



Differential synovial fluid white blood cell count for the diagnosis of chronic peri-prosthetic joint infection – a systematic review and meta-analysis

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Abstract. Introduction: Peri-prosthetic joint infection (PJI) is a significant complication of arthroplasty, lacking a single gold standard diagnostic test. Synovial fluid white blood cell (WBC) count and polymorphonuclear neutrophil (PMN) proportion are widely used diagnostic tools, but their optimal cutoffs remain unclear, particularly for chronic PJI. **Material and methods:** This systematic review and meta-analysis included 74 studies published between 2000 and 2024. Data on diagnostic performance (sensitivity, specificity, and diagnostic odds ratios – DORs) of WBC count and PMN proportions were analysed. Sub-group analyses and heterogeneity assessments were performed, and optimal cutoffs for diagnostic accuracy were identified. **Results:** The meta-analysis revealed a WBC count summary DOR of 58.38 (95 % CI – confidence interval: 48.48–70.32) with an area under the curve (AUC) of the summarized receiver operating characteristic curve of 0.952. The PMN proportion showed a DOR of 43.17 (95 % CI: 35.31–52.79) and an AUC of 0.941. Optimal diagnostic thresholds for chronic PJI were WBC count > 2600 cells per microlitre and PMN > 70 %. Rule-in thresholds (specificity > 95 %) were WBC count ≥ 3000 cells per microlitre and PMN ≥ 75 %, while rule-out thresholds (sensitivity > 95 %) were WBC count ≤ 1500 cells per microlitre and PMN ≤ 65 %. Confounding conditions such as fractures, inflammatory arthritis, and metal-related reactions reduced test accuracy. **Conclusions:** Synovial fluid analysis remains a critical diagnostic tool for chronic PJI. Thresholds of WBC count < 1500 and > 3000 cells per microlitre and PMN < 65 % and > 75 % provide reliable negative and positive predictive values. A standardized diagnostic framework is essential for addressing remaining controversies and ensuring consistent interpretation across clinical settings.

1 Introduction

Peri-prosthetic joint infection (PJI) is a potentially dismal complication of total joint arthroplasty. As the expected number of arthroplasties is rising worldwide, so, too, is the burden of the small but consistent infection rate (Premkumar et al., 2021; Rupp et al., 2020). In fact, infection is a leading cause of total joint replacement failure, and it is critical to accurately diagnose it, as failure to do so will hamper treatment success (Sousa et al., 2023). Still, there is no available gold standard diagnostic test on its own. The definition of PJI thus relies on the combined interpretation of multiple different tests (Osmon et al., 2013; Parvizi and Gehrke, 2014; Shohat et al., 2019; Sousa et al., 2023; Workgroup Convened by the Musculoskeletal Infection Society, 2011).

Synovial fluid differential white blood cell (WBC) count is a widely available and rather inexpensive test that has long been recognized as a critical part of the preoperative workup before revision arthroplasty. Its accuracy for the diagnosis of PJI in the setting of chronically painful joints has been studied extensively and gives consistently good results.

There are, nevertheless, open questions. First, different proposed cutoffs exist due to variations in PJI definitions and joint-specific studies. Second, conditions such as peri-prosthetic fractures, inflammatory arthritis, crystal arthropathy, or metal-ion-related tissue reactions can elevate WBC counts irrespective of infection, affecting accuracy. Third, the role of differential WBC count in acute postoperative PJI remains less clear due to post-surgical inflammation.

This systematic review aimed to (1) determine the overall diagnostic accuracy of synovial WBC counts and polymorphonuclear neutrophil (PMN) proportions for chronic PJI, (2) establish optimal interpretation cutoffs, and (3) evaluate test performances under confounding conditions.

2 Material and methods

This systematic review adheres to PRISMA of Diagnostic Test Accuracy Studies (PRISMA-DTA) (McInnes et al., 2018).

2.1 Search strategy

A computer-aided search on MEDLINE and EMBASE (1 January 2000–1 February 2024) identified studies evaluating synovial WBC count and PMN proportion for PJI diagnosis. Reference lists of included articles were also reviewed. The search strategy combined terms related to arthroplasty infection, synovial fluid diagnosis, and diagnostic accuracy (see Table S1 in the Supplement).

2.2 Inclusion and exclusion criteria

Studies were included if they evaluated synovial fluid WBC count and/or PMN proportion in suspected PJI cases, pro-

vided diagnostic performance data, were conducted on humans ≥ 18 years old, and were published in English between 2000 and 2024. Only studies reporting results on chronic PJI were included. We excluded studies on infections unrelated to PJI, case reports, animal studies, and reviews.

Duplicates were removed using Mendeley. Screening was performed with Rayyan software by two independent reviewers per article, first by title or abstract and then by full text. Disagreements were resolved by consensus. The study selection process is shown in Fig. 1 (Page et al., 2021).

2.3 Data extraction

Data were extracted in duplicate, resolving discrepancies by consensus. Collected data included study characteristics, diagnostic criteria, infection type, patient characteristics (e.g. inflammatory diseases, fractures, metallosis, or inflammatory arthritis), WBC count and PMN cutoffs, sensitivity, specificity, predictive values, area under the curve (AUC), accuracy, and Youden index. True positive, true negative, false positive, and false negative values were calculated.

2.4 Risk of bias and quality assessment

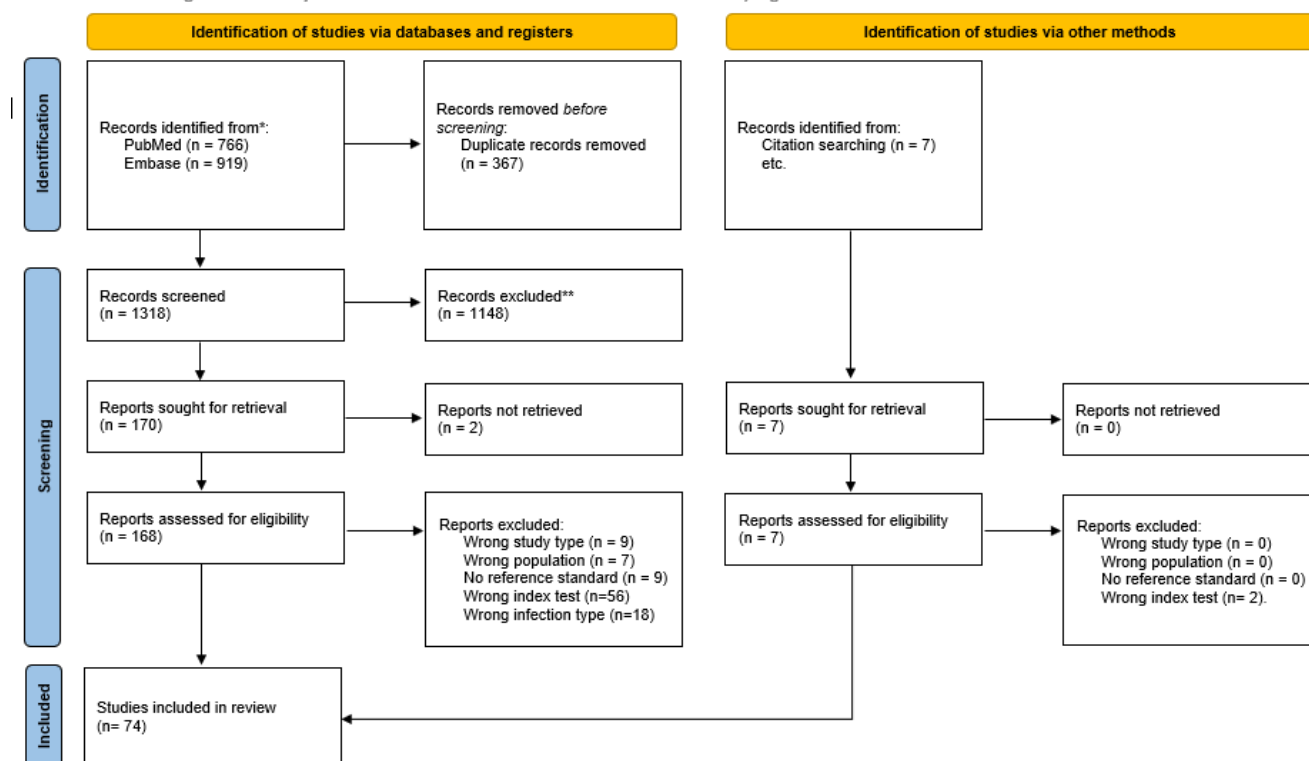
Two independent investigators per article assessed the risk of bias and applicability of each included study by using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) (Whiting et al., 2011) tool, with ratings of “low”, “high”, or “unclear”. Discrepancies were resolved by consensus.

