Diagnostic accuracy of serum inflammatory markers in late fracture-related infection

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Published in:
Bone & joint journal

DOI:
10.1302/0301-620X.100B12.BJJ-2018-0586.R1

Publication date:
2018

■ SYSTEMATIC REVIEW

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A SYSTEMATIC REVIEW AND META-ANALYSIS

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doi:10.1302/0301-620X.100B12.BJJ-2018-0586.R1 $2.00

Bone Joint J 2018;100-B:1542–50.

Aims

To assess the diagnostic value of C-reactive protein (CRP), leucocyte count (LC), and erythrocyte sedimentation rate (ESR) in late fracture-related infection (FRI).

Materials and Methods

PubMed, Embase, and Cochrane databases were searched focusing on the diagnostic value of CRP, LC, and ESR in late FRI. Sensitivity and specificity combinations were extracted for each marker. Average estimates were obtained using bivariate mixed effects models.

Results

A total of 8284 articles were identified but only six were suitable for inclusion. Sensitivity of CRP ranged from 60.0% to 100.0% and specificity from 34.3% to 85.7% in all publications considered. Five articles were pooled for meta-analysis, showing a sensitivity and specificity of 77.0% and 67.9%, respectively. For LC, this was 22.9% to 72.6%, and 73.5% to 85.7%, respectively, in five articles. Four articles were pooled for meta-analysis, resulting in a 51.7% sensitivity and 67.1% specificity. For ESR, sensitivity and specificity ranged from 37.1% to 100.0% and 59.0% to 85.0%, respectively, in five articles. Three articles were pooled in meta-analysis, showing a 45.1% sensitivity and 79.3% specificity. Four articles analyzed the value of combined inflammatory markers, reporting an increased diagnostic accuracy. These results could not be pooled due to heterogeneity.

Conclusion

The serum inflammatory markers CRP, LC, and ESR are insufficiently accurate to diagnose late FRI, but they may be used as a suggestive sign in its diagnosis.

Cite this article: *Bone Joint J* 2018;100-B:1542–50.

Fracture-related infection (FRI) is a challenging complication in orthopaedic trauma surgery and uncertainties exist in both diagnostic and treatment strategies.[1] Regardless of antibiotic prophylaxis and sterile precautions observed at operation, the incidence of infection after fracture treatment is relatively high, generally varying between 1% and 30% depending on comorbidities, fracture type, and soft-tissue injury.[2-5] FRIs often result in multiple re-operations, long antibiotic treatment, immobilization, and restrictions in work and social activities.[6-9]

Although classical clinical signs typically seen in infection (such as redness, swelling, pain, and warmth) are often more prominent in early compared with late cases, symptoms can be subtle in both groups and may be relapsing and remitting over long periods of time.[10] Accordingly, dedicated imaging[11] and histological testing[12] are advised. In the FRI Consensus Definition, criteria to establish the presence or absence of FRI may be considered as confirmatory (infection definitely present) or suggestive (infection possibly present).[13] Suggestive diagnostic criteria include elevated CRP, leucocyte count (LC), and/or ESR. Although these markers are part of the FRI Consensus Definition and commonly used as a diagnostic and severity parameter for postoperative infections after orthopaedic trauma surgery, their accuracy has mainly been investigated in prosthetic joint infections (PJI) and patients with osteomyelitis due to diabetic foot disease.[14-19]

Generally, raised inflammatory markers are considered to be suggestive of infection when a secondary rise occurs after an initial decrease, or when a consistent elevation is present over a long period of time.[13] In FRI, elevations in inflammatory markers may be more subtle compared with PJI or diabetic foot osteomyelitis.[20] In addition, an elevation in these markers may be seen in trauma

Table I. Inclusion and exclusion criteria

Criteria
Inclusion criteria
1. The study must analyze serum inflammatory parameters C-reactive protein (CRP), leucocyte count (LC) (or: white blood cell count), and erythrocyte sedimentation rate (ESR).
2. The study must evaluate late fracture-related infection (or a synonym), defined as onset later than six weeks after surgical intervention.
3. A valid reference test must be used in the study defined as intraoperative cultures or clinical follow-up of at least five months.
4. The study must provide a clear analysis of the investigated serum inflammatory parameters in order to construct contingency tables of relevant results.
5. The study must be conducted on humans.
Exclusion criteria
1. Articles that investigate forms of non-traumatic osteomyelitis, such as acute osteomyelitis and osteomyelitis due to prosthetic infections, diabetic feet, and haematogenous infections.
2. Articles that included fewer than five participants.
3. Articles not written in the English, Dutch, or German language.
4. Poster/conference papers.

patients due to a systemic inflammatory response, postoperative or post-trauma tissue damage or other, non-surgical infections during the postoperative period.[21-24] It is this clinical variation, together with limited evidence in the literature, that makes the exact role of serum inflammatory markers, as part of the diagnostic algorithm for FRI, unclear.

