Evaluation of White Cell Count and Differential in Synovial Fluid for Diagnosing Infections after Total Hip or Knee Arthroplasty

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Abstract

Background: The accuracy of synovial fluid (SF) white cell count (WCC) and polymorphonuclear (PMN) cell evaluation for predicting prosthetic joint infection (PJI) at the total hip arthroplasty (THA) or total knee arthroplasty (TKA) site is unknown. Therefore, we performed a meta-analysis to summarize the diagnostic validity of SF-WCC and SF-PMN for diagnosing PJI.

Methods: The MEDLINE, EMBASE, and OVID databases were searched for studies that had evaluated the diagnostic validity of SF-WCC and SF-PMN between January 1990 and May 2013. Meta-analysis methods were used to pool sensitivity, specificity, diagnostic odd ratios (DORs), the area under the receiver-operating characteristic curve (AUC), positive likelihood ratios (PLR), negative likelihood ratios (NLR), and post-test probability. We also conducted heterogeneity, publication bias, subgroup, and meta-regression analyses.

Results: Fifteen articles (15 SF-WCC and 14 SF-PMN) that included a total of 2787 patients fulfilled the inclusion criteria and were considered for analysis. The pooled sensitivity and specificity for PJI detection was 0.98 (95% confidence intervals [CI], 0.81–0.93) and 0.95 (95% CI, 0.88–0.96) for SF-WCC and 0.90 (95% CI, 0.84–0.93) and 0.88 (95% CI, 0.83–0.92) for SF-PMN, respectively. The AUC was 0.96 for SF-WCC and 0.95 for SF-PMN. PLR and NLR were 13.3 and 0.13 for SF-WCC, and 7.6 and 0.81–0.93) and 0.93 (95% CI, 0.88–0.96) for SF-WCC and 0.90 (95% CI, 0.84–0.93) and 0.88 (95% CI, 0.83–0.92) for SF-PMN, respectively. There was no evidence of publication bias. Low-clinical-scenario (pre-test probability, 20%) post-test probabilities were 3% for both negative SF-WCC and SF-PMN results. The subgroup analyses indicated that the sensitivity/specificity of THA were 0.73/0.96 for SF-WCC and 0.85/0.83 for SF-PMN, whereas those of TKA were 0.90/0.91 for SF-WCC and 0.90/0.88 for SF-PMN. We also found that collection of SF-WCC preoperatively had a higher sensitivity than that obtained intraoperatively (0.91 vs. 0.77).

Conclusions: SF-WCC and SF-PMN have an adequate and clinically acceptable diagnostic value for detecting PJI, particularly after TKA.

Introduction

Prosthetic joint infection (PJI) is one of the most common complications of total hip arthroplasty (THA) and total knee arthroplasty (TKA) that occurs in 1–12% surgical cases and is associated with a number of adverse outcomes [1,2]. A multitude of tests have been developed for diagnosing PJI, including preoperative laboratory testing, radiological examination, nuclear medicine detection, intraoperative culture, and histopathology [3]. However, there is no established gold standard test for diagnosing PJI, and the limited sensitivity and specificity of the available tests make it difficult to distinguish between PJI and other causes of prosthetic failure, such as metal allergy or aseptic loosening [2,4].

Synovial fluid (SF) white cell count (WCC) and polymorphonuclear (PMN) cell counts, which can be rapidly obtained from preoperative or intraoperative aspiration, and have a faster turnaround-time, may play a role in diagnosis of PJI [5–9]. The guidelines of the American Academy of Orthopaedic Surgeons (AAOS) and Infectious Diseases Society of America (IDSA) strongly recommend SF-WCC and SF-PMN for the assessment of PJI [10–12]. However, despite the increasing number of publications focused on SF-WCC and SF-PMN for the diagnosis of PJI, the effectiveness of these tests still remains unknown.
Therefore, to provide evidence-based advice to physicians on this, we sought to evaluate the detection validity of SF-WCC and SF-PMN for the diagnosis of PJI by using a meta-analysis approach.