Quality was assessed by two independent investigators per article with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool (Schünemann et al., 2023). This tool is used to evaluate the quality of the evidence and the strength of the recommendations. Studies were classified as “high (A)”, “moderate (B)”, “low (C)”, or “very low (D)” quality.

2.5 Information synthesis and statistical analysis

With the information extracted, we calculated the diagnostic odds ratio (DOR) for every study. Although sensitivity and specificity are commonly used in diagnostic test research due to their clinical relevance, these metrics can introduce a threshold effect when multiple studies are compared. Although the DOR has limited direct clinical application, it is particularly useful in systematic reviews of diagnostic accuracy because it reflects the overall effectiveness of a diagnostic test (Arias and Molina, 2015; De Sousa et al., 2009). We used DORs along with 95 % confidence intervals (CIs) and summarized receiver operating characteristic (sROC) curves as part of the meta-analysis (De Sousa et al., 2009). The analyses were conducted by using a random-effects model and the DerSimonian–Laird approach. In addition, a sub-group

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71.

Figure 1. PRISMA flow diagram.

analysis was performed based on the joint involved (hip or knee).

Heterogeneity in the reported sensitivities and specificities was assessed by using Higgins' I^2 statistic. All statistical analyses were performed with Jamovi (version 2.2.5) and Meta-disc (versions 1–4).

2.6 Cutoff determination

To determine interpretation cutoff values, we used only those articles that calculated their own ideal cutoff based on their data and excluded all papers that used pre-determined cutoffs. We excluded from this analysis studies that focused on patients with confounding circumstances such as fractures or dislocation, inflammatory arthritis, crystal arthropathy, or adverse local tissue reactions due to metal ions.

We used three different data interpretation strategies: (1) the “optimal” cutoff based on the best combination of specificity and sensitivity, (2) a “rule-in” cutoff that focused on optimizing specificity, and (3) a “rule-out” cutoff that focused on optimizing sensitivity.

We used the Youden index and extracted cutoffs and presented them in a scatterplot diagram. The optimal cutoff was determined by using median values. We obtained optimal

cutoffs for combined total knee arthroplasty (TKA) and total hip arthroplasty (THA) as well as for TKA and THA individually.

To estimate an ideal rule-in/rule-out threshold, we decided to use only specificity or sensitivity values of $> 95\%$. We used specificity or sensitivity vs. extracted cutoffs and presented them in a scatterplot diagram, and the rule-in/rule-out cutoff was determined using median values. We obtained the rule-in/rule-out value for the combined TKA and THA. There were not enough data to extract a rule-in value for TKA and THA individually.

We performed a post hoc sub-analysis by sub-dividing groups between the modern or more sensitive PJI definition criteria (International Consensus Meeting ICM, European Bone and Joint Infection Society EBJIS, and Infectious Disease Society of America IDSA) and the old PJI definition criteria (Musculoskeletal Infection Society MSIS and clinical outcome) to analyse the sensitivity and specificity cutoff values of these two groups. Information concerning other joints (e.g. shoulders, elbows, hemi-hips, uni-knees, or ankles) was too scarce to merit meaningful calculations.

3 Results

3.1 Search results

The search identified 1685 records. After removing duplicates, 1318 studies underwent title and abstract screening. Of 170 full-text studies assessed, 96 were excluded for reasons such as wrong study type (9), incorrect population (7), unspecified reference standard (9), different index test (56), or lack of chronic PJI separation (18). Five additional studies were identified through bibliography review, yielding 74 included studies (Fig. 1).

3.2 Risk of bias and quality assessment

Results from QUADAS-2 (Whiting et al., 2011) are presented in Fig. 2. Most studies had a high risk of bias but good applicability, largely due to retrospective study designs. Patient selection was unclear in more than 10 studies, while index test and reference standard issues were found in more than 20 studies.

GRADE assessment classified 13 studies (17.6 %) as B, 43 (58.1 %) as C, and 18 (24.3 %) as D (Fig. 2). Because of the retrospective nature of the majority of the papers, more than 50 % of the studies included were classified as GRADE C.

3.3 Characteristics of the studies

We included 74 studies (Table 1). The publication years ranged from 2003 to 2024, the year with the highest publication rate being 2023 with 13 papers. Twenty-six papers were prospective cohorts (35.1 %) and 48 were retrospective cohorts (64.9 %), covering 18 960 patients (19 to 4462). Papers used different PJI reference standards: 14 used clinical definitions (18.9 %), 3 the IDSA 2013 definition (4.1 %), 35 the MSIS 2013 definition (47.3 %), 17 the ICM 2018 definition (23 %), and 4 the EBJIS 2021 definition (5.4 %). One paper combined MSIS 2013 and ICM 2018.

We extracted 135 different cutoffs for synovial WBC count and 114 different cutoffs for synovial PMN. The distribution by joint for synovial WBC count was 63 for hips and knees together, 28 for knees only, 31 for hips only, 4 for shoulders only, and 7 for all four joints together. The distributions by joint for synovial polymorphonuclear proportion (PMN %) were 52, 29, 29, 2, and 4, respectively. There was also one study that focused on unicompartmental knee replacements (Schwartz et al., 2012), one on hip hemiarthroplasties (Salimy et al., 2024), and one on total ankle replacement (Thiesen et al., 2019), which provided information on synovial WBC count and PMN % (Table 2).

Considering all papers with no sub-groupings at all, the proposed optimal cutoffs varied widely between 700 and 19 240 cells per microlitre and between 53 % and 99 % PMN. Median values were 3000 cells per microlitre and 75.4 % PMN for all joints and all conditions. Median values for

