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A meta-analysis of synovial biomarkers in periprosthetic joint infection: Synovasure™ is less effective than the ELISA-based alpha-defensin test

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Abstract

Purpose (1) To determine the overall accuracy of synovial alpha-defensin, synovial C-reactive protein (sCRP), interleukin-6 (sIL-6), and leukocyte esterase (sLE) as diagnostic markers for periprosthetic joint infection (PJI) and (2) to independantly evaluate the accuracy of both the laboratory-based ELISA alpha-defensin test and the Synovasure™ alpha-defensin test kit.

Methods An EMBASE and MEDLINE (PubMed) database search was performed using a set of professionally set search terms. Two independent reviewers rated eligible articles. Sensitivity and specificity were meta-analysed using a bivariate random-effects model.

Results Accuracy values were extracted from 42 articles. Pooled sensitivity and specificity of the represented biomarkers were: alpha-defensin ELISA 0.97 (95% CI 0.91–0.99) and 0.97 (95% CI 0.94–0.98), respectively; Synovasure™ test kit assay 0.80 (95% CI 0.65–0.89) and 0.89 (95% CI 0.76–0.96), respectively; sLE 0.79 (95% CI 0.67–0.87) and 0.92 (95% CI 0.87–0.92), respectively; sIL-6 0.76 (95% CI 0.65–0.84) and 0.91 (95% CI 0.88–0.94), respectively; sCRP 0.86 (95% CI 0.81–0.91) and 0.90 (95% CI 0.86–0.93), respectively.

Conclusion The labararory-based alpha-defensin ELISA test showed the highest ever reported accuracy for PJI diagnosis. However, this did not apply for the Synovasure™ alpha-defensin test, which was comparable in its overall diagnostic accuracy to sCRP, sIL-6 and sLE. The later biomarkers also did not yield an overall diagnostic accuracy higher than that previously reported for synovial white cell count (sWBC) or culture bacteriology. Based on current evidence, no synovial biomarker should be applied as a standalone diagnostic tool. Furthermore, the use of the laboratory-based alpha-defensin ELISA test should be encouraged, still, the Synovasure™ alpha-defensin test kit should be critically appreciated.

Lever of evidence III.

Keywords Alpha-defensin · Alpha defensin · α Defensin · α-Defensin · Synovasure · Synovial · Biomarker · Leukocyte esterase, CRP · Synovial CRP · Interleukin 6 · Interleukin-6 · Synovial interleukin-6

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Introduction

A reliable establishment of early and correct diagnosis is crucial for effective management of periprosthetic joint infection (PJI). Early detection and subsequent management are warranted to control the systemic inflammatory response and to avoid biofilm formation on the implants. It also often allows for less aggressive surgical treatment [28].

In contrast to acute PJI, chronic PJI frequently presents with a more subtle clinical picture, and 'conventional' diagnostic methods are often unremarkable. Consequently, PJI may be misinterpreted as instability, aseptic loosening, or implant malposition. In fact, this clearly highlights the urgent need for accurate and reliable testing methods for the diagnosis of PJI.

Synovial fluid biomarkers are increasingly used in the diagnostic workup of PJI. The theoretical advantage is the direct measurement and prompt result of the affected joint. Synovial fluid biomarkers well described in association with PJI include Interleukin-6 [7], CRP [31], alpha-defensin [3], and leukocyte esterase [30]. Some previous studies have revealed a high accuracy of these biomarkers for detecting PJI. However, the reality is that lack of consensus currently persists, complicating the smooth translation of biomarker-based diagnostic tests to standard algorithms in clinical practice. This emphasizes the need for meta-analyses in the field that could compute the large pool of accuracy reports into comprehendible output values clinicians could employ with simplicity, ultimately easing the process of research translation and ensuring evidence-based practice.

The aim of the current meta-analysis was to (1) determine the overall accuracy of synovial alpha-defensin, synovial C-reactive protein (sCRP), interleukin-6 (sIL-6), and leukocyte esterase (sLE) as diagnostic markers for periprosthetic joint infection (PJI) and (2) to independently evaluate the accuracy of both the laboratory-based ELISA alpha-defensin test and the commercially available Synovasure™ test kit.

Materials and methods

Search strategy

A systematic literature search was conducted using the databases MEDLINE (PubMed) and OVID (EMBASE), including all publications from database inception until 21 August 2017. The search terms are provided in the supplementary material alongside the manuscript.

Eligibility criteria

Potentially relevant publications were screened by two independent reviewers to ensure adherence to the following inclusion criteria: (1) test accuracy as a primary research question, (2) inclusion of quantitative accuracy information (sensitivity, specificity or likelihood ratios). Articles not focusing on diagnostic tests (e.g. on therapeutic or economic aspects) or not containing original quantitative values of sensitivity and specificity, systematic reviews or narrative reviews, guidelines, recommendations and expert opinions and case reports were excluded (Fig. 1).

