HIP

The diagnostic thresholds for synovial fluid analysis in late periprosthetic infection of the hip depend on the duration of symptoms

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Aims
We hypothesised that the synovial white blood cell (WBC) count in patients with a late periprosthetic joint infection (PJI) of the hip would depend on the duration of a patient’s symptoms, and that the optimal diagnostic threshold would also depend on this period of time.

Patients and Methods
The synthetic WBC count and percentage of polymorphonuclear cells (%PMN), and the serum CRP and ESR levels obtained > six weeks after primary THA were compared between 50 infected and 88 non-infected THAs, and in patients with symptoms for more than or less than two weeks. Diagnostic thresholds for the synovial WBC count were calculated using area under the curve calculation.

Results
The synovial WBC count was significantly higher in patients with symptoms for ≤ two weeks compared with those with symptoms for > two weeks (p = 0.03). The optimal threshold for diagnosing PJI for the synovial WBC count was 5750 cells/μL (sensitivity 94; specificity 100; PPV 100%; NPV 99%; AUC 99%) and 1556 cells/μL (sensitivity 91; specificity 94; PPV 87% and NPV 97%; AUC 95%), respectively. The thresholds for the cut-offs based on duration of symptoms improved the diagnostic performance of this test.

Conclusion
This study shows that the diagnostic thresholds for synovial fluid analysis in late periprosthetic infection following THA may depend on duration of symptoms.

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The incidence of periprosthetic joint infection (PJI) after primary total hip arthroplasty (THA) is between 1% and 2%.1,2 This has remained largely unchanged since the era of Charnley.3,4 An accurate diagnosis of PJI is critical as the treatment of THAs which fail due to sepsis is vastly different from those with aseptic failure. There is, however, no single test with sufficient and consistent sensitivity and specificity to be considered a ‘benchmark’.5,6 Many tests are often combined to confirm or rule out the presence of PJI.7,9

The white blood cell (WBC) count in synovial fluid from the joint is a reliable test for diagnosing PJI.10-14 However, the wide range of diagnostic thresholds which have been reported makes the interpretation of these results difficult and a cut-off value for the synovial WBC count in PJI has not been established.

Many factors may cause an elevated synovial WBC count after THA which might lead to an inaccurate diagnosis and inappropriate treatment. The duration of symptoms in late PJIs may affect the diagnostic threshold of synovial WBC in patients with possible PJI. In this study, we hypothesised that this diagnostic threshold would depend on the duration of a patient’s symptoms.

Patients and Methods
Our institutional database was used to identify all patients who, between 2000 and 2010, underwent aspiration of the hip a minimum of six weeks after primary THA. The aspiration was undertaken by radiologists with or without ultrasound guidance following requests from orthopaedic surgeons, based on the clinical suspicion of PJI. All patients had local discomfort in the hip, without generalised symptoms of infection. Only those whose synovial fluid had been analysed for WBCs, polymorphonuclear cells percentage (%PMN), and culture (including aerobic, anaerobic, acid-fast bacilli and fungal) were included. Patients were
excluded if the duration of symptoms was not clear; the diagnosis was of inflammatory arthropathy; antibiotics had been administered within two weeks of the aspiration; there had been previous treatment for PJI, and/or concomitant treatment for leukaemia or lymphoma.

The diagnosis of PJI was based on criteria outlined by the Musculoskeletal Infection Society (MSIS)\(^\text{15}\) and the International Consensus Meeting on Periprosthetic Joint Infection (ICMPJI)\(^\text{16,17}\) and modified to reflect current practice at that time. The duration of symptoms prior to aspiration was recorded. The patients were divided into two groups based on whether symptoms had been present for more or less than two weeks. The synovial WBC count, the %PMN, CRP and ESR were recorded for all patients.

**Statistical analysis.** Laboratory data for infected and non-infected THAs were compared, as well as between infected THAs in the two subgroups of the duration of symptoms. Continuous variables were analysed using student t-tests and categorical data using the chi-square test. Receiver operating characteristic (ROC) curves were used to evaluate the optimal diagnostic threshold for synovial WBC count, the %PMN, CRP and ESR in each group. The Youden J statistic was used to aid selection of optimal cut-off points, maximising the sensitivity, specificity, and area under the curve (AUC) of each test. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) at the selected cut-off points and AUC were calculated with 95% confidence intervals (CIs). A p-value of < 0.05 was considered statistically significant.