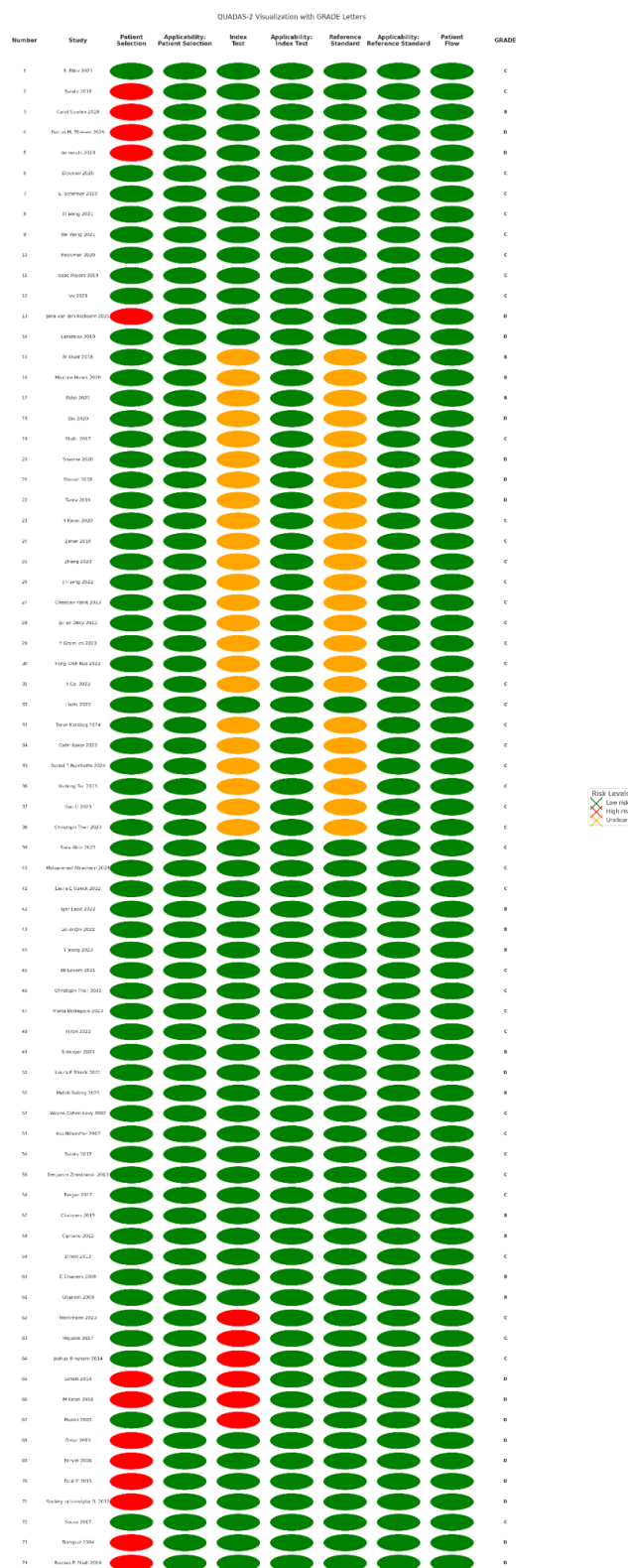


Figure 2. QUADAS-2 and GRADE assessment.

Table 1. General characteristics of primary studies.

Author	Year	Type of study	Infected patients/ total	Joints	PJI reference standard	Special condition	WBC count cutoff	Sensitivity and specificity	PMN count cutoff	Sensitivity and specificity	Cutoff determination	Reporting funds
Bernd Fink (Fink et al., 2021)	2021	Prospective	112/434	Hips and knees	ICM 2018	No	1400 500 1000 1500 2000 3000	90.2 %/91.9 % 98.8 %/91 % 93.8 %/92.9 % 90.2 %/95.7 % 86.6 %/91.2 % 80.6 %/94.9 %	NA	NA	Youden Youden Youden Youden Youden Youden	NM
Giovanni Balato et al., 2018a)	2018	Retrospective	31/167	Knees	MSIS	No	3000	80.6 %/91.2 %	80 %	83.9 %/94.9 %	Youden	NM
Carol Strahm (Strahm et al., 2018)	2018	Retrospective	13/19	Shoulders	IDSA	No	12 200	92 %/100 %	54 %	100 %/75 %	Youden	NM
Darius M. Thiesen (Thiesen et al., 2019)	2019	Retrospective	2/31	Ankles	MSIS	No	NA	100 %/37.5 %	NA	100 %/77.8 %	Youden	No funding
Elena De Vecchi (De Vecchi et al., 2018)	2018	Retrospective	32/66	Hips and knees	MSIS	No	3000 1600	93.7 %/91.2 % 100 %/82.3 %	NA	NA	Pre-determined TWC	NM
Casper Dijkman (Dijkman et al., 2020)	2020	Retrospective	13/89	Hips and knees	MSIS	No	2575 1865	92 %/84 % 100 %/97 %	NA	NA	Youden Youden	NM
Erik Schiffner (Schiffner et al., 2020)	2020	Retrospective	32/149	Knees	MSIS	No	3000	84 %/96 %	65 %	84 %/94 %	Pre-determined	NM
Hai Wang (Wang et al., 2021b)	2021	Prospective	37/93	Hips and knees	MSIS	No	NA	NA	69.96 %	94.6 %/92.8 %	Youden	NM
Hai Wang (Wang et al., 2021a)	2021	Prospective	39/97	Hips and knees	MSIS	No	NA	NA	69.8 %	84.6 %/74.1 %	Youden	NM
Heckman Nathanael Heckmann (Heckmann et al., 2020)	2020	Prospective	16/78	Hips and knees	MSIS	No	3000 (pre-lavage) 3000 (post-lavage)	100 %/100 % 62.5 %/98.4 %	80 % (pre-lavage) 80 % (post-lavage)	81.3 %/96.8 % 75 %/95.2 %	Pre-determined Pre-determined	NM
Isaac Majors (Majors and Jagdale, 2019)	2019	Prospective	32/59	Knees	MSIS	No	1804	%/81 %	86 %	82.4 %/73.7 %	Youden	NM
Ivy (Ivy et al., 2021)	2021	Prospective	18/99	Knees Hips	MSIS	No	1700 3000	83.3 %/93.8 % 83.3 %/93.8 %	65 % 80 %	83.3 %/94.9 % 83.3 %/94.9 %	Pre-determined Pre-determined	NM

Table 1. Continued.

Author	Year	Type of study	Infected patients/ total	Joint	PJI reference standard	Special condition	WBC count cutoff	Sensitivity and specificity	PMN cutoff	Sensitivity and specificity	Cutoff determination	Reporting funds
Jana van den Kieboom (van den Kieboom et al., 2021)	2021	Retrospective	41/144	Hips and knees	MSIS	Fracture	3000 4552	87 %/77.9 % 86.4 %/85.3 %	80 % 79.5 %	79 %/63.2 % 73.7 %/63.2 %	Pre-determined Q point	NM
Alexander Lazarides (Lazarides et al., 2019)	2019	Retrospective	16/87	Hips and knees	MSIS	Immunosuppression	1293	93.3 %/84.4 %	65 %	81.3 %/87.3 %	Youden	Yes
Michael M. Kheir (Kheir et al., 2018)	2018	Retrospective	54/91/202	Hips and knees	ICM 2018	No	2659 3000	85 %/93 % 83 %/94 %	64.5 % 80 %	91 %/86 % 78 %/93 %	Youden Pre-determined	No funding
Maxime Huard (Huard et al., 2020)	2020	Prospective	41/138 50/138 68/138 35/138	Hips and knees	MSIS IDSA EBJIS Positive culture Positive culture	No	3000 3000 3000 881	87.7 %/95.7 % 70 %/94.2 % 55.8 %/97 % 80 %/91 %	NA	NA	Pre-determined Pre-determined Pre-determined Youden	NM
Vikas V. Patel (Patel et al., 2021)	2021	Retrospective	20/87	Shoulders	ICM 2018	No	3000	30 %/100 %	80 %	20 %/100 %	Pre-determined	NM
Leilei Qin (Qin et al., 2020)	2020	Prospective	25/50	Hips and knees	MSIS	No	NA	NA	69.79 %	92 %/80 %	Youden	NM
Alisina Shahi (Shahi et al., 2017)	2017	Retrospective	822/4462	Hips and knees	MSIS	No	3000	85.8 %/83 %	80 %	85.8 %/80.8 %	Pre-determined	NM
Katayini Sharma (Sharma et al., 2020)	2020	Retrospective	50/107	Hips and knees	MSIS	No	1100	89 %/98 %	72 %	92 %/91 %	Pre-determined	NM
Noam Shohat (Shohat et al., 2018)	2018	Retrospective	567/1220	Hips and knees	MSIS	No No Inflammation Inflammation	3000 2533 3000 2683	81.8 %/95.1 % 83.4 %/93.3 % 88.2 %/78.6 % 91.2 %/78.6 %	80 % 73 % 80 % 72 %	77.7 %/94.3 % 86.8 %/89.9 % 93.7 %/84.6 % 100 %/82.7 %	Pre-determined Youden Pre-determined Youden	NM
Mesut Tahta (Tahta et al., 2019)	2019	Prospective	17/38	Knees	MSIS	Inflammation	2347	84.6 %/76.4 %	76.7 %	79.2 %/90.3 %	Youden	NM
Young-Min Kwon (Kwon et al., 2020)	2020	Retrospective	11/89	Hips	MSIS	ATRLs	2144 13 796	93 %/84 % 100 %/100 %	84 % 82 %	84 %/86 % 93 %/82 %	Youden Youden	No funding
Akos Zahar (Zahar et al., 2018)	2018	Retrospective	134/337	Hips and knees Hips and knees	MSIS	No	2582 1630 3063	80.6 %/85.2 % 83.5 %/82.2 % 78.1 %/80 %	66.1 % 60.5 % 66.1 %	80.6 %/83.3 % 80.3 %/77.1 % 82.2 %/82.4 %	Youden Youden Youden	NM

Table 1. Continued.