Materials and Methods

The current protocol was performed as recommended by the methodological guidelines for conducting systematic reviews studying diagnostic accuracy [13] and according to the PRISMA statement [14].

Search Strategy

The MEDLINE, EMBASE, and OVID databases were searched for articles published between January 1990 and May 2013. All searches were performed using the medical subject headings “joint prostheses,” “prosthesis infection,” “septic loosening,” “aseptic loosening,” “replacement,” and “arthroplasty,” and the free text words “white cell,” “leucocyte,” “PMN,” “polymorphonnuclear,” and “synovial fluid.” We did not restrict the search by language. We also manually searched the reference lists of eligible studies and review articles.

Selection of Studies

Two investigators read the abstracts and used a standardized data extraction form to identify potentially eligible articles. They subsequently read the full text of these articles to determine whether they were eligible for inclusion. Disagreements were resolved by discussing with a third investigator.

The articles required to meet the following qualifications for inclusion in the analysis: (i) collection of data on SF-WCC or SF-PMN along with an accurate diagnosis of PJI as defined by visible purulence of the joint aspirate or at the surgical site, presence of a sinus tract (fistula) communicating with the prosthesis, acute inflammation in histopathology sections of periprosthetic tissue, or simultaneously obtained microbiologic cultures from at least 2 periprosthetic tissue samples (the reference standard); (ii) studies had sufficient data to allow the calculation of the true-positive (TP), false-negative (FN), false-positive (FP), and true-negative (TN) values; and (iii) included ≥10 patients. Discrepancies were resolved by discussing with other investigators and by consulting the original articles.

Data Extraction and Assessment of Study Quality

Two investigators independently extracted relevant data about the design and results of each study using a standardized form. Observers were not blinded to the journal name, the authors’ names and affiliations, or the year of publication since blinding to these study characteristics has been shown to be unnecessary [15]. To resolve disagreement between reviewers, another reviewer assessed all discrepancies, and the majority opinion was used for the analysis. The methodological quality of the included studies was independently assessed by 2 observers using the QUADAS tool [16], which has been specifically developed for systematic reviews studying diagnostic accuracy.

To perform validity analyses, we extracted the following items from each study using a standardized form: description of study participants, the authors’ names, country where the study was conducted, number of patients, mean age, study design, patient enrolment, the time at which the sample was obtained, exclusion of inflammatory arthropathy, sample type, operative site, the test cut-off, and characteristics of the reference standard used. If a cut-off of >1 was reported, the cut-off values that offered the best test performance were used.

Statistical Analysis

For each study, we constructed a 2×2 contingency table consisting of TP, FP, FN, and TN results according to the SF-WCC or SF-PMN values and the reference standard. We then calculated the sensitivity as TP/(TP+FN), specificity as TN/(FP+TN), and the diagnostic odds ratios (DOR) as (TP×TN)/(FP×FN). To evaluate the capability of SF-WCC or SF-PMN assays for diagnosing PJI, we estimated the sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), DOR, post-test probability, and area under the summary receiver operating characteristic curves (AUC) [17]. Likelihood ratio F² index and χ² tests were used to assess the heterogeneity of the included studies [18]. The F² index is a measure of the percentage of total variation across studies due to heterogeneity. If F² is >50%, it suggests more heterogeneity between studies than that expected by chance alone [10]. For the likelihood ratio χ² test, all p-values <0.05 were considered to indicate heterogeneity between studies. If heterogeneity existed, a random effects model was used for the primary meta-analysis to obtain a summary estimate for the test sensitivity with 95% confidence intervals (CI). We performed meta-regression analyses to assess potential heterogeneity and constructed a Deeks’ funnel plot asymmetry test to evaluate potential publication bias [19]. Subgroup analyses were performed to evaluate different study characteristics (i.e., number of patients, study design, patient enrolment, the time at which the sample was obtained, exclusion of inflammatory arthropathy, and operative site). All the statistical analyses were performed using STATA version 12 (StataCorp, College Station, TX, USA).