**Results**

A total of 5682 primary THAs were carried out in our hospital during this time. Of these, 138 joint aspirations after THA in 134 patients fulfilled the inclusion criteria: 51 patients were excluded for the reasons outlined above. A total of 50 of the aspirates (36%) were diagnosed as infected; 17 of these (34%) presented with symptoms for ≤ two weeks and 33 (66%) with symptoms for > two weeks. Of the 88 non-infected THAs, 11 (13%) had symptoms for ≤ two weeks and 77 (87%) had symptoms for > two weeks.

The mean values for synovial WBC count, the %PMN, CRP and ESR were significantly higher in the infected patients than the non-infected patients, regardless of the duration of symptoms (Table I), except for the CRP and ESR in patients with symptoms for ≤ two weeks (Table II).

The optimal threshold of the WBC count for all infected hips irrespective of the duration of symptoms was 2689 cells/μL (sensitivity 92; specificity 93; PPV 95%; NPV 72%; AUC 96%). The optimal thresholds for diagnosing PJI for the synovial WBC count in patients with symptoms for ≤ two weeks was 5750 cells/μL (sensitivity 94; specificity 100; PPV 100%; NPV 89%; AUC 99%) compared with 1556 cells/μL (sensitivity 94; specificity 94; PPV 87% and

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**Table I.** Comparison of laboratory data between infected and non-infected patients

<table>
<thead>
<tr>
<th>Test</th>
<th>Infected (n = 50)</th>
<th>Non-infected (n = 88)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (μL)</td>
<td>75973.7 (SD 24539.1)</td>
<td>849.6 (SD 315.1)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>%PMN (%)</td>
<td>88.2 (SD 0)</td>
<td>39.2 (SD 0)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>81.9 (SD 34.2)</td>
<td>12.9 (SD 8.6)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>ESR (mm/hr)</td>
<td>75.3 (SD 9.4)</td>
<td>30.1 (SD 5.5)</td>
<td>&lt; 0.001*</td>
</tr>
</tbody>
</table>

* Statistically significant

WBC, white blood cell; PMN, polymorphonuclear cell; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SD, standard deviation

**Table II.** Mean values of diagnostic measures between infected and non-infected THAs based on the duration of symptoms

<table>
<thead>
<tr>
<th>Test</th>
<th>Sx duration</th>
<th>Infected (n = 50)</th>
<th>Non-infected (n = 88)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (μL)</td>
<td>≤ 2 wks</td>
<td>112056.471 (SD 60696.719)</td>
<td>1607.727 (SD 1254.604)</td>
<td>p = 0.001*</td>
</tr>
<tr>
<td></td>
<td>&gt; 2 wks</td>
<td>57385.697 (SD 20676.34)</td>
<td>741.377 (SD 319.329)</td>
<td>p &lt; 0.001*</td>
</tr>
<tr>
<td>%PMN (%)</td>
<td>≤ 2 wks</td>
<td>0.867 (SD 0.1)</td>
<td>0.463 (SD 0.246)</td>
<td>p = 0.004*</td>
</tr>
<tr>
<td></td>
<td>&gt; 2 wks</td>
<td>0.89 (SD 0.0582)</td>
<td>0.381 (SD 0.0684)</td>
<td>p &lt; 0.001*</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>≤ 2 wks</td>
<td>118.3 (SD 105.612)</td>
<td>41.529 (SD 46.314)</td>
<td>p = 0.15</td>
</tr>
<tr>
<td></td>
<td>&gt; 2 wks</td>
<td>68.764 (SD 33.317)</td>
<td>9.146 (SD 7.961)</td>
<td>p = 0.001*</td>
</tr>
<tr>
<td>ESR (mm/hr)</td>
<td>≤ 2 wks</td>
<td>74.75 (SD 21.56)</td>
<td>42.5 (SD 23.676)</td>
<td>p = 0.074</td>
</tr>
<tr>
<td></td>
<td>&gt; 2 wks</td>
<td>75.7 (SD 9.944)</td>
<td>27.153 (SD 5.25)</td>
<td>p &lt; 0.001*</td>
</tr>
</tbody>
</table>

