (1 − specificity), were constructed for the fluid leukocyte count and the neutrophil

percentage. The Youden index J was used to determine the best cut-off value for both the overall cell count and the differential. Sensitivity, specificity, positive predictive value, and negative predictive value of single test proposed by the International Consensus Meeting on PJI were also calculated using 2 × 2 contingency tables. Areas under the ROC curves (AUC) were assessed to better evaluate the diagnostic accuracy of a single test. An AUC of 1 demonstrates an ideal test with a 100% sensitivity and 100% specificity, whereas an area under the curve of < 0.5 indicates that the diagnostic test is less useful.

Statistical significance was assumed at a p value of < 0.05. IBM SPSS Statistics 21.0.0.1 software (IBM Corp, Armonk, NY, USA) was used for the database construction and the statistical analysis.

Results

One hundred and sixty-seven patients were included in the study. The median age was 72 years (range 51–88), 58% were females. On the basis of the criteria specified above, 31 knees were judged to be infected. Positive cultures were obtained in 23/31 cases (74%). The most common microorganism retrieved was coagulase-negative *Staphylococcus* (32%) followed by non-methicillin-resistant *Staphylococcus aureus* (19%), *Enterococcus faecalis* (10%), methicillin-resistant *S. aureus* (7%), and others (7%).

Table 1 provides a summary of the median and interquartile range (IQR) of the preoperative ESR and CRP levels, white blood-cell count and the percentage of polymorphonuclear cells in the SF aspirated from both infected and non-infected knees. All values were significantly different between the two groups ($p < 0.001$). ROC curves, used for comparing the sensitivity and specificity of SF leukocyte count and neutrophil percentage differentiating aseptic failure from PJI, showed that a leukocyte count > 2.8×10^3/μL yielded a sensitivity of 83.9% and a specificity of 89.7%, whereas a neutrophil percentage of 72% had a marginally higher sensitivity of 84% and a specificity of 91% (Fig. 1).

Applying the ICM criteria, we found a significant correlation between all these diagnostic measures and PJI ($p < 0.001$) except for a single positive culture (Table 2). The single positive culture was higher in patients with aseptic loosening of TKA (14/136, 10.3%) than those with septic TKA (3/31, 9.7%) but the finding did not achieve statistical significance. Coagulase-negative Staphylococci were always cultured in the cases without infection.

The sensitivity, specificity, positive predictive value, and negative predictive value for all diagnostic criteria are shown in Table 3. Furthermore, when at least three minor criteria (elevated inflammatory markers, one positive culture, elevated SF leukocyte count or elevated synovial differential count) were positive, the sensitivity, specificity, positive predictive value, and negative predictive value were 71, 100, 92.3, and 95.7%, respectively.

ROC curves obtained for each parameter are shown in Fig. 2.

Discussion

Although a definite preoperative diagnosis of septic failure of a TKA is imperative for proper treatment and management, the diagnosis of PJI remains a clinical challenge. Preoperative aspiration with synovial fluid analysis represents the best diagnostic tool because it is rapid, low cost, and does not require specialized equipment [21].

This method allows the evaluation of leukocyte and differential counts as well as microbiological analysis. Although pre-operative knee aspiration is frequently implemented in the initial workup for a PJI, its role remains to be elucidated [22, 23]. The majority of studies focusing on synovial cell counts and reporting diagnostic threshold, does not report details on preanalytical and analytical phase aspects so the cut off values suggested or recommended, as well as the diagnostic accuracy values, appear to be questionable.

Furthermore, there is little consensus regarding the cut-off values for the SF leukocyte count and neutrophil percentage [14, 24, 25]. Trampuz et al. were the first to report cut-off values for the SF cell count and differential [14]. The

Table 1 Summary results for perioperative testing in infected and non-infected knees

	Median (IQR)		p value
	Infected ($N = 31$)	Non-infected ($N = 136$)	
ESR (mm/h)	65 (45–81)	23.0 (12.2–24.7)	<0.001*
CRP (mg/L)	22 (9.3–50)	3.7 (1.1–3.7)	<0.001*
SF WBC count (cells/μL)	7892 (3210–27,800)	807.5 (438–1832)	<0.001*
SF PMN percentage	84 (81–90)	47 (31.2–62)	<0.001*

CRP C-reactive protein, *ESR* erythrocyte sedimentation rate, *IQR* interquartile range, *PMN* polymorphonuclear, *SF* synovial fluid, *WBC* white blood cell