Author	Year	Type of study	Infected patients/ total	Joints	PJI reference standard	Special condition	WBC count cutoff	Sensitivity and specificity	PMN cutoff	Sensitivity and specificity	Cutoff determination	Reporting funds
Zeyu Zhang (Zhang et al., 2020)	2020	Retrospective	21/63	Hips and knees	MSIS	No	3000	85.7 %/83.3 %	65 %	90.5 %/85.7 %	Youden	NM
Jiaxing Huang (Huang et al., 2022)	2022	Prospective	43/99	Hips and knees	MSIS	No	3000	85.7 %/83.3 %	75 %	95.3 %/78.6 %	Youden	NM
Christian Klemm (Klemm et al., 2023)	2023	Retrospective	191/464	Hips	ICM 2018	No	3000	86.9 %/79.1 %	80 %	87.9 %/78.7 %	Pre-determined	NM
Julian E. Dilley (Dilley et al., 2023)	2023	Retrospective	321/730	Hips and knees	MSIS	No	5600 3000	71.8 %/85.6 % 76 %/80.2 %	82 % 80 %	81 %/77.5 % 82.2 %/76 %	Youden Pre-determined	NM
Y. Gramlich Yves Gramlich (Gramlich et al., 2023)	2023	Prospective	111/405	Hips, knees, and shoulders Knees Hips	ICM 2018	No	2478.9 1500 1750 2000 2500 3000 3085.7 2267.8	87.7 %/88.1 % 91.5 %/75 % 89.6 %/78.7 % 89.6 %/83.4 % 86.6 %/88.1 % 82.1 %/91 % 86.7 %/91.8 % 87.5 %/83.5 %	67 % 65 % 70 % 80 % 67.01 % 67.04 %	86 %/88.8 % 86 %/88.8 % 82.6 %/90 % 66.3 %/96.5 % 87.5 %/88.2 % 81.5 %/94.1 %	Youden Pre-determined Youden Youden	NM
Feng Chih Kuo (Kuo et al., 2022)	2022	Retrospective	42/76	Hips and knees	ICM 2018	No	3000	68 %/94 %	70 %	71 %/84 %	Pre-determined	No funding
Yuanqing Cai (Cai et al., 2023)	2023	Retrospective	46/74	Hips and knees	MSIS	No	3000	63 %/74 %	80 %	78.2 %/71.4 %	Pre-determined	NM
Igor Lazic (Lazic et al., 2022a)	2022	Prospective	17/32	Hips and knees	EBJIS	Fracture	6130	41 %/100 %	79.5 %	71 %/100 %	Youden	NM
Taner Karlidag (Karlidag et al., 2024)	2024	Retrospective	50/144 59/116	Knees Hips	ICM 2018	No	2553.5 3512.5	92 %/91.4 % 83 %/85.9 %	81.7 % 83.6 %	88 %/93.6 % 86.4 %/93.6 %	Youden Youden	No funding
Colin M. Baker (Baker et al., 2022)	2022	Retrospective	194/621	Hips and knees	ICM 2018	No	3000	85.7 %/100 %	80 %	92.6 %/96 %	Pre-determined	NM
Daniel Timothy Burchette (Burchette et al., 2024)	2024	Retrospective	162/520 32/68	Knees Hips	ICM 2018	No	3000 3000	92 %/99 % 92.8 %/98.5 %	80 % 80 %	86.4 %/99.2 % 85.3 %/99.4 %	Pre-determined Pre-determined	NM
Daniel Timothy Burchette (Burchette et al., 2024)	2024	Retrospective	185/362	Hips and knees	ICM 2018	No	2581	74.3 %/88 %	75.4 %	68.8 %/97.6 %	Youden	NM
Xudong Su (Su et al., 2023)	2023	Retrospective	30/60	Hips and knees	MSIS	No	NA	NA	51.1 %	96.7 %/73.3 %	Youden	NM
Hao Li (Li et al., 2023)	2023	Retrospective	48/90	Hips and knees	ICM 2018	No	3000	74 %/94.4 %	70 %	79.6 %/79.6 %	Pre-determined	NM

Table 1. Continued.

Author	Year	Type of study	Infected patients/ total	Joints	PJI reference standard	Special condition	WBC count cutoff	Sensitivity and specificity	PMN cutoff	Sensitivity and specificity	Cutoff determination	Reporting funds
Cristoph Theil (Theil et al., 2024)	2023	Retrospective	55/108	Knees	MSIS	ALTRs	1200 1500	94.5 %/75.5 % 89.1 %/79.2 %	63 % 65 %	85.5 %/73.6 % 85.5 %/77.4 %	Youden Pre-determined	NM
Sara Elisa Diniz (Diniz et al., 2023)	2023	Retrospective	36/102	Hips and knees	EBJIS	No	1470 2645 3280	91.7 %/92.4 % 77.8 %/98.5 % 77.8 %/100 %	62.5 % 64.4 % 79.5 %	88.9 %/83.9 % 86.1 %/88.7 % 75 %/98.4 %	Youden Youden Youden	NM
Mohammed F. Alkadhem (Alkadhem et al., 2024)	2024	Retrospective	19/137	Hips and knees Knees Hips	EBJIS	No	1500 3000 3000 3000	74 %/71 % 75 %/86 % 100 %/87 % 58 %/84 %	65 % 80 % 80 % 80 %	89 %/78 % 89 %/85 % 100 %/85 % 91 %/84 %	Pre-determined Pre-determined Pre-determined Pre-determined	NM
Sara Elisa Diniz (Streck et al., 2022b)	2022	Retrospective	21/35	Shoulders	ICM 2018	No	700	85.7 %/100 %	NA	NA	Youden	NM
Igor Lazic (Lazic et al., 2022b)	2022	Prospective	14/30	Hips and knees	EBJIS	Fracture	4550	40 %/100 %	79 %	30 %/100 %	Youden	NM
Lei Lei Qin (Qin et al., 2022)	2022	Prospective	35/70	Hips and knees	MSIS	Inflammation	NA	NA	69.8 %	88.6 %/80 %	Youden	NM
Yulai Wang (Wang et al., 2023)	2023	Retrospective	164/348	Hips and knees	MSIS	No Inflammation	2673 3654	80.5 %/96.4 % 80.5 %/94.4 %	62 % 65.9 %	92.8 %/92.9 % 85.4 %/77.8 %	Youden Youden	Yes
Ali Levent (Levent et al., 2021)	2021	Retrospective	109/260	Hips and knees	ICM 2018	No	3000 2950	87.2 %/88.1 % 88.1 %/88.1 %	70 % 77.8 %	89.9 %/84.1 % 89.9 %/91.4 %	Pre-determined Youden	No funding
Cristoph Theil (Theil et al., 2022)	2022	Prospective	30/92	Hips and knees	ICM 2018	No	3000	90 %/88 %	80 %	73 %/98 %	Pre-determined	NM
Martina Bottagisio (Bottagisio et al., 2023)	2023	Prospective	12/55	Hips and knees	ICM 2018	No	6740	85.7 %/97.1 %	85 %	85.7 %/97.1 %	Youden	NM
Yi Ren (Ren et al., 2022)	2020	Retrospective	63/NA	Hips and knees	Cultures	Inflammation	1948	83.3 %/72.7 %	85.3 %	83.3 %/73 %	Youden	NM
Steven Denyer (Denyer et al., 2023)	2023	Retrospective	124/283 122/289	Knees Hips	IDSA	No	3000 3000	89.9 %/89.7 % 82.5 %/80 %	80 % 80 %	89.5 %/100 % 82.5 %/62.5 %	Pre-determined Pre-determined	NM
Laura Elisa Streck (Streck et al., 2022a)	2021	Retrospective	15/31	Shoulders	IDSA	No	2800	86.7 %/87.5 %	NA	NA	Youden	NM
Mehdi S. Salimni (Salimni et al., 2023)	2023	Retrospective	116/207	Hips and knees	ICM 2018	Antibiotic	2339	95.2 %/93.3 %	83 %	90.5 %/80 %	Youden	No funding
Wayne B. Cohen-Levy (Cohen-Levy et al., 2022)	2002	Retrospective	20/109	Knees	MSIS + ICM 2018	No	2695	94 %/90 %	52.5 %	94 %/93 %	Youden	No funding

Table 1. Continued.

