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ORIGINAL ARTICLE • KNEE - INFECTION

Serum interleukin 6 could be a valuable initial diagnostic tool in prosthetic knee joint infections

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Abstract

Background Accurate preoperative diagnosis of prosthetic joint infection (PJI) in the absence of obvious clinical signs or laboratory findings is challenging. Interleukin 6 (IL-6) has been proposed as an infection marker but supportive data are limited. We studied the diagnostic utility of serum IL-6 in infected total knee arthroplasty (TKA).

Methods A prospective cohort study was done in 52 patients (59 knees) with a painful TKA. The abnormal limits for serum IL-6, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), synovial fluid white cell counts (WBC) and synovial fluid neutrophils (PMN) were determined from receiver operating characteristic curves. An infection was defined as the presence of sinus tract or positive culture > two separate tissue or fluid samples. We utilized Mann–Whitney test, Spearman's correlation and Fischer's exact test to determine the sensitivity, specificity, positive predictive value, negative predictive value (NPV) and accuracy of serum IL-6.

Results The optimal threshold concentration of serum IL-6 was 9.14 pg/ml. Independently, this yielded a sensitivity, specificity and NPV of 81%, 63% and 85%, respectively, and when combined with synovial fluid WBC, values were 100%, 90%, 100%, respectively. The sensitivity and specificity of ESR (70%, 63.6%), CRP (66.7%, 66.7%), synovial WBC (66.7%, 81%) and synovial PMN (82.4%, 73.7%) were also calculated. Serum IL-6 levels strongly correlate with all markers in PJI.

Conclusions Serum IL-6 improves the diagnosis of PJI over existing methods, especially when combined with synovial fluid WBC. Its optimal usage is as an excellent screening test to rule out infected total knee arthroplasty.

Level of Evidence Diagnostic Level II.

Keywords Interleukin 6 · Prosthetic joint infection · Total knee arthroplasty

Introduction

The diagnosis of prosthetic joint infection (PJI) in the absence of draining sinus, positive cultures or gross purulence is challenging. For this reason, additional supporting evidence is often necessary, and multiple biomarkers are being studied for their accuracy [1]. The prevalence of infection has been reported to be 0.4% to 2%, 5.6% and 15.8% following primary total knee arthroplasty (TKA) [2, 3], revision TKA [2] and a two-stage revision TKA [4], respectively.

The recently proposed definition by the Musculoskeletal Infection Society (MSIS) includes multiple secondary criteria such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), synovial white blood cell counts (WBC) and synovial polymorph nuclear leukocyte (PMN) percentage, D-dimer, alpha defensin as well as histology ("Appendix 1") [4]. This definition also has a scoring system to improve the probability of diagnosing the PJI, but the authors have cautioned about its usefulness in the presence of adverse local tissue reactions, slowly growing organisms as well as crystal arthropathies [5]. No single laboratory test can accurately detect infection before revision hip or knee arthroplasty [3]. Tunney et al. [6] studied immunofluorescence microscopy and PCR amplification of bacterial DNA in 120 patients undergoing revision total hip surgery and concluded that the incidence of prosthetic joint infection is grossly underestimated by current culture detection methods.

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Serum interleukin-6 (IL-6) is a pro-inflammatory cytokine released in the blood stream, especially in acute or low-grade chronic inflammations, in response to specific microbial molecules that precedes the appearance of other cytokines in the circulation and has been proposed as another biomarker in the diagnosis of chronic, low-grade PJI [7–12]. However, limited data are available regarding its actual role in the diagnosis of PJI. The diagnostic value of serum IL-6 has not been previously compared with synovial fluid markers, and limited data are available on its value in detecting or ruling out a PJI. Prior studies have not determined the strength of the correlation between IL-6 and other routine blood and synovial fluid markers in identifying PJI. The literature lacks evidence supporting the best screening or confirmatory test [11, 13]. We believe that identifying an ideal initial screening test could be very helpful in accurately ruling out or detecting infection following a TKA and avoid unnecessary or repeated joint aspirations as well as unindicated or wrong procedures that would have a significant impact on morbidity, mortality, cost of care and patient-reported outcomes.