* Significance levels with Mann–Whitney *U* test

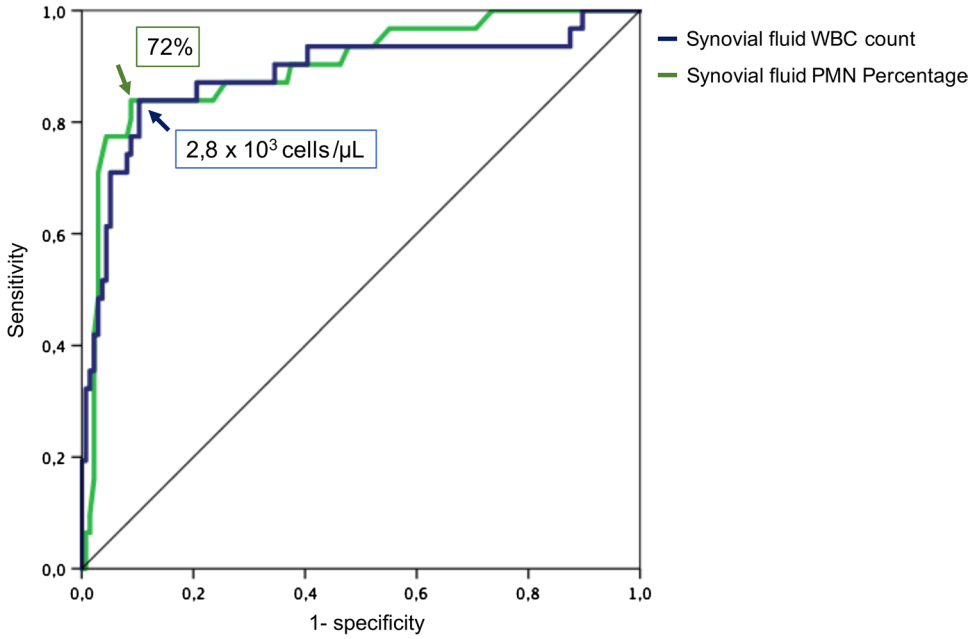

Fig. 1 ROC curves for synovial fluid leukocyte count and percentage neutrophils predicting a periprosthetic joint infection

Table 2 Comparison of the positive results of clinical and laboratory tests according to criteria proposed by the International Consensus Meeting on PJI

	Number (%)		*p* value
	Infected (*N* = 31)	Non-infected (*N* = 136)	
Two positive periprosthetic cultures with phenotypically identical organisms	21 (67.7)	0 (0)	<0.001*
A sinus tract communicating with the joint	6 (19.4)	0 (0)	<0.001*
Elevated CRP (> 10 mg/L) and ESR (> 30 mm/h)	25 (80.6)	15 (11)	<0.001**
SF WBC count > 3000/µL	25 (80.6)	12 (8.8)	<0.001**
SF PMN percentage > 80%	26 (83)	7 (5.1)	<0.001**
A single positive culture	3 (9.7)	14 (10.3)	1*

CRP C-reactive protein, *ESR* erythrocyte sedimentation rate, *IQR* interquartile range, *MSIS* Musculoskeletal Infection Society, *PMN* polymorphonuclear, *SF* synovial fluid, *WBC* white blood cell

* Significance levels by Fisher's exact test

** Significance levels by Chi-squared test

Table 3 Diagnostic accuracy of the criteria proposed by the International Consensus Meeting on chronic infection

Test	Sensitivity[a]	Specificity[a]	PPV[a]	NPV[a]
Two positive periprosthetic cultures with phenotypically identical organisms	67.7 (60–74.6)	100 (97.2–100)	100 (97.2–100)	93.2 (87.9–97.3)
A sinus tract communicating with the joint	19.4 (13.8–26.3)	100 (97.2–100)	100 (97.2–100)	84.5 (77.9–89.4)
Elevated CRP (> 10 mg/L) and ESR (> 30 mm/h)	80.6 (73.7–86.2)	89.0 (83.8–93.1)	62.5 (54.6–69.8)	95.2 (90.5–97.8)
SF WBC count > 3000/µL	80.6 (73.7–86.2)	91.2 (85.5–94.8)	67.5 (59.8–74.5)	95.4 (90.7–97.9)
SF PMN percentage > 80%	83.9 (77.2–88.9)	94.9 (90.0–97.5)	78.8 (71.7–84.6)	96.3 (91.8–98.4)
A single positive culture	9.7 (5.8–15.5)	89.7 (83.8–93.7)	17.6 (12.4–24.5)	81.3 (74.4–86.8)