Data extraction

Two authors worked independently to classify studies and extract data. Sensitivity, specificity, positive and negative likelihood ratios (LR), positive and negative predictive values as well as area under the curve (AUC) were extracted. Quality assessment of each study was also performed using the QUADAS (Quality Assessment of Diagnostic Accuracy Studies) tool [44].

Statistical analysis

Four biomarkers were analysed: alpha-defensin, CRP in synovial fluid, synovial interleukin-6 and leukocyte esterase. All calculations were performed using continuity-corrected cell counts. The continuity correction was added to the whole data as soon as one cell in one study was zero. Sensitivity and specificity were meta-analysed using the bivariate diagnostic random-effects model described by Reitsma et al. [33] and were estimated by restricted maximum likelihood (REML). For alpha-defensin, two different assay types were included (laboratory ELISA versus Synovasure™ lateral flow test kit) and analysed using a bivariate random-effects meta-regression with the assay type as covariate, or using two separate models. The combined, meta-analysed estimates for sensitivity and specificity were reported with 95% confidence intervals (95% CI). Combined estimates for postive and negative likelihood ratio (LR), and diagnostic odds ratio (DOR) were calculated using a sampling approach according to Zwinderman and Bossuyt [45]. A summary receiver operating characteristic curve (ROC) curve was constructed based on Monte Carlo simulations [11]. The area under the curve (AUC) was calculated using the trapezoidal rule also including the extrapolated points of the ROC curve. A sensitivty analysis was performed to assess the effect of the inclusion of more than one value of sensitivity/specificity from the same study. All analyses were performed using R (MADA package Boston, Massachusetts, USA).

This study did not involve experiments or direct analysis of patient data. No ethical approval was necessary.