Author	Year	Type of study	Infected patients/ total	Joints	PJI reference standard	Special condition	WBC count cutoff	Sensitivity and specificity	PMN cutoff	Sensitivity and specificity	Cutoff determination	Reporting funds
Asa Nilsson (Nilsson et al., Augustinsson et al., 2007)	2007	Prospective	25/85	Hips	Symptoms Cultures Sinus	No	1700	86 %/92 %	NA	NA	Youden	NM
Giovanni Balato (Balato et al., 2018b)	2017	Prospective	16/51	Knees	MSIS	No	3000	75 %/91.4 %	80 %	75 %/97 %	Pre-determined	NM
Benjamin Zmislowski (Zmislowski et al., 2012)	2013	Retrospective	73/150	Knees	Cultures Synovial fluid	No	3000	93 %/94 %	75 %	93 %/83 %	Youden	NM
Pieter Berger (Berger et al., 2017)	2017	Prospective	34/121	Hips and knees	MSIS	No	3000	89.3 %/96.2 %	80 %	89.3 %/92.2 %	Pre-determined	NM
Peter N. Chalmers (Chalmers et al., 2014)	2015	Prospective	91/433	Knees	Cultures Sinus Synovial fluid	Fracture	4450	90 %/98.5 %	73 %	89.4 %/93.6 %	Youden	NM
Cara A. Cipriano (Cipriano et al., 2012)	2012	Prospective	165/871	Hips and knees	Cultures Synovial fluid	No	3450 3444	91 %/93 % 88.2 %/80 %	78 % 75 %	95.5 %/87.3 % 100 %/93 %	Youden Youden	No funding
Alex Dinnen (Dinnen et al., 2013)	2013	Prospective	34/75 knees	Hips and Histology Hips Knees	Cultures	No	1590	89.5 %/91.3 %	65 %	89.7 %/86.6 %	Youden	NM
Eli Ghanem (Ghanem et al., 2008b)	2008	Retrospective	91/128	Knees	Cultures X-rays Purulence CRP	No	1760	95.6 %/68.6 %	73 %	95.6 %/73 %	Youden	Yes
Eli Ghanem (Ghanem et al., 2008a)	2008	Retrospective	161/429	Knees	Abscess Sinus Cultures Purulence	No	1100	90.7 %/88.1 %	64 %	95 %/94.7 %	Youden	Yes
Nathaniel Heckmann (Heckmann et al., 2023)	2023	Retrospective	21/172	Knees	ICM 2018	No	3000	85.7 %/100 %	80 %	79.2 %/99.1 %	Pre-determined	NM
Carlos A. Higuera (Higuera et al., 2017)	2017	Retrospective	79/453	Hips	MSIS	No	3966	89.5 %/91.2 %	80 %	92.1 %/85.8 %	NA	No funding
Joshua Bingham (Bingham et al., 2014)	2014	Retrospective	19/61	Hips and knees	MSIS	No	1700	95 %/85 %	NA	NA	Youden	Yes

Table 1. Continued.

Author	Year	Type of study	Infected patients/ total	Joints	PJI reference standard	Special condition	WBC count cutoff	Sensitivity and specificity	PMN cutoff	Sensitivity and specificity	Cutoff determination	Reporting funds
Markus Lenski (Lenski and Scherer, 2014)	2014	Retrospective	3/69	Hips, knees, and shoulders	MSIS	No	2300	60 %/94.3 %	NA	NA	Youden	NM
Young-Min Kwon (Kwon et al., 2016)	2016	Retrospective	7/62	Hips	MSIS	ALTRs	730 892 2700 2930 3835 4400 6800 12 600	86 %/80 % 71 %/80 % 71 %/93 % 57 %/93 % 57 %/95 % 43 %/95 % 43 %/96 % 14 %/96 %	65 % 74 % 75 % 80 % 84 % 87 % 89 % 94 %	100 %/70 % 83 %/70 % 83 %/79 % 50 %/79 % 50 %/85 % 33 %/85 % 33 %/89 % 17 %/94 %	Youden Youden Youden Youden Youden Youden Youden Youden	No funding
J. Bohannon Mason (Mason et al., 2003)	2003	Retrospective	3/86	Knees	Cultures Histology	No	5000 2500	19 %/100 % 69 %/98 %	80 % 60 %	57 %/100 % 76 %/89 %	Paired Paired	No funding
Mohamed Omar (Omar et al., 2015)	2015	Prospective	21/80	Hips	Sinus Purulence Cultures	No	3089	85 %/86.3 %	72.1 %	90 %/99 %	Youden	NM
Javad Parvizi (Parvizi et al., 2006)	2006	Prospective	94/145	Hips and knees	Cultures Purulence CRP/ESR	No	1760	90 %/99 %	73 %	93 %/95 %	Youden	NM
Paul H. Yi (Yi et al., 2015)	2015	Retrospective	19/150	Hips	MSIS	ATLRs	4350	100 %/95 %	85 %	82 %/87 %	Youden	Yes
Society Unicondylar Knee (Schwartz et al., 2012)	2012	Retrospective	28/259	Unicondylar knees	Cultures Sinus Purulence Histology	No	6200	90 %/96.5 %	60 %	90.8 %/93.8 %	Youden	NM
Ricardo Sousa (Sousa et al., 2017)	2017	Prospective	23/55	Hips and knees	ICM 2018	No	1463 2064	100 %/71.9 % 91.3 %/75 %	78 % 81 %	87 %/71.9 % 78.3 %/75 %	Youden Youden	No funding
Andrei Trampuz (Trampuz et al., 2004)	2004	Prospective	34/133	Knees	Cultures Purulence Histology	No	1700	94 %/88 %	65 %	97 %/98 %	NM	Yes
Roshan P. Shah (Shah et al., 2016)	2016	Retrospective	14/121	Hips and knees	MSIS	Fracture	2707	100 %/65 %	77 %	100 %/63 %	Youden	Yes

NA means "not available".

Table 2. Proposed interpretation cutoffs for joints other than TKA and THA.

	WBC count (cells per microlitre)		PMN (%)	
	Range	Median	Range	Median
Total shoulder	700–12 200	2900	54 %–80 %	67 %
Unicompartmental knee		6200*		60 %*
Hip hemiarthroplasty		2700*		81 %*
Total ankle		NA*		NA*

* Only one paper for this condition. TKA: total knee arthroplasty. THA: total hip arthroplasty. WBC: white blood cell. PMN %: polymorphonuclear proportion. NA: not available.

knees, hips, and shoulders separately were 3000 cells per microlitre and 71.5 % PMN, 3000 cells per microlitre and 80 % PMN, and 2900 cells per microlitre and 67 % PMN, respectively.

3.4 Meta-analysis

WBC count showed a summary DOR of 58.38 (95 % CI: 48.48–70.32), an AUC of the sROC of 0.952 (SE: 0.0042), and a *Q* index of 0.893. PMN proportion showed a summary DOR of 43.17 (95 % CI: 35.31–52.79), an AUC of the sROC of 0.941 (SE: 0.057), and a *Q* index of 0.879 (Fig. 3).