This study was undertaken to determine the overall diagnostic value of serum IL-6 levels in infected TKA. The study goals were to specify: (1) the optimal threshold concentration of serum IL-6 to differentiate infected from noninfected TKA; (2) sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of serum IL-6 in infected TKA; and (3) the diagnostic utility of serum IL-6. The thought was to find out its usefulness as either an individual marker or combined with other blood and synovial fluid markers of PJI for optimal use as a screening or confirmatory test.

Materials and methods

From January 2017 to December 2019, we prospectively identified patients undergoing revision TKA at our institution. The study was approved by our institutional review board.

A cohort of 59 knees (52 patients) had serum IL-6 evaluated simultaneously with ESR, CRP, synovial fluid WBC and synovial fluid PMNs (Table 1).

The PJI was defined based on major criteria outlined in the MSIS definition ("Appendix 1") [4] as the literature lacks adequate supporting evidence for the accuracy of the individual minor criteria [5, 14, 15]. These patients presented with a painful TKA underwent treatment for infection or another implant-related problem and were managed by a single surgeon at a single institution. Patients were excluded from the study when either data were incomplete or if patients had active inflammatory diseases that could be responsible for a preexisting higher level of IL-6.

Table 1 Patient demographics

Data	Total	Infected	Non-infected
Knees in the study	59	32	27
Female/male	40/19	20/12	20/07
Median age at presentation (range 33–88 years)	65	69	64
Time since index TKA in years (range 4 months–11 years)	6.7	4.2	6.9

Table 2 Methods of testing the markers of prosthetic joint infection

Markers	Laboratory technique	Analyzer
Serum		
Interleukin 6	High-sensitivity enzyme-linked immunosorbent assay	Multiplex bead-based Luminex 100
CRP	Immunorate reflectance spectrometry	Vitros 5.1
Synovial		
ESR	Laser kinetic analysis	ESR Stat Plus
WBC	Flow cytometry	Sysmex XE 5000
PMN (%)	Flow cytometry	Sysmex XE 5000

All samples were collected, analyzed and processed (Table 2) within 6 h of procurement at our institution's laboratory. Samples that were clotted or grossly bloody were excluded from the study.

Based on the tests, results were plotted using receiver operating characteristic (ROC) curves (Fig. 1a, b) to determine the optimal threshold concentration of serum IL-6, CRP, ESR, synovial fluid WBC and synovial fluid PMN percentage in the PJI. Their sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy and likelihood ratios within the 95% confidence interval were determined. These markers were then studied individually as well as in combination using a first strategy where either of the markers in the mix could have laboratory values above the threshold concentration and second strategy where all laboratory values must be above the threshold concentration.

Fischer's exact tests were used to analyze the statistical differences in performance of each test in infected versus noninfected group, and p value of < 0.05 was considered to be statistically significant. Mann–Whitney U test and two-sample test were used to evaluate the univariate data. Spearman's rank correlation was used to correlate and compare IL-6 with other markers in the MSIS definition of PJI [4].