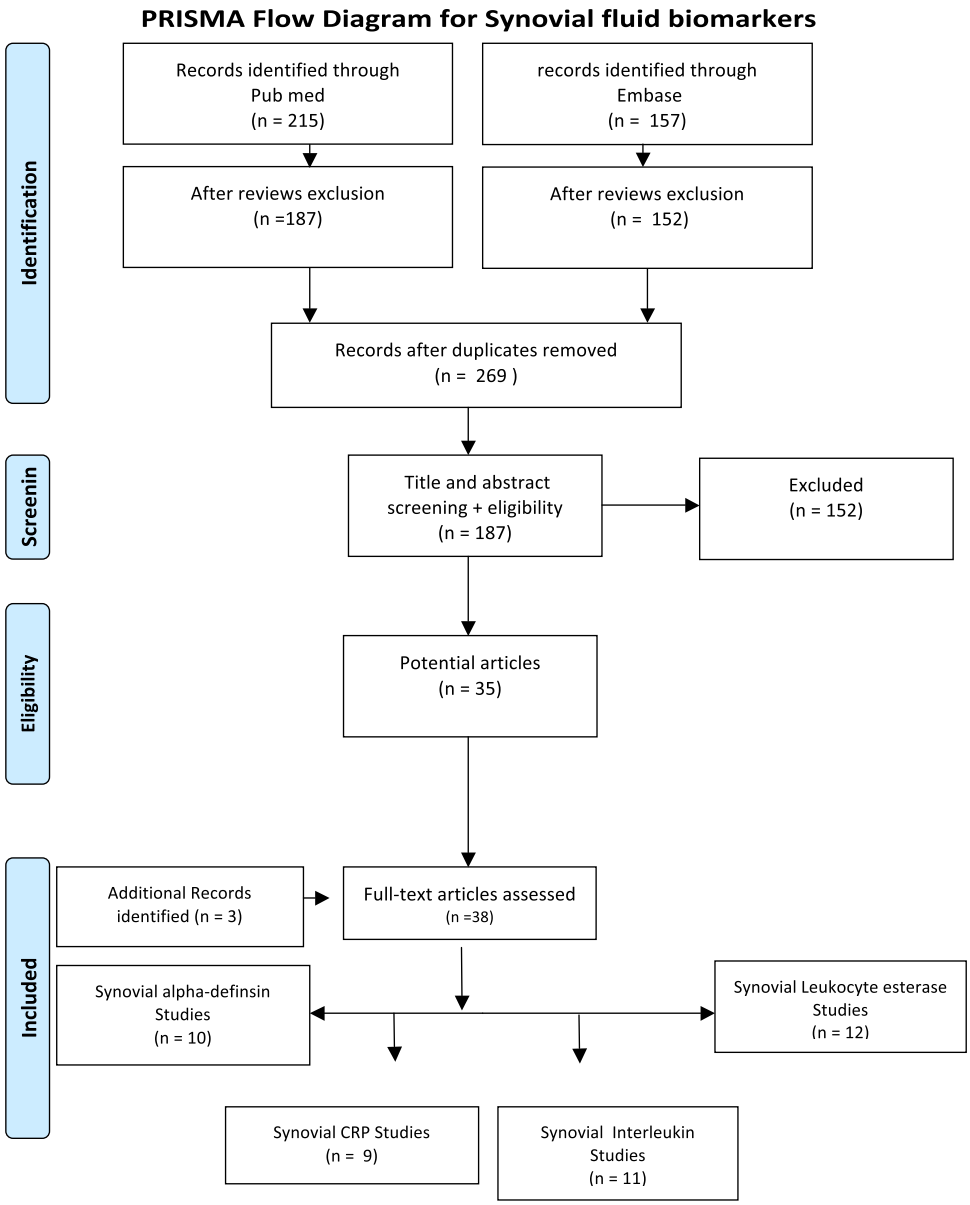

Fig. 1 Flowchart demonstrating the process of article allocation according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA)

Results

Four synovial biomarker groups were covered: alpha-defensin ($n = 10$ articles), synovial CRP ($n = 9$ articles), synovial leukocyte esterase ($n = 12$ articles) and synovial interleukin-6 ($n = 11$ articles) (Fig. 1). Articles were published between the years 2007 and 2017. A total of 3734 prosthetic joints were examined, of which 1107 were infected. The median (range) QUADAS-2 quality score was 13 (13; 14) for articles dealing with synovial CRP, 12 (12; 13) for articles dealing with IL-6, 12.5 (11; 14) for articles dealing with leukocyte esterase and 13 (12; 14) for articles dealing with alpha-defensin. This demonstrates the good quality of diagnostic studies included here, given that the maximum possible score of 14 points.

Diagnostic values and meta-analysed estimates

Characteristics of diagnostic studies with the corresponding pooled values from this analysis are illustrated in Tables 1, 2, 3 and 4. Forest plots showing the study-specific and meta-analysed estimates of sensitivity and specificity for each synovial fluid biomarker are seen in Figs. 2, 3, 4 and 5. Summary ROC curves constructed for all assays based on Monte Carlo simulations are shown in Fig. 6.

Table 1 Characteristics of diagnostic studies for CRP in synovial fluid with 95% confidence intervals

	Sensitivity	Specificity	Positive LR	Negative LR	DOR
Buttaro [5]	89 (70–97)	94 (84–98)	14.0 (5.03–39.0)	0.12 (0.04–0.37)	121 (22–662)
Deirmengian [10]	95 (81–99)	89 (79–94)	8.49 (4.30–16.7)	0.06 (0.01–0.27)	151 (25–920)
Jacovides [20]	86 (70–94)	97 (86–99)	24.6 (5.08–119)	0.15 (0.06–0.34)	169 (25–1141)
Omar [27]	93 (75–98)	92 (83–96)	11.7 (5.20–26.3)	0.07 (0.02–0.35)	158 (24–1027)
Pravizi [29]	71 (52–85)	99 (89–100)	56.9 (3.58–904)	0.29 (0.16–0.53)	195 (11–3597)
Pravizi [29]	83 (64–93)	96 (85–99)	22.1 (4.54–107)	0.18 (0.08–0.42)	123 (18–838)
Pravizi [31]	83 (63–94)	94 (83–98)	14.7 (4.33–49.6)	0.18 (0.07–0.46)	83 (15–462)
Ronde-Oustau [34]	96 (70–100)	79 (57–91)	4.47 (1.96–10.2)	0.05 (0.00–0.81)	84 (4–1723)
Ronde-Oustau [34]	88 (60–97)	88 (68–96)	7.35 (2.25–24.0)	0.14 (0.03–0.64)	52 (6–450)
Tetreault [39]	86 (71–94)	84 (77–90)	5.56 (3.58–8.63)	0.16 (0.07–0.38)	34 (11–105)
Vanderstappen [41]	96 (70–100)	82 (56–94)	5.37 (1.73–16.6)	0.05 (0.00–0.77)	106 (5–2455)
Vanderstappen [41]	88 (60–97)	89 (64–97)	8.17 (1.77–37.6)	0.14 (0.03–0.63)	58 (5–648)
Pooled	86 (81–91)	90 (86–93)	9.12 (6.29–12.9)	0.15 (0.11–0.21)	62 (36–99)