Results

The database search yielded 675 primary studies. Of these, 625 were excluded after reviewing the title and abstract, and 36 were excluded after reviewing the full article. An additional study was obtained from a review article [20]. Thus, 15 articles that included a total of 2787 patients fulfilled all the inclusion criteria and were
| Study          | Country            | Patients number | Mean age (y) | Study design, Enrollment | Sample obtain | Excluded inflammatory arthropathy | Sample type | Cut-off | Sample part | Ref | Standard |
|---------------|--------------------|-----------------|--------------|--------------------------|---------------|---------------------------------|--------------|---------|-------------|-----|----------|
| Dinneen et al, 2013 | United Kingdom     | 75              | 70.3         | Prospective, NA          | Preoperatively | Yes                             | SF WCC; SF PMN | 1590/μL; 65% | Hip or Knee | IOF, H, M |          |
| Cipriano et al, 2012 | United States      | 871             | 65           | Prospective, Consecutive | Preoperatively or Intraoperatively | Yes | SF WCC; SF PMN | 3450/μL; 78% | Hip or Knee | IOF, H, M |          |
| Schwartz et al, 2012 | United States      | 96              | 65           | Retrospective, Consecutive | No            | SF WCC; SF PMN | 6200/μL; 60% | Knee | IOF, H, M |          |
| Kusuma et al, 2011 | United States      | 76              | 65           | Retrospective, Consecutive | Preoperatively | NA | SF WCC; SF PMN | 1102.5/μL; 71.5% | Knee | IOF, H |          |
| Shukla et al, 2010 | United States      | 86              | 64.2         | Retrospective, Consecutive | Intraoperatively | No | SF WCC; SF PMN | 3528/μL; 79% | Hip | IOF, H, M |          |
| Lee et al, 2010 | Korea              | 56              | 69.6         | Retrospective, NA        | Preoperatively | Yes | SF WCC; SF PMN | 3800/μL; 89% | Knee | IOF, H, M |          |
| Schinsky et al, 2008 | United States      | 220             | 64.9         | Prospective, Consecutive | Intraoperatively | Yes | SF WCC; SF PMN | 4200/mL; 80% | Hip | M, H |          |
| Ghanem et al, 2008 | United States      | 429             | 67           | Retrospective, NA        | Preoperatively | Yes | SF WCC; SF PMN; SF PMN | 1100/μL; 64%; 73% | Knee | IOF, H, M |          |
| Trampuz et al, 2007 | United States      | 160             | 69           | Prospective, NA          | Preoperatively | No | SF WCC; SF PMN | 1700/μL; 69% | Hip or Knee | IOF, H |          |
| Nilsdotter-Augustinsson et al, 2007 | Sweden | 54              | 71.5         | Prospective, Consecutive | Preoperatively | Yes | SF WCC | 1700/μL | Hip | M |          |
| Della Valle et al, 2007 | United States      | 94              | 66.6         | Retrospective, Consecutive | Preoperatively | NA | SF WCC; SF PMN | 3000/mL; 65% | Knee | IOF, H, M |          |
| Pavizi et al, 2006 | United States      | 168             | 68           | Prospective, NA          | Intraoperatively | Yes | SF WCC; SF PMN | 1760/μL; 73% | Hip or Knee | IOF, M |          |
| Trampuz et al, 2004 | United States      | 133             | 71           | Prospective, NA          | Preoperatively | Yes | SF WCC; SF PMN | 1700/μL; 69% | Knee | IOF, H, M |          |
| Mason et al, 2003 | United States      | 86              | NA           | Retrospective, NA        | Preoperatively | No | SF WCC; SF PMN | 2500/mL; 60% | Knee | H, M |          |
| Spangehl et al, 1999 | Canada             | 183             | 65           | Prospective, NA          | Intraoperatively | Yes | SF WCC; SF PMN | 50000/μL; 80% | Hip | IOF, H, M |          |

H: histological examination; IOF: Intraoperative finding; M: microbiological or laboratory examination; NA, not available; SF: Synovial fluid; PMN: polymorphonuclear leukocytes; WCC: white cell count. doi:10.1371/journal.pone.0084751.t001
considered in the analysis [5–8,20–28] (Figure.1). The observers reached agreement on which studies should be included (Cohen's unweighted $\kappa = 0.89$).

