■ SYSTEMATIC REVIEW

Histological analysis in the diagnosis of periprosthetic joint infection of the hip and knee

A SYSTEMATIC REVIEW AND META-ANALYSIS

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Aims

The aim of this systematic review and meta-analysis was to assess the diagnostic value of the histological analysis of deep tissue samples in the diagnosis of periprosthetic joint infection (PJI) following total hip (THA) or knee arthroplasty (TKA). The efficacy of the most prevalent diagnostic thresholds (≥ 23 polymorphonuclear neutrophils (PMNs)/ten high-power fields (HPFs), ≥ five PMNs/HPF, and ≥ ten PMNs/HPF) was investigated to determine the optimal threshold to differentiate between septic and aseptic cases.

Methods

PubMed (MEDLINE) and Embase were searched for studies evaluating the performance of histology to diagnose PJI in THAs and TKAs. A meta-analysis of the 43 included studies determined the pooled sensitivity, specificity, the diagnostic odds ratio (DOR) and the area under the summary receiver operating characteristic curve (AUSROC) of permanent (formalin-fixed) and frozen sections.

Results

The performance of permanent sections was evaluated in 22 studies (n = 2,697; PJI 761/2,697; 28%). When considering only studies analyzing intraoperatively collected tissue samples (n = 17), the pooled sensitivity, specificity, DOR, and AUSROC were 82.0% (95% CI 80.4 to 83.5), 96.0% (95% CI 95.1 to 96.7), 153.7 (95% CI 69.3 to 340.9), and 0.965 (standard error (SE) 0.01). The threshold of ≥ five PMNs/HPF demonstrated the best diagnostic performance (sensitivity 82.0% (95% CI 80.0 to 84.0), specificity 94.7% (95% CI 93.5 to 95.8), DOR 133.5 (95% CI 41.6 to 428.6), and AUSROC 0.963 (SE 0.02)). The performance of intraoperatively collected frozen sections was evaluated in 25 studies (n = 3,137; PJI 538/3,137; 17%). The same diagnostic estimates were 67.8% (95% CI 66.1 to 69.4), 94.3% (95% CI 93.4 to 95.1), 47.1 (95% CI 27.7 to 80.2), and 0.960 (SE 0.01), respectively.

Conclusion

Due to their high accuracy, permanent sections of intraoperatively collected samples can be recommended as a confirmatory criterion for diagnosing PJI in THAs and TKAs. While frozen sections demonstrated lower sensitivities, specificities remained robust and comparable with those of permanent sections. Thus, they can also be used to confirm PJI, particularly when the findings of other preoperative diagnostic tests are inconclusive. In order to differentiate septic from aseptic cases, a threshold of ≥ five PMNs/HPF in each of at least five HPFs is advocated. High-quality prospective multicentre studies are needed to validate these findings.

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Introduction

Histological analysis of deep tissue samples for diagnosing periprosthetic joint infection (PJI) was first proposed by Mirra et al[1] in 1976. Subsequent authors have shown a strong correlation between the presence of polymorphonuclear neutrophils (PMNs) in periprosthetic tissue and septic failure following total hip (THA) and knee arthroplasty (TKA).[2-7]

Due to its high diagnostic value, histological analysis has become firmly embedded in the workup of patients with a suspected PJI. In 2019, the American Academy of Orthopaedic Surgeons reported "strong evidence supporting the use of histology to aid in the diagnosis of PJI".[8] It is included in the standardized definition of infection of the European Bone and Joint Infection Society (EBJIS),[9] the Infectious Diseases Society of America (IDSA),[10] the Musculoskeletal Infection Society (MSIS)[11,12] and the International Consensus Meeting (ICM) of 2018.[13] While positive histology is defined as a confirmatory criterion in the EBJIS and IDSA definitions, it is only considered a minor criterion in the MSIS[11,12] and ICM 2018 definitions.[13] Hence, the role of histology in diagnosing PJI (suggestive vs confirmatory) has not yet been standardized between societies or in clinical practice.