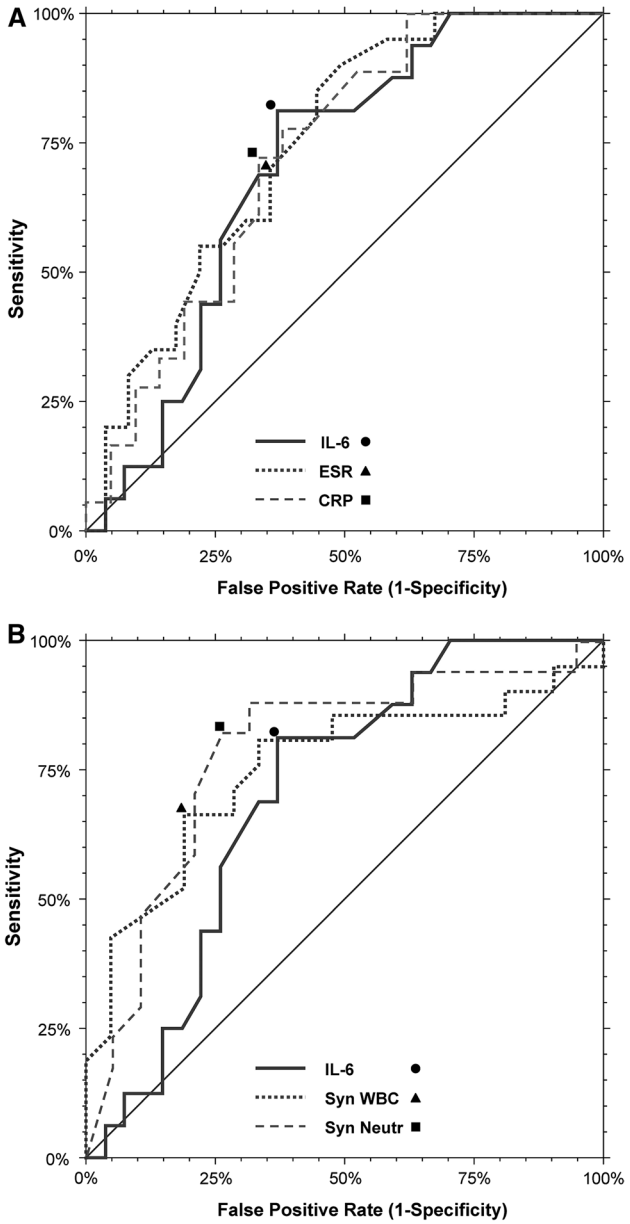

Fig. 1 **a** Receiver operating characteristic curves for serum interleukin 6, ESR and CRP in infected total knee arthroplasty. **b** Receiver operating characteristic curves for serum interleukin 6, synovial fluid WBC and synovial fluid PMN percentage in infected total knee arthroplasty. The diagonal line indicates area under the curve of 50% or less and indicates the test is not useful in the diagnosis of infected total knee arthroplasty. The threshold value determined from the ROC curves was the value closest to 1 (upper left corner on graph) and is the most accurate value for that marker in the diagnosis of PJI

Results

The optimal threshold concentration of serum IL-6 for differentiating between an infected versus noninfected TKA is 9.14 pg/ml as determined by the ROC curve (Fig. 1a). This value is almost three times higher than the average value for our laboratory (< 3 pg/ml).

When tested alone, an IL-6 threshold concentration of 9.14 pg/ml has 81.3% sensitivity (95% confidence interval CI, 54% to 95%), 63% specificity (95% CI, 43% to 80%), 85% NPV (95% CI, 61% to 96%), 56.5% PPV (95% CI, 35% to 76%) and 70% accuracy for diagnosing PJI (Table 3).

The optimal threshold concentrations for ESR (> 27 mm/h), CRP (> 17 mg/L), synovial WBC (> 1804 cells/10^{-3} cm^3), synovial PMNs (> 86%) from the ROC curves were determined, and the values were comparable to those published in the available literature (Table 4). The sensitivity of serum IL-6 is higher than that of ESR (70%), CRP (67%) and synovial WBC (67%) (Table 3; "Appendix 2") and almost equivalent to that of the synovial PMN percentage (82%). The serum IL-6 concentration of 9.14 pg/ml has a highest overall accuracy of 70% when compared with ESR (67%), CRP (67%), but is less accurate than synovial fluid WBC (74%) and synovial fluid PMN percentage (78%) based on the study findings.

When serum IL-6 results are combined with those of ESR and CRP with either of these values being above the threshold concentration, the sensitivity of detecting PJI increases up to 94% (95% CI, 67% to 100%) and NPV increases up to 91% (95% CI, 57% to 100%). Similarly, if serum IL-6 results are combined with those of synovial PMNs or synovial WBC and if either of these values was above the threshold level, then the sensitivity, as well as NPV, increases up to 100% (95% CI, 73% to 100%). We also found out that if serum IL-6 results are combined with those of synovial WBC and when both values were above the cutoff level, the specificity and accuracy of detecting PJI were highest and went up to 90% (95% CI, 67% to 98%) and 78.1%, respectively (Table 3; "Appendix 2").

Serum IL-6 levels strongly correlate with those of ESR ($p < 0.0001$), CRP ($p < 0.0003$), synovial fluid WBC ($p < 0.0400$) and synovial fluid PMN ($p < 0.0070$) when tested simultaneously in patients with infected TKA (Table 5).