The aim of this study was to assess the diagnostic value of CRP, LC, and ESR in late fracture-related infection.

Materials and Methods

Search strategy. On 26 March 2018, a computer-aided systematic literature search was performed in the PubMed, EMBASE, and Cochrane libraries. Articles in the English, Dutch, and German language were included. No time limitation was applied. Search terms were defined by the authors and reviewed by a professional information retrieval specialist. The search strings are available in Supplementary Table i. Articles were first screened on title and abstract. Two reviewers (JK and PB) scored all articles independently. A third reviewer (GG) was consulted in the event of uncertainty to assess whether the articles met the inclusion criteria. Subsequently, the full-text of the included articles was reviewed by all three reviewers. In addition, cross-reference checking of included articles and of relevant review articles was performed.

Study selection. This review focuses on the diagnostic accuracy of the most commonly utilized serum inflammatory markers for detecting late FRI, namely CRP, LC, and ESR, individually or combined. Therefore, information on other diagnostic inflammatory markers was disregarded. Articles solely reporting on early FRI (onset less than six weeks after the operation)[10] were excluded as: 1) early FRI usually poses a less complex diagnostic dilemma; and 2) it was felt by the authors that early and late infections are different entities and should be analyzed separately to prevent confounding bias. Patients with or without fracture fixation in situ were eligible for inclusion. Articles solely reporting on other types of bone or non-trauma related infections such as PJI, diabetic feet, spondylodiscitis, and haematogenous osteomyelitis were excluded. Furthermore, articles without a definitive reference test, defined as intraoperative cultures or clinical follow-up of at least five months, for confirmation of the infection, were excluded. Papers reporting on the results of a heterogeneous patient population were included, as long as separate analyses for FRI were provided. This accommodation is specifically stated in the results section if applicable. No concessions were made for non-trauma-related articles. The inclusion and exclusion criteria are presented in Table I.

Data collection and extraction. From all included articles, the following data were extracted: 1) author; 2) year of publication; 3) study type and population; 4) number of patients included; 5) results of index test; 6) results of reference test; 7) diagnostic accuracy (any measures) of the serum inflammatory markers for late FRI. Data were extracted by two reviewers independently (JK and PB). All authors were contacted when raw data were not reported in the articles.

Methodological quality assessment. Assessment of risk of bias and applicability of the study design of the included articles was performed using the QUADAS-2 tool (Quality Assessment of Diagnostic Accuracy Articles, version 2). The QUADAS-2 tool consists of four domains: patient selection, index test, reference standard, and flow and timing.[25] The methodological quality of the articles was assessed by two reviewers independently (JK and PB). A third reviewer (GG) confirmed the outcomes of the QUADAS-2 tool for the included articles. Since one selected study[26] was (co-)authored by the same authors as the current review, its methodological quality was assessed by an independent author (WJM). Authors were contacted when information regarding the quality of the study was not provided in the articles.

Statistical analysis. To assess the diagnostic performance per study, first the sensitivity and specificity were calculated from the (reconstructed) 2×2 contingency tables from the included articles. These were graphically visualized in a forest plot, along with their 95% confidence interval (CI). The individual sensitivities and specificities in summary measurement were not directly pooled, because the included articles are likely to have used different (explicit or implicit) threshold values. Explicitly, researchers often use the threshold that is in use at their institution and these thresholds often differ between institutions.