Conflicting results concerning the performance of histological analysis have been reported in the literature. Sensitivities have ranged between 11% and 100%,[14,15] and specificities between 78% and 100%.[3,16]

Furthermore, the optimal threshold of PMNs per high-power field (HPF) to distinguish between septic and aseptic failure remains unclear. Various thresholds of PMNs in histological sections have been suggested. The most commonly used thresholds are ≥ 23 PMNs/ten HPFs, ≥ five PMNs/HPF, and ≥ ten PMNs/HPF.[3,4,17,18] While the EBJIS has defined a threshold of ≥ five PMNs/HPF in each of five HPFs to diagnose PJI, thresholds of either five PMNs/HPF or ten PMNs/HPF in each of five HPFs were recommended in the ICM guidelines of 2018. The IDSA guidelines do not provide information about the optimal threshold.

The aims of this systematic review and meta-analysis were: 1) to assess the role of both permanent and frozen section histological analysis of deep tissue samples in the diagnosis of PJI following THA and TKA; 2) to compare the diagnostic accuracy of histological samples collected preoperatively versus intraoperatively; 3) to evaluate the performance of the most commonly used thresholds (≥ 23 PMNs/ten HPFs, ≥ five PMNs/HPF, and ≥ ten PMNs/HPF) in both permanent and frozen sections; and 4) to identify the most accurate threshold for diagnosing PJI in THA and TKA.

Methods

A systematic review with meta-analysis on the role of histology in the diagnosis of PJI was conducted in preparation for the ICM meeting in 2025, using the PRISMA guidelines.[19] PubMed (MEDLINE) and Embase were searched with MeSH terms developed by librarians (Supplementary Table i). Titles and abstracts were screened for eligibility using Covidence (Covidence systematic review software; Veritas Health Innovation, Australia), followed by verification by an additional expert in the field of PJI. The full-text review of the selected studies was then performed by two experts. Meta-analyses and reviews were screened for further studies not included in the original search process.

Studies in English evaluating the performance of histology, based on permanent or frozen sections in the diagnosis PJI following THA and TKA, were eligible for inclusion. Studies needed to be confined to adults with suspected PJI, including a control group (aseptic failure), and providing diagnostic test measures (sensitivity and specificity). Studies assessing other anatomical sites were excluded, as well as animal studies, case reports and studies investigating the diagnostic value of histology at the second stage of a two-stage exchange. Studies were only included if they clearly described the criteria used to define PJI. This included those in which a standardized definition such as EBJIS 2021,[9] MSIS 2011,[11] MSIS 2013,[12] ICM 2018,[13] or IDSA 2013[10] was used, and those in which a clearly defined diagnostic gold standard based on microbiological culture, other diagnostic tests and/or clinical findings was used.

The characteristics of the study including the PJI reference standard, site, number of PJIs, aseptic failures, THAs, TKAs, samples and HPFs, pre- or intraoperative samples and measures of diagnostic accuracy (sensitivity, specificity, positive and negative predictive value (PPV and NPV)) from all included studies were extracted by one author using a standardized form. The data were then proofread by at least one other author.

The risk of bias and applicability of each study was evaluated using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool containing four domains (patient selection, index test, reference standard and enrolment flow of patients/timing of index and reference tests).[20] Risks were rated as 'high', 'low', or 'unclear'. The quality of each study was then graded based on the QUADAS-2 results as follows: A, high quality (low risk); B, moderate quality (one or two domains 'high' or 'unclear'); C, low quality (more than two domains 'high' or 'unclear') and D, very low quality (studies with ≤ 20 events/PJIs).