Articles cited more than once denote more than one mentioned threshold value

LR likelihood ratio, *DOR* diagnostic odds ratio

Table 2 Characteristics of diagnostic studies for synovial leukocyte esterase with 95% confidence intervals

	Sensitivity	Specificity	Positive LR	Negative LR	DOR
Colvin [6]	98 (80–100)	96 (83–99)	22.1 (4.62–106)	0.03 (0.00–0.40)	845 (33–21,781)
Deirmengian [8]	69 (49–84)	98 (83–100)	33.0 (2.10–519)	0.32 (0.18–0.58)	103 (6–1939)
Guenther [19]	99 (90–100)	96 (94–98)	27.5 (15.6–48.6)	0.01 (0.00–0.18)	2441 (141–42,138)
Kheir [22]	28 (13–49)	86 (74–92)	1.91 (0.74–4.91)	0.85 (0.63–1.13)	2 (1–8)
Koh [23]	83 (69–92)	98 (82–100)	38.3 (2.46–597)	0.17 (0.08–0.34)	225 (12–4198)
Nelson [25]	28 (13–49)	75 (64–84)	1.12 (0.49–2.55)	0.96 (0.71–1.30)	1 (0–4)
Parvizi [30]	79 (62–90)	99 (94–100)	125 (7.83–1991)	0.21 (0.11–0.42)	592 (32–10,885)
Shafafy [35]	80 (59–91)	92 (85–96)	10.4 (4.82–22.4)	0.22 (0.10–0.51)	47 (13–174)
Shafafy [35]	84 (64–94)	86 (78–92)	6.22 (3.52–11.0)	0.18 (0.07–0.48)	34 (9–124)
Tarabichi [38]	79 (72–85)	99 (96–100)	87.8 (17.8–433)	0.21 (0.16–0.29)	412 (79–2155)
Tischler [40]	79 (56–92)	81 (74–86)	4.12 (2.80–6.08)	0.25 (0.10–0.65)	16 (5–56)
Tischler [40]	68 (44–85)	97 (93–99)	21.4 (8.83–51.9)	0.33 (0.17–0.66)	64 (17–241)
Wang [42]	83 (69–92)	96 (83–99)	19.4 (4.04–93.6)	0.17 (0.09–0.35)	112 (18–703)
Wetters [43]	92 (81–96)	89 (83–93)	8.07 (5.27–12.4)	0.10 (0.04–0.23)	84 (29–247)
Wetters [43]	93 (83–98)	77 (70–83)	4.07 (3.06–5.4)	0.09 (0.03–0.24)	47 (15–148)
Pooled	79 (67–87)	92 (87–92)	10.5 (5.82–17.6)	0.23 (0.14–0.36)	49 (18–108)

Articles cited more than once denote more than one mentioned threshold value

LR likelihood ratio, *DOR* diagnostic odds ratio

Discussion

The most important findings of this meta-analysis are: (1) the laboratory-based alpha-defensin enzyme-linked immunosorbent assay (ELISA) test demonstrated the highest ever reported accuracy for PJI diagnosis; (2) the accuracy of the Synovasure™ alpha-defensin test kit is markedly lower than that of the laboratory ELISA; (3) the Synovasure™ alpha-defensin test kit, synovial CRP, synovial Interleukin-6 and synovial leukocyte esterase showed an overall good and similar accuracy, however, not higher than the accuracy previously reported for synovial white cell count (sWBC) or culture bacteriology.

In clinical practice, the diagnostic workup of PJI is based on the initial assumption that every painful prosthetic joint is infected until proven otherwise [2]. From there, it is the responsibility of the clinician to provide arguments for the absence of an infection. It was previously mentioned that the majority of available tests show effectiveness in either excluding a PJI or confirming it, but not necessarily both [2]. A measure used for detecting the strengths of diagnostic tests in that regard is the likelihood ratio (LR), which incorporates both sensitivity and

Table 3 Characteristics of diagnostic studies for synovial interleukin-6 with 95% confidence intervals