The heterogeneities (*I*²) of sensitivity and specificity for WBC count were 99.3 % and 88.3 %, respectively, and for PMN % they were 93.9 % and 88.5 %, respectively. DOR heterogeneity was 77.4 % for WBC count and 77.9 % for PMN %.

In the sub-group analysis by joint, knees presented a WBC count summary DOR of 83.1 (95 % CI: 54.72–126.21), an AUC of the sROC of 0.954 (SE: 0.0082), a *Q* index of 0.896, a PMN proportion summary DOR of 63.29 (95 % CI: 38.62–103.74), an AUC of the sROC of 0.936 (SE: 0.011), and a *Q* index of 0.882. In hips, results showed a WBC count summary DOR of 33.58 (95 % CI: 21.44–52.63), an AUC of the sROC of 0.952 (SE: 0.019), a *Q* index of 0.893, a PMN proportion summary DOR of 27.12 (95 % CI: 16.22–45.35), an AUC of the sROC of 0.954 (SE: 0.012), and a *Q* index of 0.897 (Figs. 4 and 5).

3.5 Cutoff determination

In the chronic stage, when no confounding circumstances were present, and excluding papers that used pre-determined cutoffs, the suggested cutoffs varied between 1100 and 5000 cells per microlitre and 53 % and 86 % PMN. The optimal cutoff values were 2537 cells per microlitre for knees, 2696 cells per microlitre for hips, and 70 % PMN for both (Fig. 6, Table 3).

Rule-in cutoffs of ≥ 2700 cells per microlitre and ≥ 75 % consistently demonstrated over 95 % specificity, and rule-out cutoffs of ≤ 1640 cells per microlitre and ≤ 66 % ex-

ceeded 95 % sensitivity for both hips and knees. There was not enough information to recommend a different cutoff for joints other than TKA and THA (Table 3).

When sub-dividing groups between more sensitive PJI definition criteria (ICM, EBJIS, and IDSA; Group 1) and other PJI definition criteria (MSIS and clinical outcome; Group 2), we could see that optimal cutoffs were very similar between them. However, when we applied a rule-in/rule-out calculation, Group 2 presented insufficient data in some cases due to the small number of papers with a specificity or sensitivity of > 95 % (Table 4).

3.6 Confounding conditions

Some papers were focused on specific conditions that can modify synovial cellularity and PMN %, the so-called confounding conditions. We found six different conditions: five papers were specific to peri-prosthetic fracture associated with PJI (Chalmers et al., 2014; van den Kieboom et al., 2021; Lazic et al., 2022a, b; Shah et al., 2016), six papers to inflammatory conditions (Cipriano et al., 2012; Qin et al., 2022; Ren et al., 2022; Shohat et al., 2018; Tahta et al., 2019; Wang et al., 2023), four papers to adverse local tissue reactions due to head–neck taper corrosion or metal-on-metal bearings (Kwon et al., 2016, 2020; Theil et al., 2024; Yi et al., 2015), one paper to immunosuppressed patients (Lazarides et al., 2019), and one paper to antibiotic use (Salimy et al., 2023).

The cutoff variability and medians of confounding conditions are presented in Table 5. We were not able to replicate our cutoff interpretation strategy due to the small sample size, but Fig. 7 shows a rough estimate of the diagnostic accuracy in each scenario.

4 Discussion

Accurate PJI diagnosis is challenging, as there is no perfect gold standard test. Definitive diagnosis must therefore rely on a set of pre-determined criteria that include both preoperative and intraoperative findings such as microbiological and histological results. In the past decade, several different

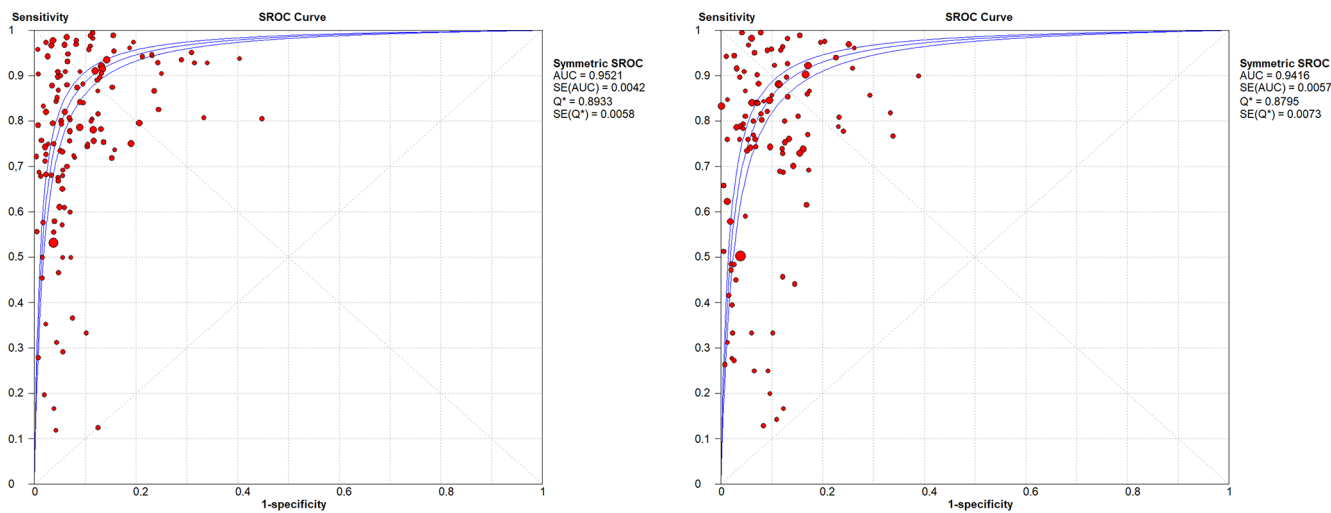


Figure 3. sROC for WBC count and PMN % in all joints.

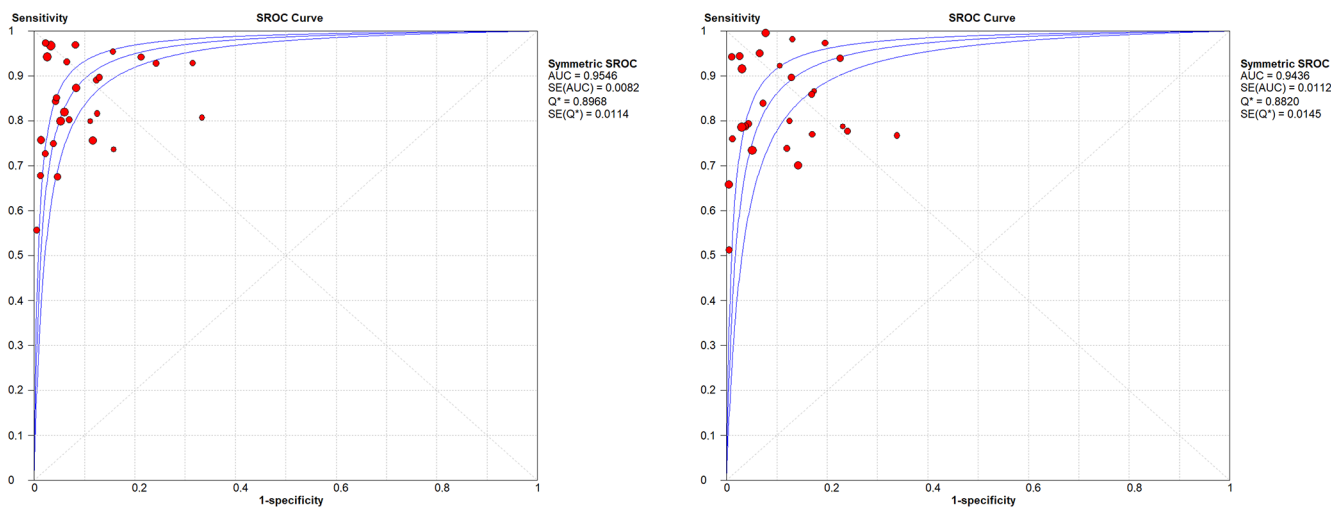


Figure 4. sROC for WBC count and PMN % in knees.