**Study Description and Quality**

We identified 15 studies in which SF-WCC and 14 studies in which SF-PMN was obtained; all these studies met the eligibility criteria. Table 1 lists the included studies and describes the baseline patient characteristics. The studies were from 5 different countries (11 from the United States and 1 study each from Canada, Sweden, Korea, and United Kingdom). The median number of patients per study was 96 (range, 54–871). The median age of the research participants was 67 years (range, 64.2–71.5). A total of 8 studies prospectively enrolled patients and 7 studies were retrospective database reviews. Patient recruitment was consecutive in 7 studies and was not documented in the other 8. Only 9 of the 15 studies excluded inflammatory arthropathy. Four studies detected PJI on the hip and knee, 4 detected PJI on the hip, and 7 on the knee. The QUADAS quality assessment tool was used to evaluate each selected study. All the eligible studies scored >9 points indicating that they were of moderate quality.

**Diagnostic Accuracy**

The pooled sensitivity, specificity, DOR, and AUC obtained from the random effects model are shown in Figure 2. The pooled sensitivity for the detection of PJI using SF-WCC and SF-PMN values were 0.88 (95% CI, 0.81–0.93) and 0.90 (95% CI, 0.84–0.93), respectively. The pooled specificity for the detection of PJI using SF-WCC and SF-PMN values were 0.93 (95% CI, 0.88–0.96) and 0.88 (95% CI, 0.83–0.92), respectively. The pooled DORs were 103 (95% CI, 54–197) for SF-WCC and 64 (95% CI, 27–149) for SF-PMN. The pooled AUC for SF-WCC and SF-PMN values were 0.96 (95% CI, 0.94–0.98) and 0.95 (95% CI, 0.93–0.96), respectively. The inconsistency index indicated that no heterogeneity was found with respect to SF-PMN ($I^2 = 0\%$, $p = 0.47$). In contrast, the inconsistency index for the overall heterogeneity of SF-WCC was 97% ($p < 0.01$), which was considered to indicate significant heterogeneity. Therefore, meta-regression analysis was subsequently performed to explore potential sources of heterogeneity in the SF-WCC studies (Figure 3). The analyses on both the sensitivity and specificity for the detection of PJI using SF-WCC indicated no influence of the number of patients ($≥ 100$ vs. $< 100$), study design (perspective vs. retrospective), patient enrollment (consecutive vs. not available), or exclusion of inflammatory arthropathy (yes vs. no). In contrast, we found that the contribution to the heterogeneity origin was the time at which the sample was obtained (preoperative vs. intraoperative) for sensitivity and the operative site (THA vs. TKA) for specificity (all $p < 0.05$).

**Evaluation of Clinical Utility**

The PLR and NLR for the diagnosis of PJI were 13.3 (95% CI, 7.7–22.8) and 0.13 (95% CI, 0.08–0.21) for SF-WCC, respectively. The PLR was 7.6 (95% CI, 4.9–11.7) and NLR was 0.12 (95% CI, 0.07–0.19) for SF-PMN (Figure 4). We used the likelihood ratios to simulate low clinical scenarios by using 20% pre-test probabilities of PJI, and further calculated and plotted post-test probability on Fagan nomograms (Figure 5). The post-test probability of PJI was 3%, given both negative SF-WCC or SF-PMN results, which could be considered sufficient to rule out PJI.