Statistical analysis. The number of true and false positives and negatives, was calculated using the number of septic and aseptic cases and sensitivities and specificities in each study. When the PPVs and NPVs were not given, they were calculated based on sensitivity and specificity. The meta-analysis was performed using MetaDisc v. 1.4 (Hospital Ramón y Cajal, Spain) and RStudio v. 4.4.1 software (meta-package) (Posit, USA). In order to assess the accuracy of permanent and frozen sections, the pooled sensitivity, specificity, PPV, NPV, positive (LR+) and negative likelihood ratios (LR-), the diagnostic odds ratio (DOR) and area under the summary receiver operating characteristic curve (AUSROC) were calculated with 95% CI using a random-effects model. I^2 (Higgins test) was calculated to determine the heterogeneity for each accuracy. Values with I^2 of > 50% are seen as having substantial heterogeneity,[21] and need to be interpreted carefully. Permanent and frozen sections were analyzed separately. In each type of section, a subanalysis by joint, threshold, and studies using a standardized PJI definition was performed. A post hoc analysis was done in studies evaluating permanent sections by type of sample (pre- or intraoperative samples). Intraoperative samples were further investigated by threshold. For the overall analysis, only the threshold with the best diagnostic accuracy was included to avoid inflating the sample size and skewing the meta-analytic estimates when different thresholds were reported in a single study.

Results

A total of 43 studies evaluating histological sections (permanent and frozen sections) of deep tissue samples for diagnosing PJI

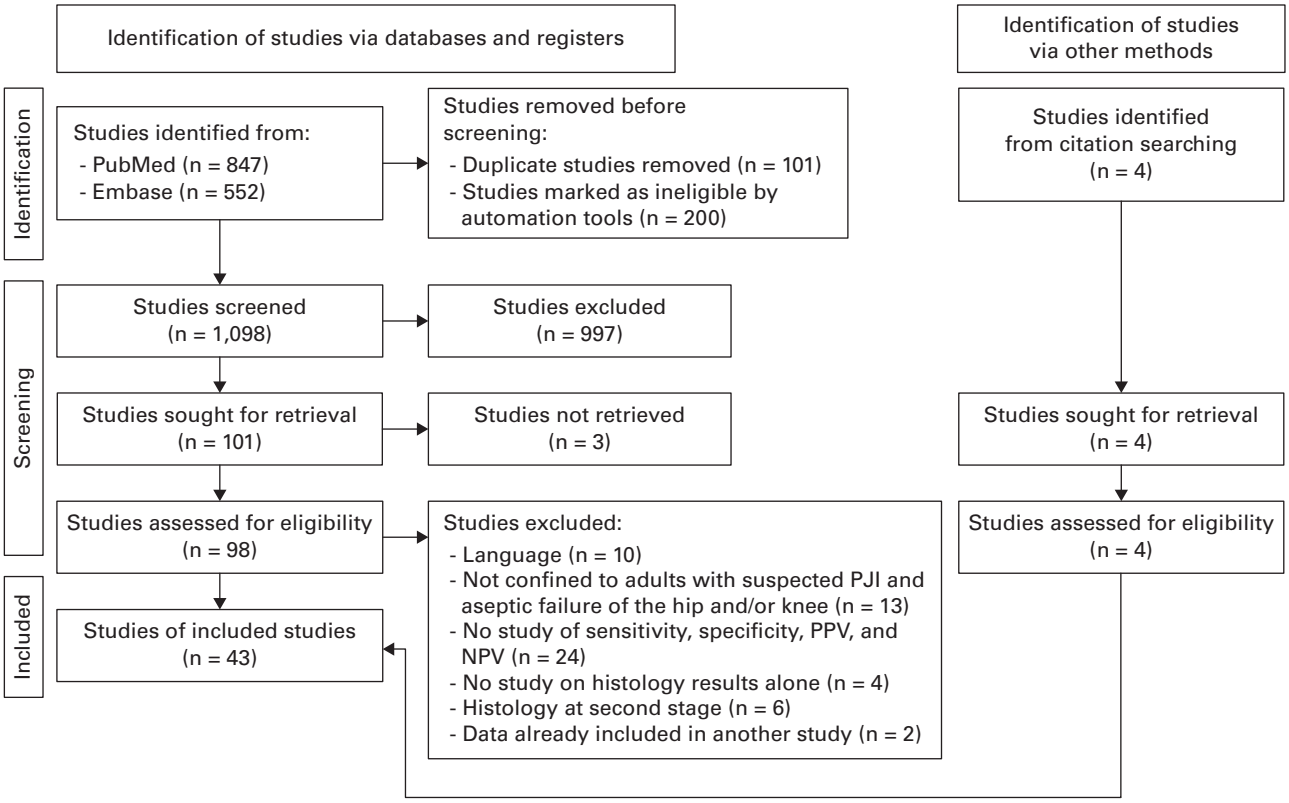

Fig. 1

PRISMA flow diagram of the screening process. NPV, negative predictive value; PJI, periprosthetic joint infection; PPV, positive predictive value.