Table 3. Summary of the proposed cutoffs.

	WBC count (cells per microlitre)			PMN (%)		
	Optimal ¹	Rule-out ²	Rule-in ³	Optimal ¹	Rule-out ²	Rule-in ³
Chronic PJI*	2600	1640	2700	70 %	66.5 %	74.5 %
Hip	2696	—	—	70.5 %	—	—
Knee	2537	—	—	67 %	—	—

* Not enough information available to recommend cutoffs for joints other than TKA and THA. ¹ Defined by the best combination of sensitivity and specificity. ² Defined by a sensitivity of > 95 %. ³ Defined by a specificity of > 95 %.

PJI definitions have been proposed, which have all included synovial fluid examination (Mcnally et al., 2021; Osmon et al., 2013; Shohat et al., 2019; Workgroup Convened by the Musculoskeletal Infection Society, 2011). Although there is no universally accepted algorithm for diagnosis, it is indis-

putable that joint aspiration with a differential synovial fluid WBC count is a critical part of current diagnosis.

Our systematic review confirms its value. The DOR and sROC results obtained in our meta-analysis demonstrated that both tests have a high diagnostic accuracy and are pow-

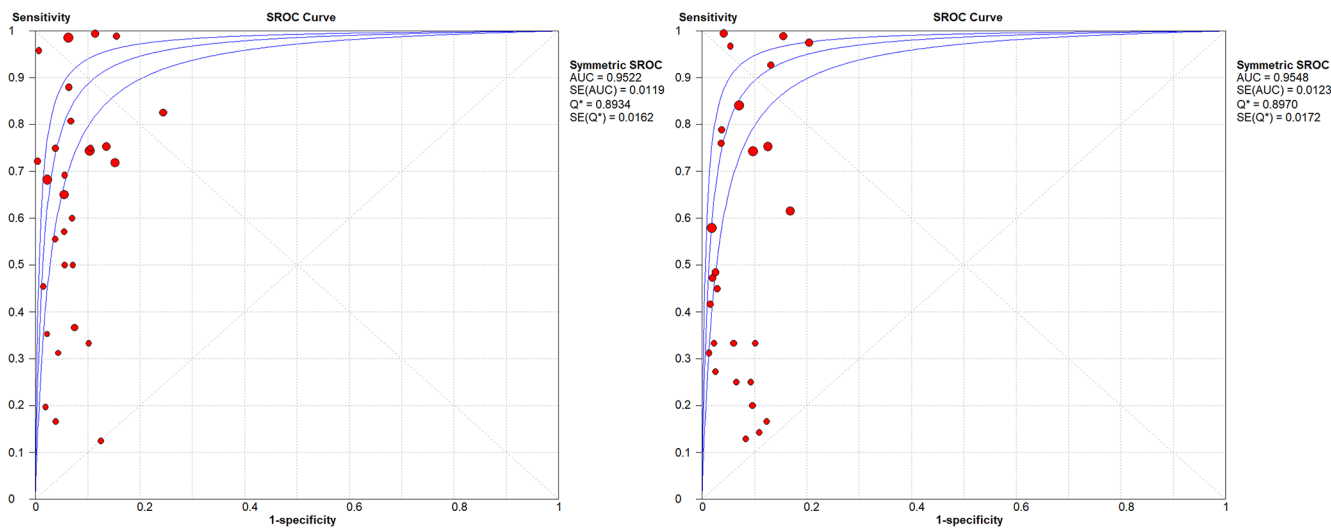


Figure 5. sROC for WBC count and PMN % in hips.

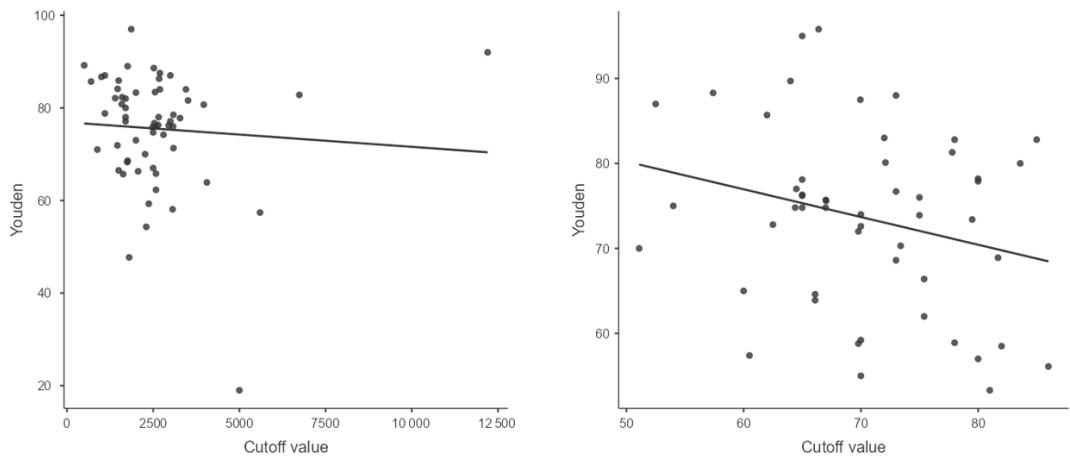


Figure 6. Scatterplot Youden cutoff WBC count and PMN.

Table 4. Cutoffs in the modern or more sensitive PJI definition (Group 1) and in the older PJI definition (Group 2).

	WBC count (cells per microlitre)			PMN (%)		
	Optimal ¹	Rule-out ²	Rule-in ³	Optimal ¹	Rule-out ²	Rule-in ³
Group 1 (ICM, EBJIS, and IDSA)	2530	982	3140	73.7 %	54 %	75.4 %
Group 2 (MSIS and clinical outcome)	2413	1813	2193*	68.5 %	66.4 %	69.7 %

¹ Defined by the best combination of sensitivity and specificity. ² Defined by a sensitivity of > 95 %. ³ Defined by a specificity of > 95 %. * No papers with > 95 % specificity in THA, leaving a reduced sample to compare with other calculations.

erful tools for reaching PJI diagnosis. On the basis of our results, WBC count analysis demonstrated the highest DOR and sROC values compared with those for PMN proportion. In addition to the high diagnostic accuracy of synovial fluid analysis, it is both inexpensive and widely available. We believe it should therefore continue to be a critical part of any diagnostic flowchart and definition criteria.

Still, there are a number of open questions that we were not able to address entirely in this paper. First, the role of synovial WBC and PMN proportion analysis in the immediate postoperative period is not as well studied. After joint replacement surgery, there is a rise in both WBC count and PMN proportion that takes several weeks to normalize despite an uneventful course (Christensen et al., 2013). We found a number of studies that focused on acute postoper-