	Sensitivity	Specificity	Positive LR	Negative LR	DOR
Deirmengian [7]	97 (75–100)	99 (89–100)	73.5 (4.67–1155)	0.03 (0.00–0.52)	2175 (41–114,840)
Deirmengian [10]	95 (81–99)	89 (79–94)	8.49 (4.30–16.7)	0.06 (0.01–0.27)	151 (25–920)
Frangiamore [15]	84 (60–95)	89 (74–96)	7.71 (2.81–21.2)	0.18 (0.06–0.55)	44 (8–252)
Frangiamore [16]	80 (63–90)	96 (87–99)	19.1 (5.61–65.2)	0.21 (0.11–0.42)	90 (20–417)
Frangiamore [14]	81 (64–91)	86 (74–93)	5.98 (2.87–12.5)	0.22 (0.10–0.47)	27 (8–95)
Gollwitzer [18]	59 (36–79)	93 (74–98)	8.31 (1.69–40.9)	0.44 (0.24–0.80)	19 (3–132)
Jacovides [20]	86 (70–94)	99 (90–100)	73.9 (4.68–1167)	0.14 (0.06–0.34)	519 (27–10,033)
Lenski [24]	89 (74–96)	94 (81–98)	13.9 (4.16–46.4)	0.12 (0.04–0.32)	119 (22–648)
Nilsdotter [26]	67 (48–82)	92 (83–96)	8.20 (3.52–19.1)	0.36 (0.20–0.62)	23 (7–76)
Randau [32]	62 (48–74)	86 (76–92)	4.33 (2.37–7.89)	0.44 (0.30–0.64)	10 (4–23)
Randau [32]	46 (33–60)	97 (90–99)	13.4 (3.82–47.1)	0.56 (0.43–0.73)	24 (6–95)
Wimmer, 2016	50 (20–80)	98 (81–100)	21.0 (1.23–358)	0.51 (0.24–1.08)	41 (2–979)
Pooled	76 (65–84)	91 (88–94)	8.92 (6.2–12.5)	0.27 (0.18–0.39)	35 (18–61)

Articles cited more than once denote more than one mentioned threshold value

LR likelihood ratio, *DOR* diagnostic odds ratio

Table 4 Characteristics of diagnostic studies for alpha-defensin with 95% confidence intervals

	Sensitivity	Specificity	Postive LR	Negative LR	DOR
ELISA					
Bonanzinga [4]	96 (83–99)	96 (91–99)	26.3 (10.6–65.4)	0.05 (0.01–0.22)	575 (87–3801)
Deirmengian [9]	96 (85–99)	96 (91–98)	24.1 (9.73–59.8)	0.04 (0.01–0.20)	587 (89–3866)
Deirmengian [10]	98 (86–100)	99 (93–100)	132 (8.32–2086)	0.02 (0.00–0.26)	7847 (152–405,031)
Deirmengian [8]	98 (83–100)	98 (83–100)	47.0 (3.02–730)	0.02 (0.00–0.33)	2209 (42–116,042)
Pooled	0.97 (91–99)	0.97 (94–98)	29.8 (15.5–52.5)	0.04 (0.01–0.09)	966 (247–2620)
Synovasure™ test					
Bingham [3]	98 (80–100)	94 (83–98)	16.8 (5.03–56.0)	0.03 (0.00–0.41)	632 (29–13,803)
Frangiamore [13]	79 (51–93)	62 (46–76)	2.11 (1.27–3.52)	0.33 (0.11–1.03)	6 (1–30)
Frangiamore [12]	95 (80–99)	97 (91–99)	34.1 (10.0–116)	0.06 (0.01–0.26)	618 (78–4902)
Kasparek [21]	65 (39–85)	91 (76–97)	7.58 (2.17–26.5)	0.38 (0.18–0.81)	20 (4–113)
Sigmund [36]	68 (42–86)	93 (80–98)	10.0 (2.88–35.1)	0.34 (0.16–0.74)	29 (5–160)
Suda [37]	75 (49–90)	81 (58–93)	3.86 (1.44–10.4)	0.31 (0.12–0.79)	12 (2–67)
Pooled	80 (65–89)	89 (76–96)	29.8 (15.5–52.5)	0.24 (0.12–0.42)	42 (8–133)

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LR likelihood ratio, *DOR* diagnostic odds ratio

specificity, is simple to understand and allows for comparison between tests. It was utilized for result interpretation in this section of the manuscript [17].

It was shown in a survey published by the European Knee Associates (EKA) in 2016 that synovial biomarker testing was performed by less than 5% of surgeons [1]. This value is obviously low; however, the question of whether to increase the utility of those tests is only to be answered by current clinical evidence. The two well-established tests and commonly used tools will be referred to for comparison: (i) synovial fluid white cell count (sWBC) as an effective test for PJI exclusion and (ii) culture bacteriology as an effective tool for confirmation of PJI [2].