following THA and TKA were included. Figure 1 shows a flow diagram of the search process. Most studies were of low quality (n = 18; 42%) or very low quality (n = 19; 44%; Supplementary Table ii). Two studies (5%) were graded as high quality and four as moderate quality (9%).

A total of 22 studies investigated permanent sections in 2,697 patients (PJI 761/2,697; 28%) (Supplementary Table iii).[3,4,14–17,22–37]

The pooled sensitivity, specificity, DOR and AUSROC, including all studies analyzing permanent sections (preoperative biopsy and intraoperatively collected deep tissue samples) were 78.7% (95% CI 77.1 to 80.3), 96.1% (95.3 to 96.8), 119.1 (60.0 to 236.6), and 0.962 (standard error (SE) 0.01), respectively (Supplementary Table iv, Supplementary Figures a to d). A standardized definition of infection (EBJIS, IDSA, MSIS, and ICM) to classify PJI was only used in four studies (n = 428 patients, PJI 214/428; 50%).[17,31,32,36] Institutional criteria were used in 12 studies,[4,15,16,24–30,35,37] and only positive cultures were used to classify PJI in six.[3,14,22,23,33,34] When considering only studies with a standardized definition (n = 428, PJI 214/428; 50%), the diagnostic accuracy measures were 90.7% (95% CI 87.5% to 93.2%), 88.8% (95% CI 85.4% to 91.6%), 98.3 (95% CI 42.6 to 226.6), and 0.959 (SE 0.01), respectively.

There was a lower pooled sensitivity (69.0% (95% CI 65.7 to 72.1)) for THAs compared with TKAs (92.5% (95% CI 87.5 to 95.9)), while specificities (98.9% (95% CI 98.0 to 99.5) vs 98.3% (95% CI 95.0 to 99.6)) were similar. The diagnostic value of histology in the diagnosis of PJI in TKA alone was analyzed in only two studies.[24,28] Hence, the AUSROC could not be calculated in TKAs (Supplementary Table iv).

The accuracy of permanent sections of preoperative biopsy samples was assessed in five studies, including 249 patients (PJI 62/249; 25%).[14,24–26,37] Of these, institutional criteria for diagnosing PJI were used in four,[24–26,37] and only positive culture(s) was used in one.[14] The pooled sensitivity, specificity, DOR, and AUSROC were 46.8% (95% CI 40.5 to 53.2), 97.2% (95% CI 94.3 to 98.9%), 37.8 (95% CI 15.3 to 93.2), and 0.923 (SE 0.03), respectively.

Permanent sections of intraoperatively collected tissue samples were investigated in 17 studies, including 2,448 patients (PJI 699/2,448; 29%).[3,4,15–17,22,23,27–36] Positive culture(s) were used to define PJI in five studies,[3,22,23,33,34] institutional criteria were used in eight,[4,15,16,27–30,35] and a standardized definition of infection was used in four.[17,31,32,36] The pooled sensitivity, specificity, DOR, and AUSROC of these 17 studies were 82.0% (95% CI 80.4 to 83.5), 96.0% (95% CI 95.1 to 96.7), 153.65 (95% CI 69.25 to 340.90), and 0.965 (SE 0.01), respectively. Studies using the threshold of ≥ 23 PMNs/ten HPFs demonstrated a pooled sensitivity, specificity, DOR, and AUSROC of 80.7% (95% CI 78.0 to 83.2), 94.9% (95% CI 93.3 to 96.3), 162.4 (95% CI 36.4 to 725.7), and 0.957 (SE 0.02), respectively, while they were 82.0% (95% CI 80.0 to 84.0), 94.7% (95% CI 93.5 to 95.8), 133.5 (95%

CI 41.6 to 428.6), and 0.963 (SE: 0.02) when the threshold of ≥ five PMNs/HPF was applied; and 88.8% (95% CI 84.6 to 92.2), 89.2% (95% CI 85.0 to 92.5), 67.1 (95% CI 39.0 to 115.3), and 0.950 (SE 0.01) when the threshold of ≥ ten PMNs/HPF was used (Supplementary Table iv).