The most common microorganisms obtained from patients with two or more positive cultures included methicillin-sensitive Staphylococcus aureus (28%), Streptococcus species (17%), Coagulase-negative staphylococci (14%), Propionibacterium acnes (14%), Corynebacterium (7.5%), methicillin-resistant Staphylococcus aureus (5%), Enterococci (5%), Candida albicans (5%) and others (4.5%).

Discussion

Accurate diagnosis of chronic, low-grade PJI remains elusive and least invasive, and workup recommended for the earliest possible way to screen a painful prosthetic joint

Table 3 Statistics of the individual and combined tests based on the threshold values[a] of the markers for infected total knee arthroplasty[b]

Strategy	Markers of infection (Threshold value[a] from the ROC curves in Fig. 1a, b)	Sensitivity[h] (%)	Specificity[h] (%)	PPV[h,e] (%)	NPV[h,f] (%)	Accuracy (%)	*p* value[g]
Individual test must be positive	Interleukin 6 (> 9.14 pg/ml)	81.3	63.0	56.5	85.0	69.8	0.010
	ESR (> 27 mm/h)	70.0	63.6	63.6	70.0	66.7	0.037
	CRP (> 17 mg/L)	66.7	66.7	63.2	70.0	66.7	0.056
	Synovial WBC (> 1804 cells/10^{-3} cm^3)	66.7	81.0	77.8	70.8	73.8	0.004
	Synovial PMNs (> 86%)	82.4	73.7	73.7	82.4	77.8	0.001
Combinations involving either test to be positive[c]	Interleukin 6 or ESR	81.3	52.0	52.0	81.3	63.4	0.050
	Interleukin 6 or CRP	93.8	45.8	53.6	91.7	65.0	0.012
	ESR or CRP	80.0	50.0	59.3	73.3	64.3	0.058
	Interleukin 6 or ESR or CRP	93.8	40.0	50.0	90.9	61.0	0.029
	Interleukin 6 or synovial WBC	93.3	47.6	56.0	90.9	66.7	0.011
	Interleukin 6 or synovial PMNs	100.0	50.0	58.3	100.0	70.6	0.002
	Synovial WBC or synovial PMNs	89.5	68.4	73.9	86.7	78.9	0.001
	Interleukin 6 or synovial WBC or synovial PMNs	100.0	45.0	56.0	100.0	67.6	0.004
Combinations involving all tests positive[d]	Interleukin 6 and ESR	53.8	76.2	58.3	72.7	67.6	0.140
	Interleukin 6 and CRP	33.3	85.0	57.1	68.0	65.6	0.380
	ESR and CRP	52.9	81.0	69.2	68.0	68.4	0.042
	Interleukin 6 and ESR and CRP	33.3	85.0	57.1	68.0	65.6	0.380
	Interleukin 6 and synovial WBC	58.3	90.0	77.8	78.3	78.1	0.006
	Interleukin 6 and synovial PMNs	60.0	77.8	60.0	77.8	71.4	0.097
	Synovial WBC and synovial PMNs	64.7	84.2	78.6	72.7	75.0	0.005
	Interleukin 6 and synovial WBC and synovial PMNs	50.0	88.9	71.4	76.2	75.0	0.063

[a]The threshold values of markers of prosthetic joint infection (PJI) have been drawn from the receiver operating characteristics curves in Fig. 1a, b

[b]Infected total knee arthroplasty is defined by the presence of either of the two major criteria from the Musculoskeletal Infection Society definition as described in the text. The details of the established criteria are elaborated in Appendix 1

[c]Either tests to be positive: In this situation, any one or more of the values must be above their threshold values to result in a positive combined test

[d]All tests positive: In this situation, all values must be above their threshold values to result in a positive combined test

[e] Highest PPV (positive predictive value) confirms infection

[f]Highest NPV (negative predictive value) rules out infection

[g]*p* value is determined by the Fischer's exact test and denotes the significance of a test in infected versus noninfected total knee arthroplasty and is statistically significant if < 0.05

[h]The 95% confidence interval values for each test are available in Appendix 2

for infection continues to be inflammatory blood markers like ESR and CRP, but they have reduced sensitivity and specificity [11]. The newer biomarkers like alpha defensin or D-dimer lack adequate multi-institutional, randomized controlled study data on their role in accurately screening or diagnosing the PJI, especially in the presence of comorbid conditions that could alter their levels in the blood and synovium [12, 16]. Our goal was to identify the most straightforward, best and most cost-effective initial screening tool from blood or synovial fluid markers to identify the low-grade prosthetic infections. IL-6, an acute phase protein, is one of the earliest pro-inflammatory cytokines released in the bloodstream by the injured tissue, and it not only acts as a precursor for CRP but also triggers a lot of other biomarkers responsible for neutrophil chemotaxis to the inflamed site [8].