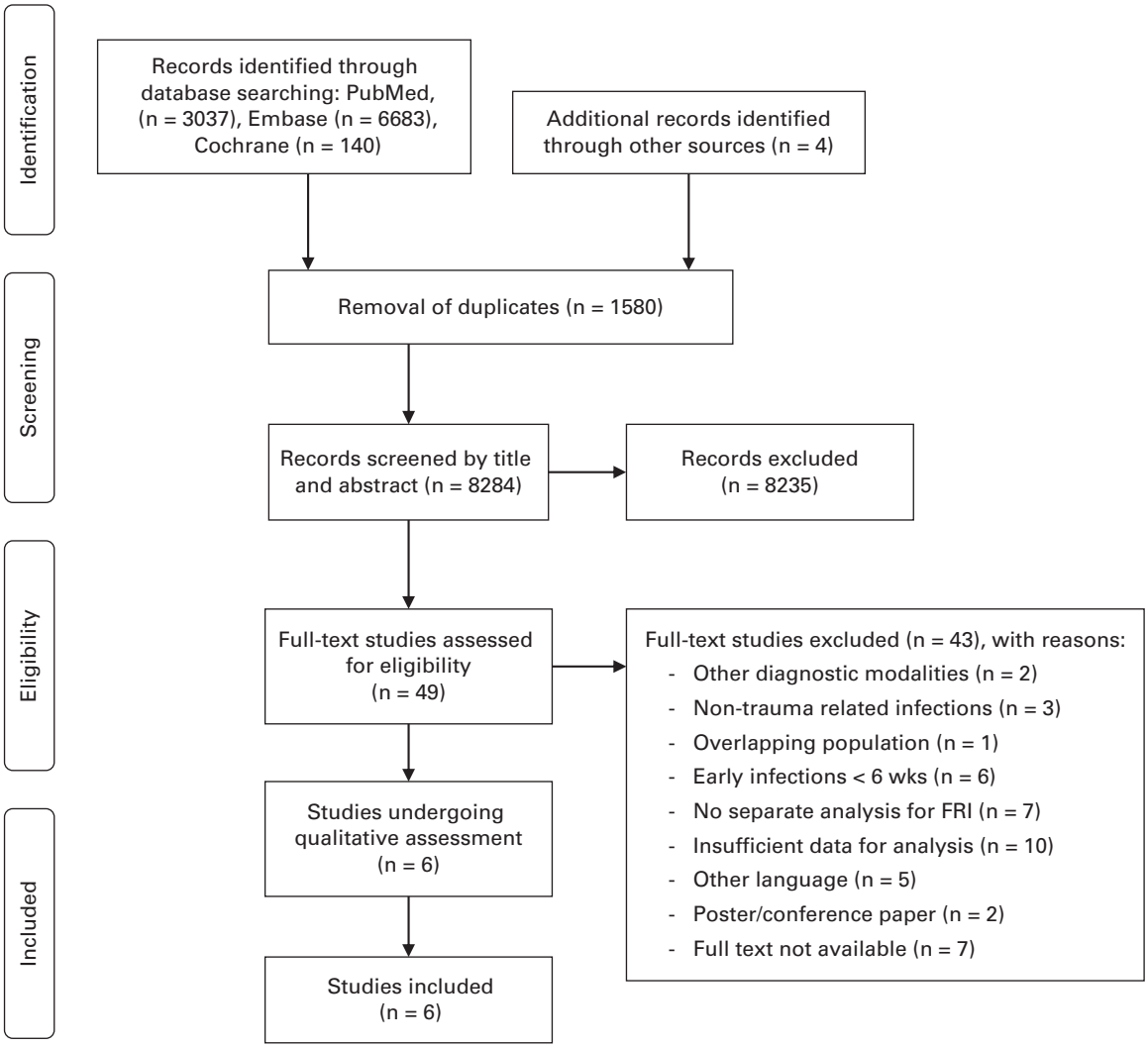

Fig. 1

Flowchart for Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). FRI, fracture-related infection.

Implicitly, there could be variations in the thresholds (even if they are explicitly the same) due to differences in observers, laboratory protocols, or equipment. These threshold values are a problem in obtaining pooled estimates of sensitivity and specificity as the natural trade-off between sensitivity and specificity means that a lower used threshold for an inflammatory marker leads to a higher sensitivity but lower specificity for FRI, and vice versa.[27]

The reported pairs of sensitivity and specificity were graphically visualized. These plots were used to assess heterogeneity in discriminative performances between the articles. If the amount of clinical and statistical heterogeneity was considered acceptable, a summary measurement and expected Receiver Operating Characteristic (ROC) curve of the sensitivities and specificities was obtained. This was done while accounting for the (explicitly and implicitly) different thresholds, using a bivariate mixed effects model.[27,28] This model first jointly incorporates both the degree of inter- and intra-study variation in sensitivity and specificity to calculate the corresponding confidence intervals per study. Second, these parameters were combined to obtain the summary ROC curve as a measure of the average discriminative performance. Summary ROC plots were obtained for both the separate and the combined inflammatory markers.