PPV positive predictive value, *NPV* negative predictive value

[a] The 95% confidence intervals are shown in parentheses

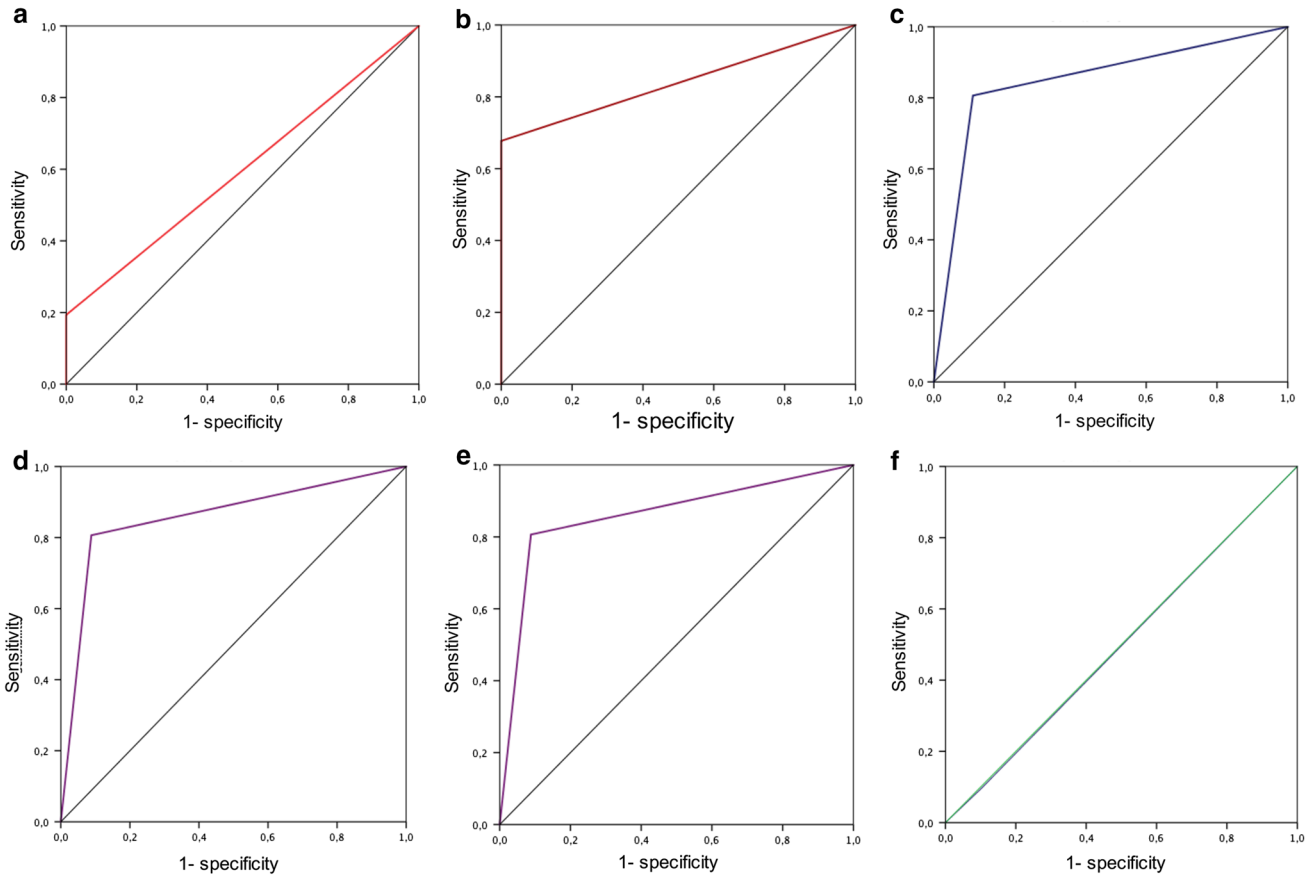

Fig. 2 Graphs showing **a** receiver operating characteristic (ROC) curve and area under curve (AUC) for Sinus tract (area under ROC curve = 0.60; 95% CI 0.47–0.72); **b** ROC curve and AUC for two positive cultures (area under ROC curve = 0.84; 95% CI 0.73–0.94); **c** ROC curve and AUC for increased inflammatory markers (ESR > 30 mm/h and CRP > 10 mg/L) (area under ROC curve = 0.85; 95% CI 0.76–0.93); **d** ROC curve and AUC for synovial WBC count (> 3000/μL) (area under ROC curve = 0.86; 95% CI 0.78–0.94); **e** ROC curve and AUC for synovial PMN percentage (PMN% > 80%) (AUC = 0.89; 95% CI 0.81–0.97); **f** ROC curve and AUC for single positive culture (area under ROC curve = 0.49; 95% CI 0.38–0.61)

cut-off values for optimal sensitivity and specificity to differentiate aseptic failure from PJI were 1.7 × 103/μL for SF leukocyte count and 65% for neutrophil percentage, reporting a sensitivity of 94 and 97% and a specificity of 88 and 98%, respectively. These results were confirmed by Nilsdotter-Augustinsson reporting lower sensitivity but higher specificity of the SF cell count [20].