According to our study, the optimal threshold concentration for serum IL-6 in the diagnosis of infected TKA

Table 4 Comparison of threshold value of markers of prosthetic joint infection with those from the published studies

Marker of prosthetic joint infection (normal range at our laboratory)	Our study[a]	Cipriano et al. (JBJS 2012)	MSIS definition[b] (CORR 2011)	Ghanem et al. (IJID 2009)	Bottner et al. (JBJS 2007)	Di Cesare et al. (JBJS 2005)
Prosthetic joint studied	Knee	Hip and knee[c]	Hip and knee[c]	Hip	Hip	Hip and knee[c]
Interleukin 6 (< 3 pg/ml)	9.14	–	–	–	12	10
ESR (males: < 20 mm/h, females: < 30 mm/h)	27	32	30	30	32	30
CRP (< 8 mg/L)	17	15	10	10	3.2	10
Synovial WBC (< 200 cell/10^{-3} cm^3)	1804	3450	1100	–	6200	–
Synovial PMN (< 25%)	86	78	64	–	–	–

[a]The threshold values of markers of prosthetic joint infection (PJI) have been calculated from the receiver operating characteristics curves in Figs. 1 and 2

[b] MSIS definition of prosthetic joint infection—Musculoskeletal Infection Society defined prosthetic joint infection using two major criteria and four out of six minor criteria were published in the CORR on November 2011. The details of the criteria are elaborated in "Appendix 1"

[c]Both hip and knee joint infections were studied together, without identifying the accuracy of markers separately in either of the joints. Craig Della Valle et al. in their studies have shown that the values of inflammatory markers could have a different threshold value in different joints

– indicates values were not determined in that study

Table 5 Strength of correlation of blood and synovial fluid markers in infected total knee arthroplasty when tested simultaneously prior to the definitive treatment

Marker 1	Marker 2	Rs[a]	*p*(Rs) value[b]
Interleukin 6 and	ESR	0.7980	< 0.0001
	CRP	0.5948	0.0003
	Synovial WBC	0.3496	0.0499
	Synovial PMNs	0.4920	0.0078
ESR and	CRP	0.6127	< 0.0001
	Synovial WBC	0.2731	0.1400
	Synovial PMNs	0.5156	0.0059
CRP and	Synovial WBC	0.3786	0.0391
	Synovial PMNs	0.3839	0.0480
Synovial WBC and	Synovial PMNs	0.6471	< 0.0001

[a]Spearman's rank correlations coefficient

[b]*p* value is determined by Fisher's exact test, correlates values in infected vs noninfected TKA and is statistically significant if < 0.05

is 9.14 pg/ml. This threshold value obtained in our study using ROC curves is close to that determined by two other studies and confirms the existing knowledge of the usefulness of IL-6 in the diagnosis of PJI [7–9]. Prior studies have determined that serum IL-6 could be diagnostic of PJI if the optimal value was above 10 pg/ml for infected THA &/TKA (based upon median of 17 patients) [11] or 12 pg/ml for infected THA ($n = 69$) [9, 10]. Data supporting our finding are more robust for infected TKAs. The normal range for serum IL-6 of 0 to 3 pg/ml in healthy patients was based on the high-sensitivity ELISA technique used with Luminex 100 analyzer at University Cytokine Reference Laboratory. The serum IL-6 level in normal individuals is approximately 1 pg/ml [10] with modest elevations of up to 10 pg/mL in patients with inflammatory diseases or malignancies [17]. The potential advantage of using this marker is that it is normal in patients with aseptic loosening [18]. It may show large elevations of 30 to 430 pg/mL for only up to 70 h after a routine arthroplasty, and then they return to normal [17, 19] and so the level of this marker is not accurate for diagnosis of prosthetic infection for up to 3 days after the surgery [19].