All analyses were performed using R software for statistical computing version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria) with the additional package 'mada'[29] and 'forestplot'.[30] This systematic review was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement[31] and its 'Explanation and Elaboration'.[32]

Results

Included articles. The search flow diagram is displayed in Figure 1. A total of 9860 articles met the search criteria. Additional data were provided by three authors.[33-35] Ultimately, six articles remained for qualitative assessment.[26,33-37] No articles were excluded after qualitative assessment, and all six articles

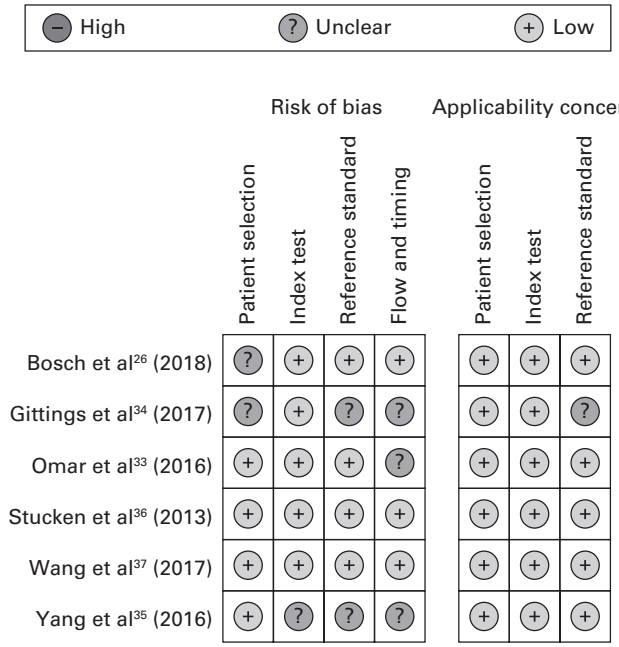

Fig. 2

Quality Assessment of Diagnostic Accuracy Articles (QUADAS)-2 assessment for risk of bias and applicability.

Table II. Characteristics and results of included articles

Author (year)	Study type and population	Sample size, n	FRI, n	Reference test	Markers	Thresholds	Sensitivity, %	Specificity, %
Bosch et al[26] (2018)	Retrospective cohort. Nuclear medical imaging for suspected FRI.	168	61	Intraoperative cultures with at least two sites revealing the same pathogen, presence of sinus tract, or intraoperative purulence, or > 6 mths follow-up.	CRP LC ESR	5 mg/l 10 × 10^9 cells/l 11 mm/h (male) 24 mm/h (female)	*83.1* *38.6* *45.0*	*34.3* *73.5* *76.1*
Gittings et al[34] (2017)	Retrospective cohort. Conversion to total hip arthroplasty after initial internal fixation.	33	6	Intraoperative cultures or pre-operative diagnosis using MSIS criteria for PJI.	CRP ESR	7 mg/l 30 mm/h	*100.0* *100.0*	*81.0* *85.0*
Omar et al[33] (2016)	Prospective cohort. Revision surgery after initial internal fixation.	62	51	Intraoperative cultures with at least two sites revealing the same pathogen, presence of sinus tract, or intraoperative purulence.	CRP LC	5 mg/l 10.2 × 10^9 cells/l	*78.4* *72.6*	*72.7* *81.8*
Stucken et al[36] (2013)	Prospective cohort. Un-united fractures.	93	30	Positive intraoperative cultures or gross infection at time of surgery or in the immediate post-operative period.	CRP LC ESR	10 mg/l 10 × 10^9 cells/l 30 mm/h	N/E N/E N/E	N/E N/E N/E
Wang et al[37] (2017)	Retrospective cohort. Un-united fractures.	42	35	Intraoperative cultures with at least two sites revealing the same pathogen.	CRP LC ESR	8 mg/l 10 × 10^9 cells/l 20 mm/h	*60.0* *22.9* *37.1*	*85.7* *85.7* *71.4*
Yang et al[35] (2016)	Retrospective cohort. Un-united fractures.	184	96	Intraoperative cultures, presence of a sinus tract, or purulence.	CRP LC ESR	8 mg/l 9.15 × 10^9 cells/l 15 mm/h (male) 20 mm/h (female)	*68.8* *40.9* *74.2*	*81.8* *79.4* *59.0*

FRI, fracture-related infection; CRP, C-reactive protein; LC, leucocyte count; ESR, erythrocyte sedimentation rate; MSIS, Musculoskeletal Infection Society; PJI, prosthetic joint infection; N/E, not estimable

were included in this systematic review,[26,33-37] drawing on information on 582 patients. All included articles covered late FRI.