**Subgroup Analysis**

As mentioned above, we performed a subgroup analyses on variables that were decided a priori (Table 2). The sensitivity and specificity of THA were 0.73 (95% CI, 0.56–0.85) and 0.90 (95% CI, 0.93–0.96) for SF-WCC and 0.85 (95% CI, 0.79–0.89) and 0.83 (95% CI, 0.80–0.86) for SF-PMN, respectively. The
sensitivity and specificity of TKA were 0.90 (95% CI, 0.78–0.96) and 0.91 (95% CI, 0.80–0.96) for SF-WCC and 0.90 (95% CI, 0.78–0.95) and 0.88 (95% CI, 0.77–0.95) for SF-PMN, respectively. The analysis also indicated that collection of SF-WCC preoperatively had a higher sensitivity than intraoperative collection of SF-WCC (0.91 vs. 0.77, \( p = 0.05 \)). However, compared with intraoperative SF-WCC (0.97; 95% CI, 0.93–0.99), preoperative collection of SF-WCC had a non-significant lower specificity of 0.89 (95% CI, 0.81–0.94) (\( p > 0.05 \)). For SF-PMN, the sensitivity and specificity of studies that excluded inflammatory arthropathy were 0.91 (95% CI, 0.83–0.95) and 0.90 (95% CI, 0.82–0.94), respectively. The studies that did not exclude inflammatory arthropathy demonstrated a sensitivity of 0.88 (95% CI, 0.75–0.95) and a specificity of 0.86 (95% CI, 0.78–0.92).

Assessment of Publication Bias
To assess for potential publication bias, Deeks’ funnel plots were created by plotting the logDOR of the individual studies against their sample size. The funnel plots for SF-WCC and SF-PMN are presented in Figure 6. The regression test of asymmetry found no evidence of a small-study effect for either SF-WCC (\( p = 0.74 \)) or SF-PMN (\( p = 0.06 \)).

Discussion
In this meta-analysis of 15 articles with a total of 2787 patients, we found that SF-WCC and SF-PMN could be used for distinguishing among PJIs among patients who underwent THA or TKA. The high sensitivity, specificity, and AUC demonstrated a high diagnostic accuracy of SF-WCC and SF-PMN. Furthermore, the PLR and NLR findings, as well low-clinical-scenarios post-test probabilities illustrate the clinical applicability SF-WCC and SF-PMN. We also found that preoperative aspiration of SF-WCC had a higher sensitivity than intraoperative aspiration and SF-PMN had a higher sensitivity for TKA, compared to THA. Lastly, studies that excluded inflammatory arthropathy had a non-significant higher sensitivity and specificity than the studies did not exclude of inflammatory arthropathy. Collectively, these meta-analysis findings demonstrate the clinical utility of SF-WCC and SF-PMN to accurately diagnose PJIs after TKA or THA.

The diagnosis of PJIs after THA or TKA remains a challenge, for which many preoperative and intraoperative tests have been employed. Unfortunately, none of current tests has perfect sensitivity and specificity [1,2]. Over the past decade, many studies have reported that fluorodeoxyglucose-positronemission tomography (FDG-PET) and antigranulocyte scintigraphy with \(^{99m}\)Tc-labeled monoclonal antibodies are good imaging modalities.
Figure 5. Pre-test probabilities and likelihood ratios for SF-WCC (A) and SF-PMN (B). With a pre-test probability of PJI of 20% (low clinical suspicion), the post-test probability of PJI, given a negative SF-WCC or SF-PMN result, is both 3%, which can be considered sufficient to rule out PJI.