* Statistically significant

WBC, white blood cell; PMN, polymorphonuclear cell; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SD, standard deviation
Diagnostic and predictive tools in the evaluation of markers (CRP and ESR) have been regarded as reliable tests. Analysis of the synovial fluid and inflammatory markers has not been studied before. Recent guidelines on the diagnosis of PJI highlight a change in the diagnostic thresholds for the synovial WBC count based on the duration of symptoms. The magnitude of the host response to PJI, as reflected by the relative value of synovial WBC is, to our knowledge, a relatively new concept with limited literature to guide its use in practice. The host response primarily depends on the ability to identify and mount an inflammatory response to a pathogen. The natural history of PJIs involves the transition from only traditional Gram stain and culture to WBC count, differential, CRP and ESR, among other tests. Analysis of the synovial fluid and inflammatory markers (CRP and ESR) have been regarded as reliable diagnostic and predictive tools in the evaluation of early and late PJI, however, at different diagnostic thresholds.

The relationship between the duration of symptoms and the synovial WBC count is important. For example, by using the cut-off for the synovial WBC count of > 4200 cells/μL with a sensitivity of 84% and a specificity of 93% in 201 suspected infected THAs. This value is higher than our cut-off value (2689 cells/μL) of infected THA regardless the duration of symptoms. It is however, within the range of cut-off based on different durations of symptom (1556 cells/μL to 5750 cells/μL).

We found that the cut-off values for synovial fluid WBC count for PJI significantly depends on the duration of symptoms. Although there is no direct way to compare the optimal cut-off value for the acute episode of infection (< two weeks, 5750 cells/μL) with the more chronic duration of symptoms (> two weeks, 1556 cells/μL) statistically, we feel that this difference is clinically relevant and significant. For example, by using the cut-off for the synovial WBC count of > 4200 white cells/μL in a previous report about the diagnosis of an infected THA, many patients with symptoms for > two weeks would not have met the diagnostic criteria for PJI and may not, therefore, have been treated appropriately. Other authors have recorded different diagnostic thresholds for the synovial WBC count based on the time that has elapsed from the operation, as reported by Yi et al.14 and Bedair et al.19 reflecting an increased inflammatory response in the early post-operative period. Based on our findings, the threshold for the diagnosis of PJI using the synovial WBC count should be lower in patients with a longer duration of symptoms and higher in those with more acute symptoms.

### Table III. Comparison of mean diagnostic measures based on the duration of symptoms in infected THAs (n = 50)

<table>
<thead>
<tr>
<th>Test</th>
<th>≤ 2 wks (n = 17)</th>
<th>&gt; 2 weeks (n = 33)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (μL)</td>
<td>112056.4 (sd 60696.7)</td>
<td>57385.6 (sd 20676.3)</td>
<td>p = 0.03</td>
</tr>
<tr>
<td>%PMN (%)</td>
<td>86.7 (sd 0)</td>
<td>89.0 (sd 0)</td>
<td>p = 0.68</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>118.3 (sd 105.6)</td>
<td>68.7 (sd 33.3)</td>
<td>p = 0.32</td>
</tr>
<tr>
<td>ESR (mm/hr)</td>
<td>74.7 (sd 21.5)</td>
<td>75.7 (sd 9.9)</td>
<td>p = 0.93</td>
</tr>
</tbody>
</table>

* Statistically significant

WBC, white blood cell; PMN, polymorphonuclear cell; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; sd, standard deviation

### Table IV. Optimal cut-off values and the performance of the WBC count in the synovial fluid based on duration of symptoms.

<table>
<thead>
<tr>
<th>Duration of symptoms</th>
<th>Threshold (WBC/μL)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV</th>
<th>NPV</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>All infected hips (regardless of symptom duration)</td>
<td>2689</td>
<td>92.0 (80.8 to 97.8)</td>
<td>93.1 (85.7 to 97.5)</td>
<td>94.7</td>
<td>72.2</td>
<td>0.962</td>
</tr>
<tr>
<td>≤ 2 wks</td>
<td>5750</td>
<td>94.12 (71.3 to 99.9)</td>
<td>100.0 (71.5 to 100.0)</td>
<td>100.0</td>
<td>88.9</td>
<td>0.992</td>
</tr>
<tr>
<td>&gt; 2 wks</td>
<td>1556</td>
<td>90.91 (75.7 to 98.1)</td>
<td>93.5 (85.5 to 97.9)</td>
<td>87.2</td>
<td>97.0</td>
<td>0.949</td>
</tr>
</tbody>
</table>

WBC, white blood cell; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; AUC, area under curve

NPV 97%; AUC 95%) in those with symptoms for > two weeks. (Table IV, Fig. 1). The sensitivity, specificity, PPV and NPV of this test were all improved in patients with symptoms for ≤ two weeks compared with the entire cohort of infected hips.