Study quality. The results of the risk of bias and applicability assessment are presented in Figure 2. Concerns were mainly raised in regard to index- and reference test, and study flow and timing.

Study characteristics. The characteristics of the included studies are presented in Table II. Four articles focused on the value of combining markers.[26,34,36,37]

C-reactive protein. All six included articles reported on CRP in their analysis. Three had populations consisting of patients with ununited fractures,[35-37] two focused on patients undergoing

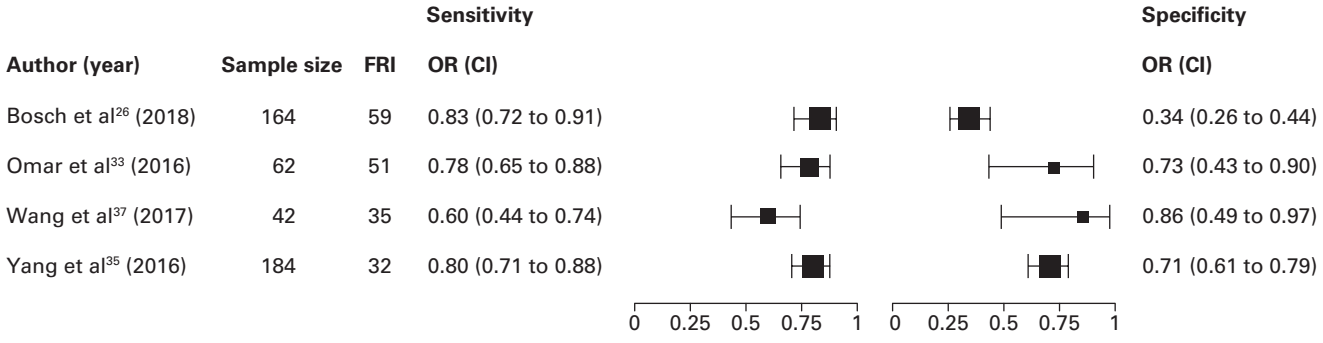

Fig. 3a

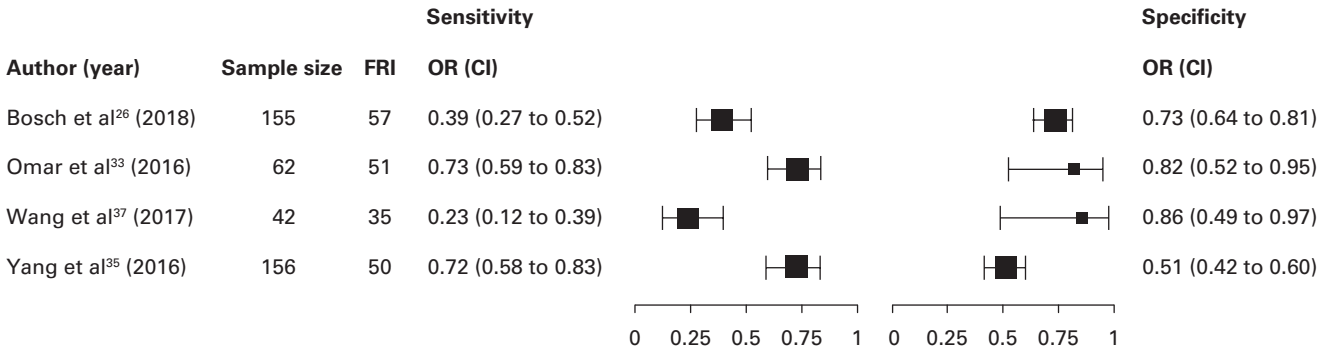

Fig. 3b

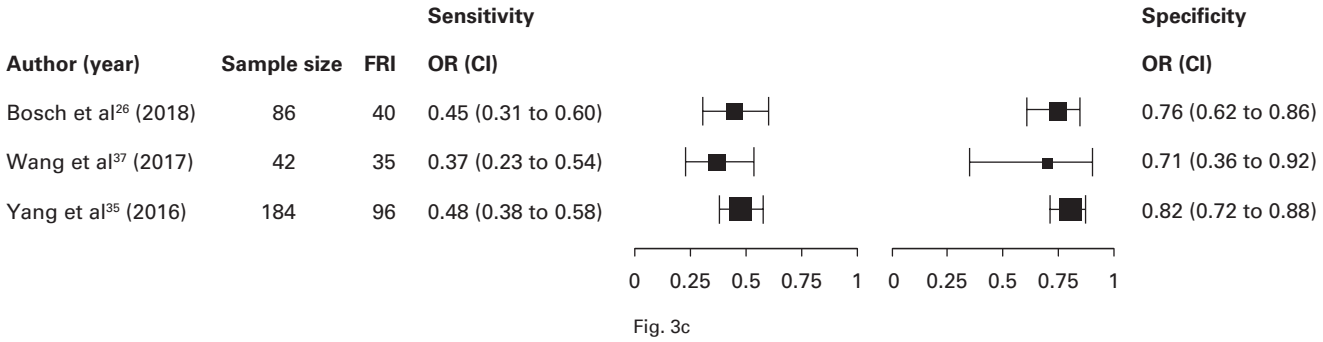

Fig. 3c

Forest plots sensitivity and specificity markers: a) C-reactive protein (CRP), b) leucocyte count (LC), and c) erythrocyte sedimentation rate (ESR). FRI, fracture-related infection; OR, odds ratio; CI, confidence interval.

revision surgery after initial internal fixation,[33,34] and one investigated patients undergoing nuclear medical imaging for suspected FRI.[26] The results can be found in Table II and Figure 3. Thresholds used to define elevation varied between 5.0 mg/l to10.0 mg/l, and all articles used intraoperative cultures as a reference test. Overall, the sensitivity for detecting FRI varied between 60.0% and 100.0%, and specificity varied between 34.3% and 85.7%.

Leucocyte count. Five articles included LC in their analysis.[26,33,35-37] Three focused on patients presenting with ununited fractures.[35-37] The other two investigated patients undergoing revision surgery after initial internal fixation[33] and patients who underwent nuclear imaging for suspected FRI.[26] Thresholds used were comparable, ranging from 9.15×10^9 cells/l to 10.2×10^9 cells/l, and all articles used intraoperative cultures as a reference test. Reported sensitivity varied between 22.9% and 72.6%, and specificity varied between 73.5% and 85.7%.

Erythrocyte sedimentation rate. Five articles reported on ESR in their analysis.[26,34-37] Three included ESR in their analysis on diagnosing infection in patients with ununited fractures,[35-37] one studied the value of ESR in diagnosing infection in patients undergoing nuclear imaging for suspected FRI,[26] and one focused on patients undergoing conversion to total hip arthroplasty after failed initial internal fixation.[34] Thresholds varied between 11.0 mm/h and 30.0 mm/h, with two articles using different threshold for men and women.[26,35] All articles used intraoperative cultures as a reference test.[36] Overall, the reported sensitivity varied between 37.1% and 100.0%, and specificity varied between 59.0% and 85.0%.