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Table 2. Subgroup analyses for diagnosing of PJI using SF-WCC and SF-PMN.

| SF-WCC | Overall Studies | Number of Patients | Sensitivity (95% CI) | Specificity (95% CI) | Area Under the Curve (95% CI) | Positive Likelihood Ratio (95% CI) | Negative Likelihood Ratio (95% CI) | Diagnostic Odds Ratio |
|--------|----------------|-------------------|---------------------|---------------------|-------------------------------|-----------------------------------|-----------------------------------|-----------------------|
| Number of Studies | 15 | 2,700 | 0.88 (0.81,0.93) | 0.93 (0.88,0.96) | 0.96 (0.94,0.98) | 13.3 (7.7,22.8) | 0.13 (0.08,0.21) | 103 (54,197) |
| Number of Patients | <100 | 8 | 623 | 0.88 (0.76,0.94) | 0.93 (0.84,0.97) | 0.96 (0.94,0.97) | 12.3 (5.2,29.2) | 0.13 (0.06,0.28) | 94 (24,367) |
| | ≥100 | 7 | 2,077 | 0.88 (0.75,0.94) | 0.94 (0.87,0.97) | 0.97 (0.95,0.98) | 13.7 (7.3,25.6) | 0.13 (0.07,0.26) | 104 (57,161) |
| Study Design | Prospective | 8 | 1,777 | 0.89 (0.77,0.95) | 0.94 (0.89,0.97) | 0.97 (0.95,0.98) | 14.4 (8.7,23.8) | 0.12 (0.06,0.24) | 120 (75,193) |
| | Retrospective | 7 | 923 | 0.88 (0.76,0.94) | 0.92 (0.82,0.97) | 0.96 (0.93,0.97) | 11.5 (4.4,30.0) | 0.13 (0.06,0.28) | 88 (20,383) |
| Patients Enrollment | Consecutive | 7 | 1,410 | 0.90 (0.84,0.93) | 0.93 (0.88,0.96) | 0.96 (0.94,0.98) | 13.2 (7.1,24.5) | 0.11 (0.07,0.18) | 120 (41,345) |
| | Not document | 8 | 1,290 | 0.87 (0.75,0.94) | 0.94 (0.86,0.97) | 0.96 (0.94,0.98) | 13.7 (6.4,29.2) | 0.14 (0.07,0.27) | 98 (54,175) |
| Sample obtain | Preoperative | 9 | 1,163 | 0.91 (0.82,0.95) | 0.89 (0.81,0.94) | 0.95 (0.93,0.97) | 8.2 (4.5,14.8) | 0.11 (0.06,0.21) | 75 (26,216) |
| | Intraoperative | 4 | 638 | 0.77 (0.51,0.91) | 0.97 (0.93,0.99) | 0.97 (0.96,0.98) | 27.8 (11.5,67.3) | 0.24 (0.10,0.56) | 116 (41,333) |
| Excluded inflammatory arthropathy | Yes | 9 | 2,102 | 0.88 (0.79,0.93) | 0.93 (0.88,0.96) | 0.96 (0.94,0.98) | 13.0 (7.7,21.9) | 0.13 (0.07,0.23) | 100 (65,153) |
| | No | 6 | 598 | 0.89 (0.72,0.97) | 0.94 (0.82,0.98) | 0.97 (0.95,0.98) | 13.8 (4.5,42.2) | 0.11 (0.04,0.34) | 122 (20,740) |
| Sample part | Hip | 4 | 524 | 0.73 (0.56,0.85) | 0.96 (0.93,0.98) | 0.96 (0.93,0.97) | 19.1 (11.3,33.0) | 0.28 (0.16,0.48) | 68 (39,117) |
| | Knee | 7 | 970 | 0.90 (0.78,0.96) | 0.91 (0.80,0.96) | 0.96 (0.94,0.97) | 9.8 (4.1,23.3) | 0.11 (0.05,0.26) | 88 (21,381) |