Firstly, it is important to underline the fact that based on the results of this meta-analysis, there is a difference between accuracy of the laboratory alpha-defensin ELISA test and the Synovasure™ test kit. The laboratory ELISA reports demonstrate the best ever reported overall accuracy compared to any other test, reflected in the efficacy in both ruling out an infection or confirming it with very high pooled sensitivity and specificity values of 97%. It is fair to note that only four studies were found and included in this meta-analysis. The Synovasure™ test kit on the other hand showed markedly lower accuracy values with a lower capacity to exclude a PJI than sWBC, and lower potency to confirm a PJI than culture bacteriology. The test could

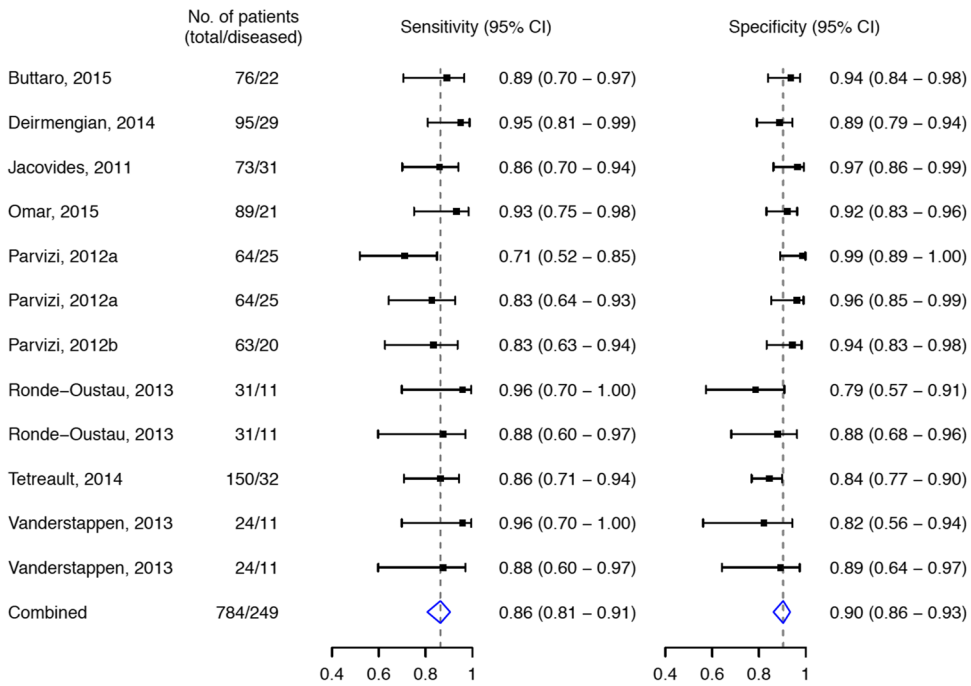

Fig. 2 A forest plot showing the study-specific and meta-analysed estimates for sensitivity and specificity for CRP in synovial fluid

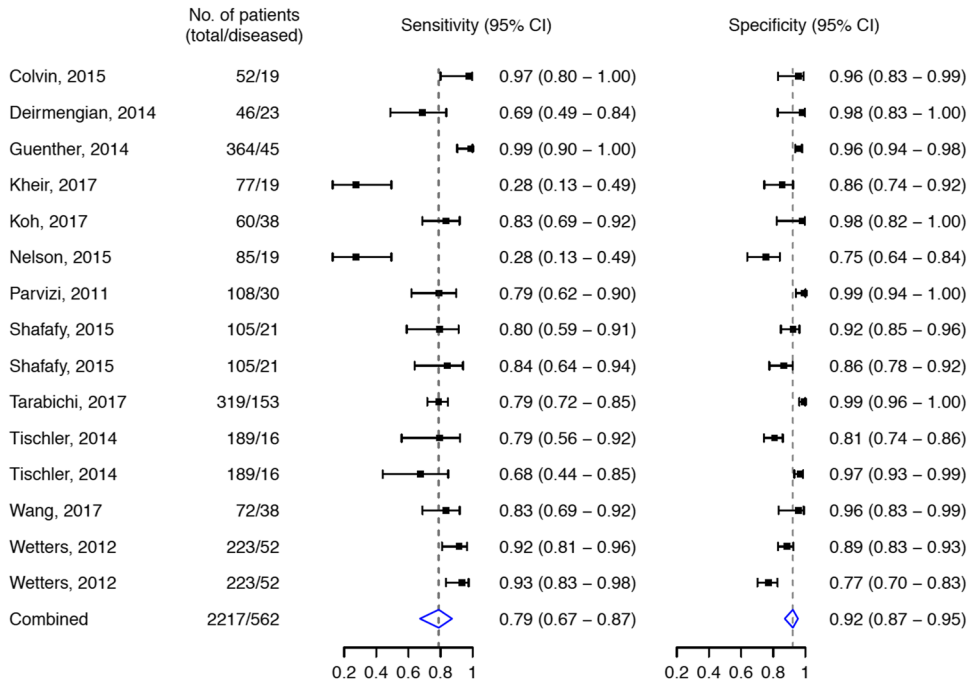

Fig. 3 A forest plot showing the study-specific and meta-analysed estimates for sensitivity and specificity for leukocyte esterase

therefore be performed as an adjunct and should not serve as a standalone test. It should be encouraged to perform comparative controlled studies in an attempt to find the reason for the aforementioned discrepancy.