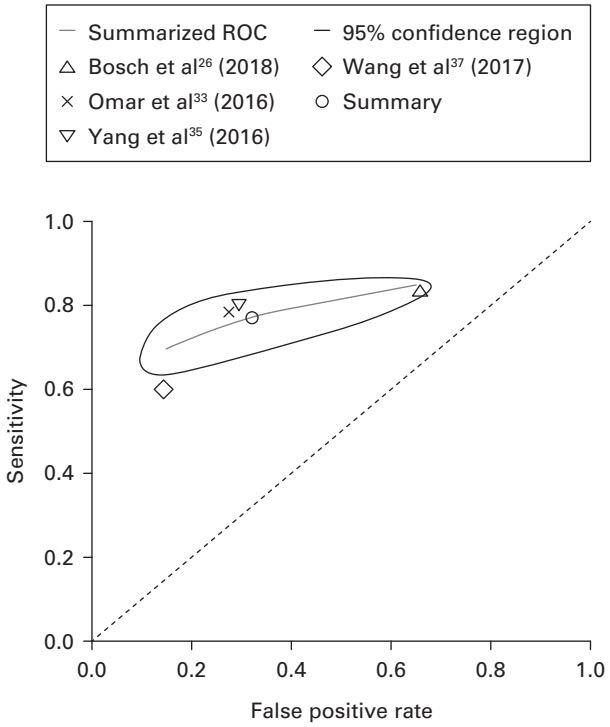

Fig. 4a

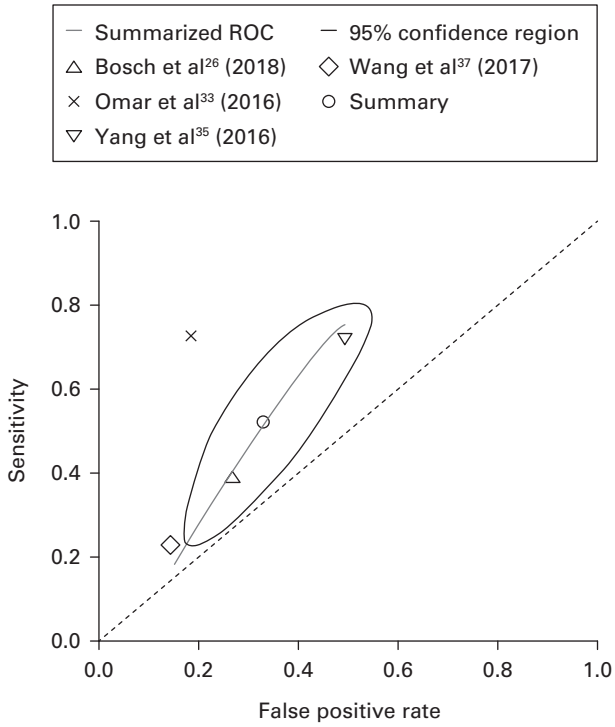

Fig. 4b

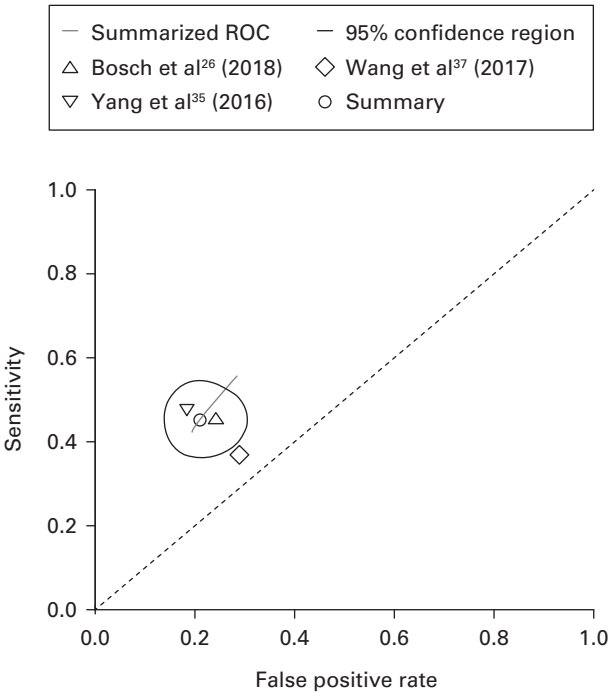

Fig. 4c

Summary receiver operating characteristic (ROC) curves individual markers: a) C-reactive protein (CRP), b) leucocyte count (LC), and c) erythrocyte sedimentation rate (ESR).

Combined scores. Four articles reported on the added value of combining markers.[26,34,36,38] Two reported on combining up to four markers without specifying which markers.[36,37] One study reported a predicted probability value of two and three combined positive tests.[36] They found a predicted probability of 56.0% when combining any two markers, and 100.0% when all three markers (CRP, LC, and ESR) are elevated. Another study also reported on combining CRP, LC, and

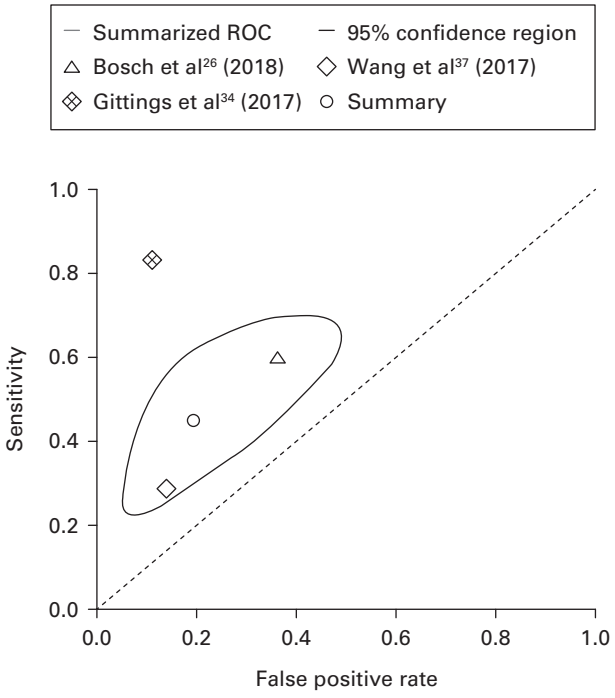

Fig. 5

Summary receiver operating characteristic (ROC) curve combined markers.