SF-PMN

| Overall Studies | 14 | 2,726 | 0.90 (0.84,0.93) | 0.88 (0.83,0.92) | 0.95 (0.93,0.96) | 7.6 (4.9,11.7) | 0.12 (0.07,0.19) | 64 (27,149) |
| Number of Patients | <100 | 7 | 564 | 0.86 (0.74,0.92) | 0.83 (0.73,0.89) | 0.91 (0.88,0.93) | 5.0 (3.0,8.3) | 0.17 (0.09,0.34) | 28 (9,85) |
| ≥100 | 7 | 2,162 | 0.93 (0.88,0.96) | 0.92 (0.87,0.95) | 0.97 (0.95,0.98) | 11.3 (6.8,19.2) | 0.08 (0.05,0.14) | 141 (53,371) |
| Study Design | Prospective | 7 | 1,808 | 0.92 (0.88,0.94) | 0.91 (0.87,0.94) | 0.96 (0.94,0.98) | 10.0 (7.0,14.3) | 0.09 (0.06,0.13) | 108 (56,209) |
| | Retrospective | 7 | 918 | 0.87 (0.75,0.93) | 0.85 (0.74,0.91) | 0.92 (0.90,0.94) | 5.7 (3.1,10.7) | 0.16 (0.07,0.27) | 36 (10,132) |
| Patients Enrollment | Consecutive | 6 | 1,438 | 0.89 (0.83,0.94) | 0.84 (0.79,0.89) | 0.93 (0.90,0.95) | 5.7 (4.1,8.1) | 0.13 (0.07,0.22) | 46 (20,106) |
| | Not Available | 8 | 1,288 | 0.90 (0.85,0.94) | 0.90 (0.86,0.94) | 0.96 (0.94,0.97) | 9.5 (6.0,14.8) | 0.11 (0.07,0.17) | 87 (37,205) |
| Sample obtain | Preoperative | 8 | 1,109 | 0.90 (0.80,0.95) | 0.88 (0.78,0.94) | 0.95 (0.93,0.97) | 7.6 (3.8,15.1) | 0.11 (0.05,0.24) | 66 (16,267) |
| | Intraoperative | 4 | 655 | 0.88 (0.80,0.93) | 0.86 (0.80,0.90) | 0.93 (0.91,0.95) | 6.3 (4.2,9.4) | 0.14 (0.08,0.24) | 44 (19,103) |
for PJI diagnosis. Two meta-analyses demonstrated acceptable diagnostic capability and indicated that the sensitivity of FDG-PET and antigranulocyte scintigraphy were 0.82 and 0.83, and the specificity was 0.87 and 0.80, respectively [29,30]. However, the expensive cost, complex techniques, and the requirement for special operators limit the clinical application of these diagnostic techniques. White blood cell (WBC) count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) are the most common preoperative laboratory tests used for the diagnosis of PJI [2,3,10]. However, a meta-analysis performed by Berbari et al. [31] showed that the diagnostic ability of these laboratory tests are

Table 2. Cont.

| Sample part | Number of Studies | Number of Patients | Sensitivity (95% CI) | Specificity (95% CI) | Area Under the Curve (95% CI) | Positive Likelihood Ratio (95% CI) | Negative Likelihood Ratio (95% CI) | Diagnostic Odds Ratio |
|-------------|------------------|--------------------|----------------------|----------------------|-----------------------------|-----------------------------------|---------------------------------|----------------------|
| Hip         | 3                | 487                | 0.85 (0.79,0.89)     | 0.83 (0.80,0.86)     | 0.88 (0.77,0.95)            | 0.95 (0.89,0.97)                  | 2.7 (3.1,143)                | 13.2 (8.3,20.7)        |
| Knee        | 7                | 965                | 0.87 (0.85,0.89)     | 0.88 (0.85,0.91)     | 0.96 (0.93,0.98)            | 1.1 (0.96,1.28)                  | 0.12 (0.06,0.22)            | 5.6 (3.7,8.1)         |

Figure 6. Funnel plots for included studies. (A) SF-WCC; (B) SF-PMN.

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not entirely reliable. Indeed, the accuracy of inflammation markers, represented with DORs, was 13.1 for CRP, 7.2 for ESR, and 4.4 for WBC.