Regarding the remaining synovial biomarkers, synovial CRP showed a very high potency for ruling out a PJI, similar to sWBC count but not better. Regarding confirmation of PJI, it did not prove better than bacterial culture examinations. Both synovial leukocyte esterase and synovial interleukin-6 were inferior to sWBC for ruling out PJI and inferior to bacterial culture examinations for confirming it.

Limitations of the study included the fact that only four studies of alpha-defensin ELISA were found and included. Two of these four studies did not find any false negatives or positives (reported a sensitivity and specificity of 100%) and a continuity correction was applied which could lead to an underestimation of the true values. Secondly, some studies were included twice in the meta-analysis as they

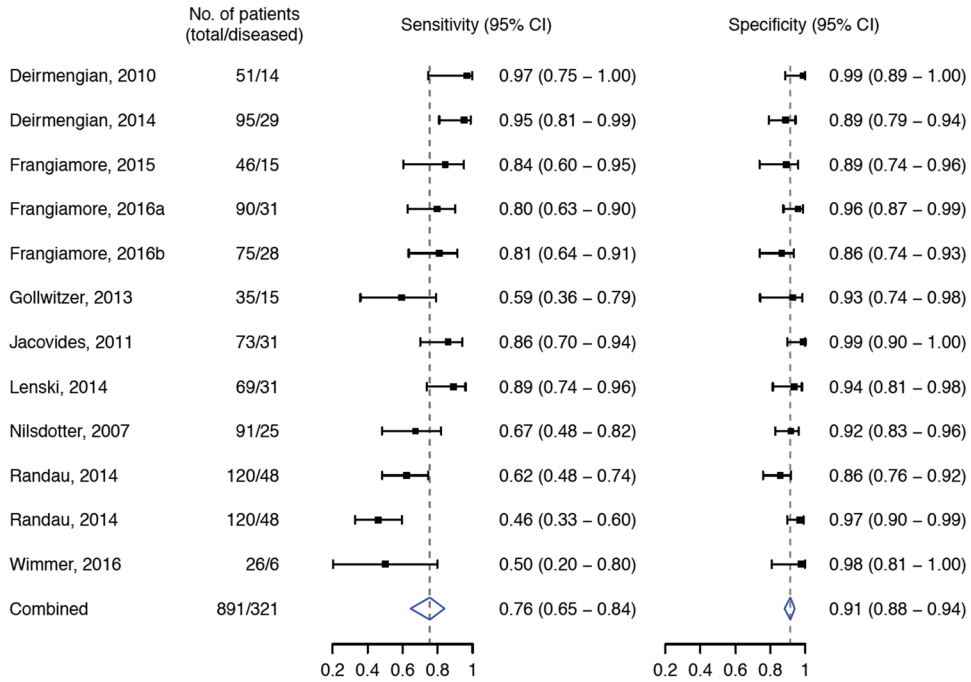

Fig. 4 A forest plot showing the study-specific and meta-analysed estimates for sensitivity and specificity for interleukin-6 in synovial fluid