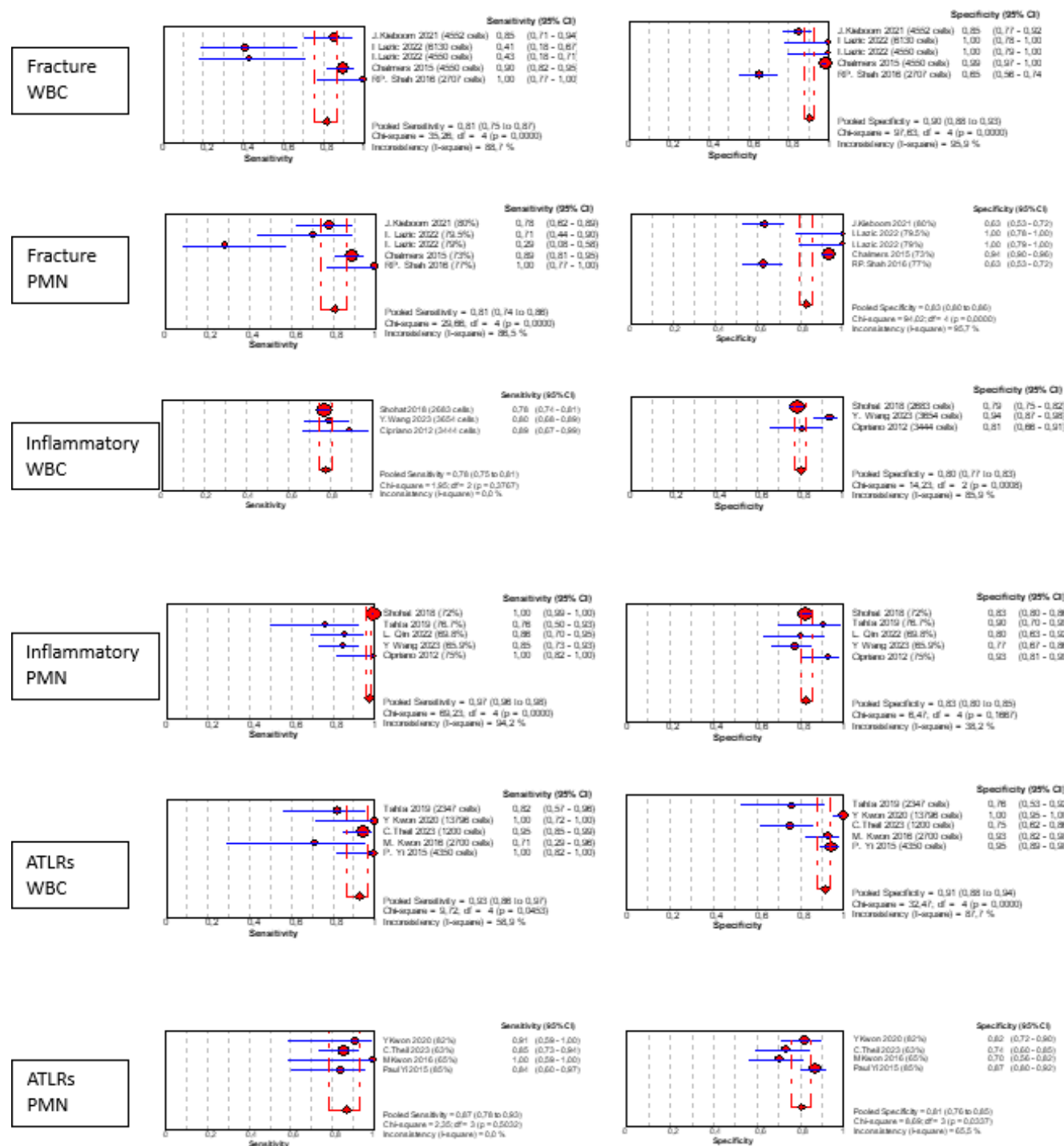


Figure 7. Sensitivity and specificity for special conditions.

ative PJI, but they lacked consistency in how to define infection or even in what timing constitutes the acute period, and therefore we chose to analyse them separately in a different paper.

A different controversy that we were not able to clarify completely is whether the affected joint has an effect on the

optimal threshold of the WBC count and/or PMN proportion. The vast majority of papers we found focused on TKA and/or THA separately or combined. We did not find significant differences to recommend adopting different thresholds for hips and knees. In addition, there is not enough available evidence

Table 5. Summary findings of confounding conditions.

	WBC count (cells per microlitre)		PMN (%)	
	Range	Median	Range	Median
Fracture	2707–6130	4500	73 %–80 %	79.3 %
Inflammatory	1948–5208	3222	65.9 %–85.3 %	75 %
ALTRs and metal-on-metal	730–13 796	2815	63 %–94 %	82 %
Immunosuppressed		1293*		
Antibiotic		2339*		83 %*

* Only one paper for this condition. WBC: white blood cell. PMN %: polymorphonuclear proportion. ALTRs: adverse local tissue reactions.

to recommend alternative cutoffs for joints other than TKA and THA.

Though it is not controversial that total WBC count and PMN proportion are highly valuable tests in the diagnostic workup for chronic PJI, still lacking is a universal consensus on what the ideal interpretation thresholds are. Many of the papers that examine the performance of these tests simply adopt previously proposed cutoffs and report on their accuracy in a specific cohort. Many others analyse their own population, adopt certain diagnostic criteria to serve as the PJI gold standard, and offer optimal cutoffs for interpretation. These results are influenced by variables such as population characteristics (e.g. PJI prevalence), a PJI definition standard, or even different laboratory (e.g. microbiology) standards that greatly influence final results. That being said, despite the wide range of proposed cutoffs, we were able to find some consistent results.

The optimal threshold, defined as the median of proposed cutoffs based on the best combination of specificity and sensitivity, was found to be around 2600 cells per microlitre and 70 % PMN overall. Nevertheless, we aimed to find a rule-in threshold by focusing on optimizing specificity at > 95 % and found that it was slightly higher (both for WBC count and PMN %). We recommend the 3000 cells per microlitre (sensitivity 88.7 %, specificity 98.5 %) and 75 % PMN (sensitivity 77 %, specificity 97.8 %) thresholds to support the infection diagnosis and definition, as these figures are easy to recall and are compatible with both previously proposed cutoffs and results specifically in papers that use more sensitive or modern definitions (i.e. EBJIS 2021, ICM 2018, and IDSA). On the other hand, when one is looking to rule out PJI during the diagnostic workup, we recommend adopting a lower threshold that optimizes sensitivity at > 95 %. Following similar principles enunciated previously, we recommend that infection be suspected and other diagnostic test(s) performed with a WBC count of over 1500 cells per microlitre (sensitivity 100 %, specificity 88 %) and 65 % PMN (sensitivity 95.8 %, specificity 78.6 %).

Lastly, it is crucial to acknowledge that there are special confounding circumstances that hamper the diagnostic accuracy of these tests. Previous antibiotic therapy is associ-

ated with a high number of false negative results (Salimy et al., 2023; Shahi et al., 2015; Trampuz et al., 2007). In the chronic setting, this limitation is simple to overcome by withholding antibiotics and repeating the joint tap at a later stage (at least 2 weeks after antibiotic discontinuation). Other pro-inflammatory conditions are perennial and may cause elevated WBC counts regardless of the presence of infection. These circumstances may be joint- or implant-related, e.g. associated peri-prosthetic fractures, dislocation, or metallosis, or may include systemic diseases such as inflammatory arthritis or crystal arthropathy. We found no evidence to justify adopting different condition-specific cutoffs, but information given by the WBC count and/or PMN proportion should be interpreted with caution, as diagnostic accuracy is inferior in these settings.

5 Conclusion

Synovial fluid WBC count is a crucial part of any PJI diagnostic workup and definition. In the absence of confounding circumstances, WBC counts of < 1500 and > 3000 cells per microlitre and proportions of PMN < 65 % and > 75 % seem to have very good negative and positive predictive values, respectively. A uniform PJI diagnostic standard is required to facilitate studies able to address persistently open questions, such as the true optimal interpretation thresholds or the need for joint-specific or even condition-specific cutoffs.

Code and data availability. Software code and data supporting the conclusions of this article will be made available by the authors on request.

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Author contributions. RS and MC designed the research. MSM, MC, AR, and RS conducted the screening and selection of the articles and the collection of the data. MSM performed the statistical analysis and wrote the first draft of the paper. MSM, MC, AS, and RS contributed to the writing of the paper. All the authors contributed to the data interpretation, revised each draft for important intellectual content, and read and approved the final manuscript.

Competing interests. Two of the (co-)authors are members of the editorial board of *Journal of Bone and Joint Infection* and are ExCom members (president Ricardo Sousa and vice-president Martin Clauss) of EBJIS. The other authors have no other competing interests to declare.

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