Guidelines by AAOS and IDSA strongly recommend that patient’s SF-WCC and SF-PMN be assessed for PJI [10-12]. Consistent with the AAOS and IDSA guidelines, our results show that SF-WCC and SF-PMN are diagnostic methods that have both a high sensitivity and specificity. However, the true diagnostic ability of these tests depends on whether the synovial fluid aspiration is successful. Many factors can influence the final result, such as synovial fluid volume or antibiotic use. In clinical, when the preoperative serum inflammation markers are above the threshold for PJI in the absence of a known cause, further aspiration of the joint is warranted [10]. Detection of SF-WCC and SF-PMN was the second step recommended by the AAOS guidelines, and it is inexpensive. [12] In addition, we must highlight that with a joint aspiration sample, culture also can be realized. Another meta-analysis evaluated preoperative aspiration culture for diagnosing PJI and found that preoperative aspiration culture has moderate to high sensitivity at 0.72 (95% CI, 0.65–0.78) and very high specificity at 0.95 (95%CI, 0.93–0.97) for diagnosing PJI [32]. Furthermore, low-grade infections caused by low-virulent microorganisms usually have normal values of SF-WCC and SF-PMN [32]. So it is important to performing preoperative aspiration culture if there is a high suspicion of PJI although values of SF-WCC and SF-PMN are normal [32]. In addition, preoperative aspiration culture may identify a pathogen for making treatment plan.

Moreover, there is little consensus regarding the cut-off values for SF-WCC or SF-PMN. In our meta-analysis, the cut-off values ranged from 2500 to 50000/μL for SF-WCC and 60–89% for SF-PMN. The workgroup convened by the Musculoskeletal Infection Society acknowledged that the cut-off level for SF-WCC or SF-PMN has not been well delineated [33]. However, due to different patient characteristics in the individual studies, it is difficult to determine the optimal cut-off values in the current study. Additional patient-level meta-analyses are required to reliably address this issue.

There are several limitations to the current study. First, there is no established gold standard for diagnosing PJI. In our meta-analysis, many reference standards were used in the individual studies, including clinical manifestation (purulence or fistula), laboratory studies (acute inflammation in histopathology or in blood) and microbiological growth (in periprosthetic tissues or in sonication fluid culture). None of these methods is perfect as a reference standard for diagnosing PJI. Misclassification bias, resulting from an imperfect reference standard, may affect the estimates of diagnostic accuracy of a tested method [29]. In general, this leads to an underestimation of the diagnostic accuracy.

Second, the summary results of SF-WCC had high statistical heterogeneity. Therefore, we performed a thorough meta-regression analysis to investigate possible sources of heterogeneity. We found that the time at which the sample was obtained and the operative site contributed to the heterogeneity origin for sensitivity and specificity, respectively. This issue may reduce the strength of the conclusions that can be drawn from this meta-analysis for SF-WCC. Moreover, due to absence of stratified data, it is hard to perform a subgroup analyses for race, gender or age, which may influence the accuracy in diagnosing PJI. Future studies are needed to certify this affection.

Third, not all the studies that were examined explicitly stated whether they were performed in a prospective manner. However, including a prospective study design such as a covariate to the bivariate statistical model (prospective design vs. retrospective design) did not significantly influence sensitivity or specificity.

Fourth, only a few studies reported the use of antibiotics or the time between the assessment of synovial fluid analysis and the validation of PJI. This may affect the diagnosis accuracy. Furthermore, various cut-off values were used in the individual studies. However, it is difficult to determine the best cut-off value of these tests. The use of antibiotics may lead to increased false negatives, and the presence of inflammatory arthropathy may induce false positives.

In summary, this diagnostic accuracy meta-analysis demonstrates that SF-WCC and SF-PMN have adequate and clinically acceptable diagnostic values for the detection of PJI, particularly after TKA. Our results are consistent with the AAOS and IDSA guidelines although the optimal cut-off values of these tests may need further large-scale validation.

Author Contributions
Conceived and designed the experiments: XQ AQ KD. Performed the experiments: XQ ZZ XL HL CW YL. Analyzed the data: XQ ZZ XL. Contributed reagents/materials/analysis tools: XQ ZZ XL HL CW YL. Wrote the paper: XQ ZZ XL HL ZZ AQ KD.

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