### Discussion

Recent guidelines on the diagnosis of PJI highlight a change in recommendations for the analysis of aspirated synovial fluid, moving from only traditional Gram stain and culture to WBC count, differential, CRP and ESR, among other tests. Analysis of the synovial fluid and inflammatory markers (CRP and ESR) have been regarded as reliable diagnostic and predictive tools in the evaluation of early and late PJI, however, at different diagnostic thresholds.

There is little published literature to suggest the values of the synovial WBC count and differential count which might act as threshold values in the diagnosis of late infection after THA. Dinneen et al. reported that the cut-off value for the synovial WBC count for the diagnosis of PJI at least six weeks after primary THA was 1425/μL, using a ROC curve. This is similar to our findings of the cut-off value for infected THA in patients with symptoms for > two weeks (1556 cells/μL). Schinsky et al. reported a cut-off value for the synovial WBC count of > 4200 cells/μL with a sensitivity of 84% and a specificity of 93% in 201 suspected infected THAs. This value is higher than our cut-off value (2689 cells/μL) of infected THA regardless the duration of symptoms. It is however, within the range of cut-off based on different durations of symptom (1556 cells/μL to 5750 cells/μL).

We found that the cut-off values for synovial fluid WBC count for PJI significantly depends on the duration of symptoms. Although there is no direct way to compare the optimal cut-off value for the acute episode of infection (≤ two weeks, 5750 cells/μL) with the more chronic duration of symptoms (> two weeks, 1556 cells/μL) statistically, we feel that this difference is clinically relevant and significant. For example, by using the cut-off for the synovial WBC count of > 4200 white cells/μL in a previous report about the diagnosis of an infected THA, many patients with symptoms for > two weeks would not have met the diagnostic criteria for PJI and may not, therefore, have been treated appropriately. Other authors have recorded different diagnostic thresholds for the synovial WBC count based on the time that has elapsed from the operation, as reported by Yi et al. and Bedair et al. reflecting an increased inflammatory response in the early post-operative period. Based on our findings, the threshold for the diagnosis of PJI using the synovial WBC count should be lower in patients with a longer duration of symptoms and higher in those with more acute symptoms.
One of the limitations of this study is its retrospective nature and inherent difficulties with analysing non-standardised treatment protocols and diagnostic algorithms. Secondly, patients may not be able to give an accurate estimate of the duration of their symptoms, which may introduce recall bias. Thirdly, the dichotomisation of the duration of symptoms into groups of > or ≤ two weeks may be an artificial cut-off. Values may have been different if we had chosen a different set of time frames. Finally, the samples of synovial fluid were analysed over a period of ten years, during which time the method of analysis has evolved and this might have affected the WBC count.

The diagnosis of PJI is often complex and depends on the interpretation of several tests. The synovial WBC count is a useful, highly discriminatory test for the diagnosis of infection. However, a single diagnostic threshold may not be appropriate for all clinical scenarios based on our study. A cut-off for the synovial WBC count of 5750 cells/μl for late PJs in patients with symptoms for ≤ two weeks is almost four times higher than that of the 1556 cells/μl in those with symptoms for > two weeks. Minimal refinements in the use of this test appear to improve its diagnostic performance, particularly in patients with more acute symptoms.
Take home message:
Diagnostic threshold for synovial white blood cell count may vary based on duration of symptoms in late PJI after THA.

Author contributions:
H-R. Choi: Data collection, Data analysis, Writing the paper, Revision of manuscript.
K. Agrawal: Data collection, Data analysis, Writing the paper, Revision of manuscript.
H. Bedair: Study design, Data analysis, Performed operations, Writing the manuscript.

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References