A total of 25 studies (n = 3,137; PJI 538/3,137; 17%) analyzed the performance of histology in frozen sections of intraoperatively collected samples (Supplementary Table v).[2,5–7,15,18,32–34,38–53] The pooled sensitivity, specificity, DOR, and AUSROC were 67.8% (95% CI 66.1 to 69.4), 94.3% (95% CI 93.4 to 95.1), 47.1 (95% CI 27.7 to 80.2), and 0.960 (SE 0.01), respectively (Supplementary Table iv, Supplementary Figures e to h). Standardized definitions were used in seven studies,[32,43,44,46,47,50,53] institutional criteria were used in six,[5,6,15,40,51,52] and only positive culture was used in 12.[2,7,18,33,34,38,39,41,42,45,48,49] Considering only studies using standardized definitions (n = 1,341, PJI 197/1,341), the measures of diagnostic accuracy were 66.9% (95% CI 64.3 to 69.4), 95.5% (95% CI 94.2 to 96.5), 69.0 (95% CI 32.8 to 145.4), and 0.953 (SE 0.02), respectively. Similar sensitivities and specificities were observed in THAs and TKAs (Supplementary Table iv).

The pooled sensitivity, specificity, DOR, and AUSROC in studies using the threshold of ≥ 23 PMNs/ten HPFs were 81.0% (95% CI 74.9 to 86.1), 95.6% (95% CI 91.8 to 98.0), 83.3 (95% CI 19.7 to 352.9), and 0.940 (SE 0.12), respectively. The threshold of ≥ five PMNs/HPF showed values of 69.4% (95% CI 67.5 to 71.3), 94.4% (95% CI 93.3 to 95.3), 56.2 (95% CI 30.4 to 103.7), and 0.964 (SE 0.01), respectively, and the threshold of ≥ ten PMNs/HPF showed values of 62.0% (95% CI 58.3 to 65.6), 96.1% (95% CI 94.4 to 97.4), 50.7 (95% CI 20.4 to 126.1), and 0.892 (SE 0.05), respectively (Supplementary Table iv).

Discussion

In this systematic review and meta-analysis, permanent formalin-fixed sections of intraoperatively collected deep tissue samples demonstrated a good performance (pooled sensitivity 82%, specificity 96%, DOR 153.7) for diagnosing PJI following THA or TKA. Due to their high accuracy, permanent sections can be recommended as a confirmatory criterion in the diagnosis of PJI.

Although specificities were similar (94% vs 96%), preoperative biopsies showed lower pooled sensitivities (47% vs 82%) when compared with intraoperative samples, highlighting the importance of accurate tissue sampling. The lower sensitivity in preoperative biopsies may be explained by the low number of samples which were analyzed. Two of the five studies reporting preoperative biopsies investigated only a single sample, showing low sensitivities (11% and 52%).[14,26] Two other studies examined five samples,[24,25] with much improved sensitivities (75% and 100%), consistent with the literature on intraoperative sampling. The infection and inflammatory cell infiltration may not be evenly spread throughout the joint. Thus, several samples should be taken at revision surgery to ensure an accurate diagnosis. In a retrospective study including 119 patients undergoing revision THA or TKA, the optimal number of deep tissue samples for histology was investigated.[54] Three to six deep tissue samples for permanent sections showed the best ability to identify PJI. Fewer than three demonstrated a lower sensitivity, and more than six showed a lower specificity. Thus, at least three samples – but no more than six – should be sent for histological analysis to ensure an accurate diagnosis.