A larger study of TKAs undertaken by Ghanem et al. with 429 cases found that their cut-off values for infection were > 1100 white cells/μL of which > 64% were neutrophils [15]. These values again yielded a slightly lower sensitivity (90.7%) as well as specificity (88.1%). Dinneen et al. suggested that the definitive synovial white cell count value for diagnosing infection in TKRs lies between 1100 and 1700 white cells/μL. This lower value is more in keeping with the values identified for TKAs and is predictably more sensitive than the higher values [17]. Recently, the proceedings of the International Consensus on PJI recommended the following thresholds for diagnostic tests for chronic PJI: SF WBC > 3000 cells/μL and %PMN > 80% [13]. In our study we performed a retrospective study in which we defined a cut-off value for SF leukocyte count and neutrophil percentage in order to differentiate aseptic failure from PJI. Our results identify a cut-off value for SF analysis for joint infections of 2.8×10^3 white cells/μL with neutrophilia of 72%. ROC curve analysis showed this to be a highly discriminatory diagnostic test with a sensitivity of 83.9% and specificity of 89.7% for leukocyte count and 84 and 91%, respectively, for the percentage of neutrophils. Although these cut-off values are slightly lower than those proposed by the ICM, the results in terms of diagnostic accuracy appears comparable to those reported by other key studies on infection in TKA by using ROC plot analysis [14, 15]. While at some centres, it is strongly believed that cultures alone should be used to diagnose PJI, the panel of experts that composed the ICM strongly agree that fulfilment of the minor criteria are sufficient to diagnose culture-negative PJIs [26]. Our results showed that the ROC curve

analysis for all patients confirmed the synovial neutrophil differential (PMN% > 80%) as a high-quality diagnostic test, followed by SF leukocyte count (WBC count > 3000/μL), and increased inflammatory markers (ESR > 30 mm/h and CRP > 10 mg/L). However, a single positive culture showed an unfavourable diagnostic accuracy. The single positive culture was higher in patients with aseptic loosening rather than in those with PJI. This test can be considered unhelpful to make a correct diagnosis in particular when coagulase-negative *Staphylococci* are identified. Similarly, this result underlines the importance to test different sample specimens for microbiological analysis as well as to associate others positive criteria during to confirm a PJI the diagnostic assessment [27].

Furthermore, when multiple perioperative diagnostic tests (minor criteria) were combined, the ROC curve analysis did not demonstrate increased diagnostic accuracy.

According to the diagnostic accuracy of major criteria proposed by the ICM, we reported that two positive cultures have a sensitivity of 67.7% and specificity of 100% with a good diagnostic accuracy. These results are lower than those reported by Gomez et al. who demonstrated that a minimum of two periprosthetic tissue samples has a sensitivity of 70.4% for diagnosing PJI [28]. The same result in terms of specificity is reached by presence of sinus tract (100%) reporting a 19.4% of sensitivity and a bad diagnostic accuracy.

Our study has some shortcomings. Major limitations are inherent to the retrospective study design and therefore the retrieved data concerning fluid cell count and differential as well as peripheral blood values are not as accurate as data that are collected prospectively. Second, this study does not include subjects with inflammatory joint diseases, which are known to be associated with high synovial fluid leukocyte counts and neutrophil percentage. Third, our study included only knee prostheses; it is not known whether the proposed cutoff values and diagnostic criteria are valid for other prosthetic joints. In contrast, this is the first paper that evaluate the diagnostic accuracy of the ICM criteria for diagnosing a PJI.

Conclusion

The present study highlights the adequate ability of fluid cell count and neutrophil differential to distinguish between knees with and without an infection at the site of a total knee arthroplasty. The clinical utility of fluid analysis in diagnosing infection can be improved by combining either of these two tests with the peripheral blood erythrocyte sedimentation rate, the C-reactive protein level, and SF as well as intraoperative periprosthetic tissues microbiological analysis as proposed by the ICM on PJI.

Compliance with ethical standards

Conflict of interest Authors have no conflict of interest to declare.

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