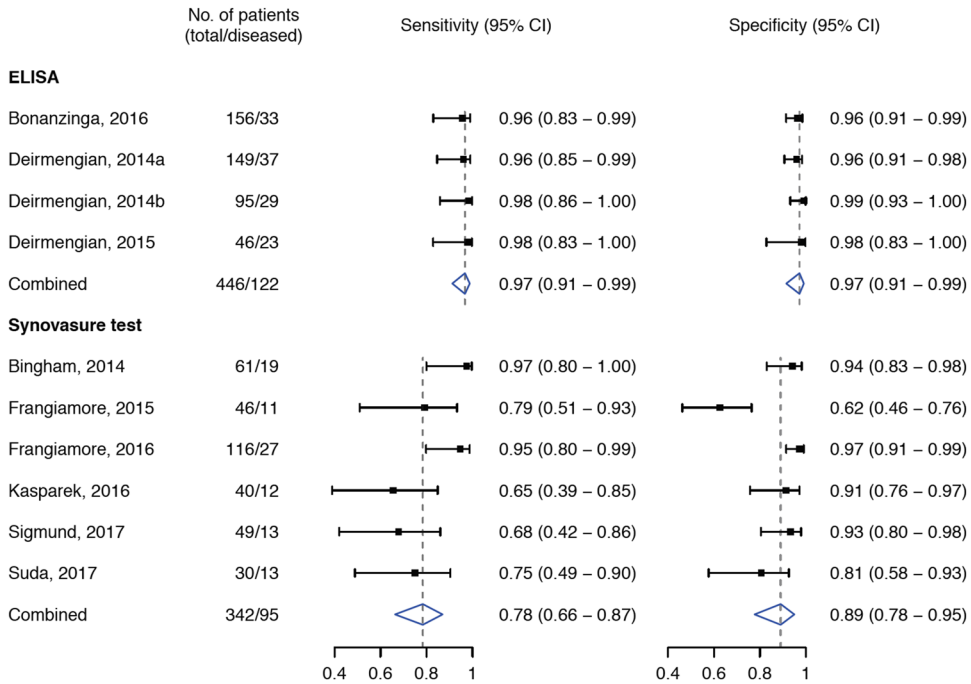

Fig. 5 A forest plot showing the study-specific and meta-analysed estimates for sensitivity and specificity for alpha-defensin. Studies with different assay types (laboratory ELISA versus Synovasure™ test) were analysed in separate models

reported sensitivity and specificity at two different cutoffs. This procedure violates the independence assumption and may lead to the underestimation of the uncertainty in the meta-analysis. Therefore, sensitivity analyses with only one cutoff were included for each study. All possible combinations were analysed for each end point (e.g. two analyses for one duplicated study, four analyses for two duplicated studies and eight analyses for three duplicated studies). Differences for both point and interval estimates were very small, and the correlation between estimates from the same studies seems not to be a major concern.

The relevance of the results to clinical practice can be reflected in that biomarkers in synovial fluid are of significance and their use should be encouraged given the relatively high accuracy. However, they do not yet provide more powerful diagnostic tools than conventional synovial exam such as synovial white blood cell count, or tissue culture. They are still not to be seen as standalone diagnostic tests.

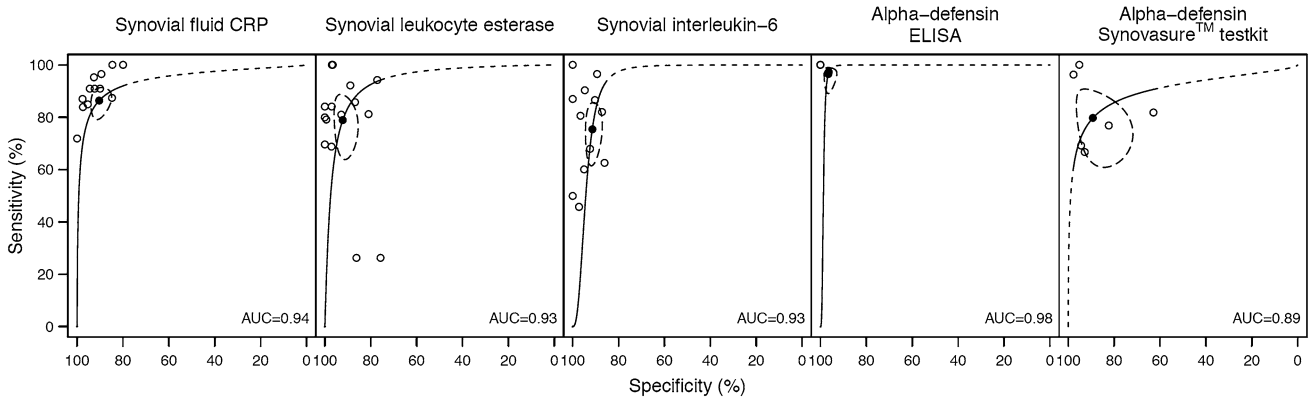

Fig. 6 Summary receiver operating characteristic curve (ROC curve). The dashed part of the curve is extrapolated beyond the observed data range. Estimates of sensitivity and specificity for each study are indicated with open circles, and the meta-analysed summary estimate with a filled circle together with the 95% confidence region. *AUC* area under the curve

Furthermore, all evidence is in favour of the laboratory-based ELISA alpha-defensin test and therefore its use should be encouraged.

Conclusion

The laboratory-based alpha-defensin ELISA test demonstrated the highest ever reported accuracy for PJI diagnosis. However, this does not apply to the Synovasure™ alpha-defensin test kit, which showed a markedly lower accuracy and should therefore be critically appreciated. Synovasure™ alpha-defensin, synovial CRP, synovial Interleukin-6 and synovial leukocyte esterase were not superior to synovial white cell count or culture bacteriology in the overall potency as diagnostic tools. Therefore, synovial biomarkers should not replace existing tools, but be used as diagnostic adjuncts.

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Compliance with ethical standards

Conflict of interest All authors declare no conflict of interest.

Ethical approval This study dealt with published data only, no ethical approval was needed.

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