However, the histological outcome is also influenced by the quality of the samples. According to Krenn et al,[55] samples taken from the pseudocapsule (neosynovium) and the periprosthetic membrane (the interface between the implant and cement/bone) are most effective for the identification of infection and inflammatory cell infiltration. In a prospective study including 69 patients undergoing revision THA, samples from the periprosthetic membrane showed a better performance compared with samples from the pseudocapsule.[23] Although both types of sample demonstrated similar specificity (98%), sensitivities varied widely (periprosthetic membrane 83%, and pseudocapsule 42%).

After histological processing, the sections should be analyzed by an experienced pathologist using a conventional light microscope with a diameter of 0.625 mm and a visual field of 0.307 mm². If a microscope with a different diameter and visual field is employed, the thresholds must be adjusted accordingly.[17] The pathologist should examine the whole section of the sample under low power to identify the areas of maximum inflammation. The PMNs are then counted within these areas under ×400 magnification HPF. PMNs located in blood vessels, within haemorrhagic areas, migrating from capillaries in granulation tissue and trapped in superficial fibrin should be ignored.[17,54] In each section, at least five ×400 magnification HPFs should be analyzed in detail and the PMNs should be counted to ensure optimal outcome. The mean PMNs/HPF is then calculated. Due to its high accuracy in our meta-analysis, a threshold of ≥ five PMNs/HPF in each of five HPFs is recommended to differentiate between septic and aseptic cases. The threshold of ≥ ten PMNs/HPF in each of five HPFs can also be used, although this risks missing some low-grade PJIs. Furthermore, lower sensitivities and higher specificities are typically expected in higher thresholds. Interestingly, the higher threshold of ≥ ten PMNs/HPF showed higher sensitivities and lower specificities compared with the threshold of ≥ five PMNs/HPF, indicating a lower reliability of the studies using the threshold of ≥ ten PMNs/HPF. A possible explanation for these findings is the lack of a uniform definition of infection and uniform histological analysis (different number of investigated HPFs). However, it is clear from the remaining high accuracy of ≥ 23 PMNs/ten HPFs that fewer than five PMNs does not exclude infection. It is suggested that these cases are interpreted carefully in conjunction with the results of the other diagnostic tests within the definition of PJI used in a multidisciplinary team.

Frozen sections demonstrated a lower pooled sensitivity (68%) compared with permanent sections (82%) in our meta-analysis, but showed a similar specificity (94% vs 96%). Nevertheless, due to their high overall performance, frozen sections can be seen as a reliable test and be recommended as a confirmatory criterion. In addition, frozen sections may support surgeons during the decision-making process, particularly in patients with inconclusive preoperative findings. In a retrospective study including 101 revision arthroplasties, 81% of those with an inconclusive preoperative diagnosis but with a definitive

postoperative diagnosis of infection were identified by frozen section, making its intraoperative value apparent.[50] Although the threshold of ≥ 23 PMNs/ten HPFs showed the best performance in frozen sections (sensitivity 81%, specificity 95%), this threshold was only used in three studies, including 60 PJIs and 145 aseptic failures. The threshold of ≥ five PMNs/HPF, on the other hand, was analyzed in 16 studies including 377 PJIs and 1,103 aseptic failures and had an acceptable sensitivity of 69% and similar specificity of 94%. Due to the better evidence and still high accuracy, we also recommend a threshold of ≥ five PMNs/HPF in frozen sections to distinguish septic from aseptic cases. It is also easier to count ≥ five PMNs in five fields, making this a more pragmatic and reproducible threshold for clinical practice. However, also in this setting, the finding of between one and five PMNs/HPF cannot exclude PJI, and needs to be interpreted with the results of other diagnostic tests.

The anatomical site of the affected joint may also influence the histological outcome. Our meta-analysis demonstrated a lower sensitivity in THAs (69%) compared with TKAs (93%) for permanent sections. However, the performance of histology in revision TKAs was only specifically analyzed in two studies, including 172 patients (PJI n = 68).[6,11] Most studies involved THAs and TKAs without further differentiation between the two sites. There was no difference between THAs and TKAs regarding the diagnostic estimates of frozen sections. Due to these inconsistent findings and lack of evidence, no definitive conclusion regarding the affected joint (hips vs knees) can be drawn.