Serum IL-6 as an individual marker has the highest sensitivity and highest NPV (rules out PJI) but lower specificity and PPV for PJI, when compared with all other routine markers analyzed in this study. These findings partially concur with those from the study published by Di Cesare et al. [10] that the serum IL-6 has the highest sensitivity and highest NPV in the diagnosis of PJI, but our study contradicts their finding that it also has higher specificity and PPV. This contradiction is possibly exposed due to the larger sample size in our study.

Serum IL-6, when combined with synovial markers (WBC, PMN), demonstrates highest sensitivity (100%), specificity (90%), PPV (78%) as well as NPV (100%) among all combinations tested ("Appendix 2"). The significance of this finding is that this combination could be very reliably used to rule out 100% of infections, thus improving the screening of an occult PJI in a painful TKA. None of the studies published so far have demonstrated this finding.

The strengths of the study are that it was performed at a single institution, the markers were tested at an only cytokine reference laboratory and they were exclusively analyzed in a painful TKA.

Table 6 Sensitivities and specificities of markers of infected total knee arthroplasty due to inflammatory response generated by specific organism groups at the threshold values

Virulence	Organisms[a]	%	Interleukin 6		ESR		CRP		Synovial WBC		Synovial neutrophils	
			Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Low virulence	Propionibacterium acnes	15	50.0	59.3	66.7	59.1	66.7	66.7	33.3	81.0	50.0	68.4
	Coagulase-negative Staphylococci	15	100.0	59.3	50.0	59.1	50.0	66.7	75.0	81.0	66.7	68.4
High virulence	Staphylococcus species (except Coag neg staphylococci)[b]	35	100.0	59.3	100.0	59.1	83.3	66.7	71.4	81.0	100.0	68.4
	Streptococcus species[c]	18	60.0	59.3	25.0	59.1	33.3	66.7	50.0	81.0	50.0	68.4
	Others (isolated)[d]	17	75.0	59.3	50.0	59.1	75.0	66.7	66.7	81.0	80.0	68.4

Refer to Table 1

[a]Intra-operatively obtained in two or more positive cultures

[b]MSSA (28%), MRSA (5%), Staph. Lugdunensis(2%)

[c]Strep. Viridans (8%), Peptostreptococci (5%), Strep Oralis (2.5%), Beta hemolytic streptococci(2.5%)

[d]Others–Anaerobic diphtheroids (2.5%), Serratia Marcescens (2.5%), Achromobacter xylosoxidans (2.5%), Corynebacterium (2%), Enterococci (5%), Candida albicans (2.5%)

The weakness of the study is that (1) a bigger sample size could have strengthened the findings in this study. (2) Patients with a different organism mix as regards low- or high-virulent organisms could impact the overall outcomes due to a variable level of inflammatory response launched by that particular low- or high-virulent organism (Table 6). Also, the major limitations of this study are that (3) we did not test other similar biomarkers and compare or correlate their utility as we were looking for the most sensitive or specific biomarker that is expressed in the bloodstream and try to find a perfect combination of biomarkers to identify PJI. (4) The criteria used to diagnose infection (positive culture on solid media or sinus tract communicating with the prosthesis) may have introduced bias as there is a possibility of identifying more patients with PJI if additional minor criterion from MSIS definition would have been used. But we decided to exclude the minor criteria as most of them are less specific than the major criteria and are still being tested for their efficacy and accuracy [20, 21]. (5) There is also a possibility of up to 20% variation in the laboratory value of interleukin 6 if it is tested in different laboratories, using different ELISA kits, different analyzers, calibration and manufacturer-recommended settings [17, 22].

This study concludes that the optimal threshold concentration of serum IL-6 at 9.14 pg/ml is diagnostic of infected TKA. Serum IL-6 levels strongly correlate with all the tested markers of PJI and could be reliably used in combination with synovial fluid markers to improve the infection screening in a painful TKA.

Funding No funds were received in support of this study.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Appendix 1

See Fig. 2.