This study focused on the numbers of PMNs in tissue samples and did not include data regarding the identification of microorganisms in the histological samples. The presence of pathogens, identified by special stains, such as Gram, Ziehl-Neelsen, or fungal stains has been included in the EBJIS definition of PJI.[9] Gram staining is widely available, particularly in low-resource areas. It has consistently shown a high specificity but low sensitivity.[56-58] This may be, in part, due to the use of the test in chronic PJIs with few organisms, making visualization difficult.[56] Thus, it is not useful in the detection of most PJIs. However, it is a cheap and rapid test which, when positive, can give an early indication of the type of causing microorganism (Gram-positive or Gram-negative). In culture-negative PJI, this may be the only information on the nature of the infection, allowing for more targeted antibiotic treatment.

The study had limitations. The quality of most of the studies which were included (86%) was moderate to low, hence, the results need to be interpreted with caution. Major limitations included the heterogeneity in reference standards and the potential for incorporation bias. There was a higher pooled sensitivity (91%) when the analysis was limited to studies using a standardized definition of infection (EBJIS, IDSA, MSIS, and ICM), albeit with a slight decrease in specificity (89%). This emphasizes how variations in the definitions of PJI can hinder the advancement of diagnostic accuracy. Nevertheless, all relevant studies with clearly defined diagnostic criteria were included to avoid excluding valuable data and to provide a comprehensive overview of the existing literature. Another limitation of the meta-analysis was the variations in the threshold values reported in the studies. In order to ensure methodological consistency and avoid inflating the sample size due to the repeated inclusion of the same cohorts of patients, only the threshold with the best diagnostic accuracy was selected from each study for the overall analysis. While this approach may restrict a comprehensive assessment of all thresholds within individual studies, subgroup analyses were conducted to evaluate the diagnostic performance of different thresholds without duplicating patient data. Further limitations included the paucity of information about the reproducibility of tests (pathologists' protocols, the microscope which was used, variability of HPFs, and thresholds), the heterogeneity of inclusion and exclusion criteria, the limited number of PJIs which were included, and the failed differentiation between acute and chronic infections. The failure to distinguish between acute (early and late acute) and chronic infections in most studies makes it unclear whether our recommendations can be generalized to all types of PJI.

In conclusion, based on the high accuracies, permanent sections of intraoperatively collected samples can be recommended as a confirmatory criterion for diagnosing PJI following THA or TKA. During revision surgery, between three and six deep samples from the periprosthetic membrane and pseudocapsule should be collected and processed by an experienced pathologist. A threshold of ≥ five PMNs/HPF in each of at least five HPFs can be recommended to differentiate septic from aseptic failure. However, between one and five PMNs/HPF cannot rule out infection, and needs to be interpreted in conjunction with other diagnostic tests within the definition of infection. Although lower sensitivities were found with frozen sections compared with permanent sections, a positive result can be endorsed as a confirmatory intraoperative criterion due to their high specificity, particularly when the preoperative results are inconclusive. Given the low quality of most studies (86%), high-quality prospective multicentre trials are required to strengthen the evidence and validate these findings.

Take home message

- This study highlights the clinical value of permanent histological sections from intraoperatively collected tissue samples as a confirmatory criterion for diagnosing periprosthetic joint infection in revision total hip or knee arthroplasty.
- A threshold of ≥ 5 polymorphonuclear neutrophils per high-power field (in at least five fields) is recommended for distinguishing septic from aseptic failure.
- While frozen sections show lower sensitivity, they can be endorsed as an intraoperative confirmatory criterion due to their high specificity, particularly when preoperative findings are inconclusive.

Supplementary material

Tables showing the full search queries, risk of bias assessment for all included studies, detailed characteristics of each study analyzing permanent and frozen sections, and diagnostic accuracies of permanent and frozen sections. Figures showing the pooled sensitivity, specificity, diagnostic odds ratio, and area under the summary receiver operating characteristic curve (AUSROC) for permanent sections (including open biopsies).

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