Fig. 2 Musculoskeletal infection society (MSIS) definition for the diagnosis of prosthetic joint infection (PJI)

Major criteria (at least one of the following)	Decision
Two positive cultures of the same organism	Infected
Sinus tract with evidence of communication to the joint or visualization of the prosthesis	

		Minor Criteria	Score	Decision
Preoperative Diagnosis	Serum	Elevated CRP *or* D-Dimer	2	≥6 Infected
		Elevated ESR	1	
	Synovial	Elevated synovial *WBC count or LE*	3	2-5 Possibly Infected [a]
		Positive alpha-defensin	3	
		Elevated synovial PMN (%)	2	0-1 Not Infected
		Elevated synovial CRP	1	

	Inconclusive pre-op score *or* dry tap [a]	Score	Decision
Intraoperative Diagnosis	Preoperative score	-	≥6 Infected
	Positive histology	3	4-5 Inconclusive [b]
	Positive purulence	3	
	Single positive culture	2	≤3 Not Infected

Appendix 2

See Table 7.

Table 7 95% confidence interval values for Table 1

Markers of PJI	Sensitivity			Specificity			PPV			NPV		
		95% CI			95% CI			95% CI			95% CI	
	Estimate	Lower	Upper	Estimate	Lower	Upper	Estimate	Lower	Upper	Estimate	Lower	Upper
IL-6	0.813	0.537	0.950	0.630	0.425	0.799	0.565	0.349	0.761	0.850	0.611	0.960
ESR	0.700	0.457	0.872	0.636	0.408	0.820	0.636	0.408	0.820	0.700	0.457	0.872
CRP	0.667	0.412	0.856	0.667	0.431	0.845	0.632	0.386	0.828	0.700	0.457	0.872
Syn WBC	0.667	0.431	0.845	0.810	0.574	0.937	0.778	0.519	0.926	0.708	0.488	0.866
Syn Neutr	0.824	0.558	0.953	0.737	0.486	0.899	0.737	0.486	0.899	0.824	0.558	0.953
IL-6 or ESR	0.813	0.537	0.950	0.520	0.318	0.717	0.520	0.318	0.717	0.813	0.537	0.950
IL-6 or CRP	0.938	0.677	0.997	0.458	0.262	0.668	0.536	0.342	0.720	0.917	0.598	0.996
ESR or CRP	0.800	0.557	0.934	0.500	0.288	0.712	0.593	0.390	0.770	0.733	0.448	0.911
IL6 or ESR or CRP	0.938	0.677	0.997	0.400	0.218	0.611	0.500	0.568	0.852	0.909	0.571	0.995
IL-6 or Syn WBC	0.933	0.660	0.997	0.476	0.264	0.697	0.560	0.353	0.750	0.909	0.571	0.995
IL-6 or Syn Neutr	1.000	0.732	1.000	0.500	0.279	0.722	0.583	0.369	0.772	1.000	0.655	1.000
Syn WBC or Syn Neutr	0.895	0.655	0.982	0.684	0.435	0.864	0.739	0.513	0.889	0.867	0.584	0.977
IL-6 or Syn WBC or Syn Neutr	1.000	0.732	1.000	0.450	0.238	0.680	0.560	0.353	0.750	1.000	0.629	1.000
IL-6 and ESR	0.538	0.261	0.796	0.762	0.525	0.909	0.583	0.286	0.835	0.727	0.496	0.884
IL-6 and CRP	0.333	0.113	0.646	0.850	0.611	0.660	0.571	0.202	0.882	0.680	0.465	0.843
ESR and CRP	0.529	0.285	0.761	0.810	0.574	0.937	0.692	0.389	0.896	0.680	0.465	0.843
IL6 and ESR and CRP	0.333	0.113	0.646	0.850	0.611	0.960	0.571	0.202	0.882	0.680	0.465	0.843
IL-6 and Syn WBC	0.583	0.286	0.835	0.900	0.669	0.983	0.778	0.402	0.961	0.783	0.558	0.917
IL-6 and Syn Neutr	0.600	0.274	0.863	0.778	0.519	0.927	0.600	0.274	0.863	0.778	0.519	0.926
Syn WBC and Syn Neutr	0.647	0.386	0.847	0.842	0.595	0.958	0.786	0.488	0.943	0.727	0.496	0.884
IL-6 and Syn WBC and Syn Neutr	0.500	0.201	0.799	0.889	0.639	0.981	0.714	0.303	0.949	0.762	0.525	0.909

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