ESR.[37] With any two markers combined, a predicted probability of 90.9% was calculated. When all three markers were elevated, a combined predicted probability of 100.0% was found. One study reported on the combination of CRP and ESR with a 83.0% sensitivity and 88.0% specificity.[37] One study reported on CRP and LC finding a 60.0% sensitivity and 64.0% specificity.[26]

Meta-analysis. Articles were grouped per individual marker. Two-by-two contingency tables (true positive (TP), false negative (FN), false positive (FP), true negative (TN)) could be constructed from the pooled results of four articles for CRP (n = 452),[26,33,35,37] of four articles for LC (n = 415),[26,33,35,37] and of three articles for ESR (n = 312).[26,35,37] The sensitivities and specificities of the articles within the analysis of each serum marker showed acceptable comparability and could therefore be pooled. This resulted in a sensitivity and specificity of 77.0% (95% CI 66.5 to 85.0) and 67.9% (95% CI 38.7 to 87.6) for CRP, 51.7% (95% CI 27.2 to 75.5) and 67.1% (95% CI 19.3 to 50.2) for LC, and 45.1% (95% CI 37.8 to 52.6) and 79.3% (95% CI 71.7 to 85.2) for ESR (Fig. 4).

Due to heterogeneity, the articles reporting on combined markers could not be pooled (Fig. 5).

Discussion

This review presents the current evidence on the diagnostic value of the serum inflammatory markers CRP, LC, and ESR for late FRI. Meta-analysis of the pooled results showed limited diagnostic value of all three markers individually. Combined scores are shown to increase diagnostic performance, yet the accuracy remains insufficient in most articles.

Overall, the results of all markers vary greatly between the included articles. One of the difficulties that we encountered in this review was the fact that serum inflammatory markers were measured using different apparatus and methods. Also, the articles included in this review used several different thresholds when dichotomizing the serum inflammatory markers. The use of different thresholds complicates direct comparison of diagnostic performance between articles. Also, as these markers are measured on a continuous scale, dichotomization decreases their diagnostic potential. Therefore, articles on their diagnostic performance should analyze these markers continuously in order to assess their potential and, subsequently, determine ideal threshold values. The value at which a sensitivity of > 90% is reached should serve as the threshold in suspected late FRI.

FRI encompasses a broad spectrum of manifestations, which can vary greatly in severity, location, and duration. Study populations often consist of sub-groups of FRI, like infected nonunion, patients undergoing revision surgery, or certain types of medical imaging without specifying the pre-test probability. This results in heterogenic study populations being analyzed, further complicating comparison of diagnostic performance between articles.

All of the included articles used intraoperative cultures as a reference test. However, there were variations in the specific culture methods used. Differences were seen in the number of samples taken, ranging from three to five. Some articles consider FRI to be present when the culture result of a single sample was positive,[34,36] while others require the same pathogen to be present in at least two different samples.[26,33,37] Also, details on collecting and culturing protocols were not always provided. Until the FRI Consensus Definition there was no uniform definition for FRI.[13] Since then, agreement has been reached on a reference standard and protocols for collecting intraoperative cultures have been formed.[13,37]

Since serum inflammatory markers are used in clinical practice to rule out FRI, a high sensitivity is needed. A high specificity is needed in order to prevent unnecessary invasive surgery and anti-microbial therapy in patients with a false positive diagnosis. Only one study found a sensitivity > 90%. However, they included only six patients with FRI, increasing the risk of overfitting (the inclusion of too many variables in the statistical model compared with the number of included cases of FRI, the one-in-ten rule).[34] Specificity was generally low in all articles, increasing the risk of over-treatment when inflammatory markers are relied upon.

Although the results of this review show that dichotomized results of individual serum inflammatory markers have insufficient diagnostic performance, they may still be a suggestive sign of FRI. One way of increasing the diagnostic performance is by combining markers. This resembles clinical practice, where inflammatory markers are rarely interpreted on a standalone basis. Usually, multiple markers are interpreted in addition to clinical signs when estimating the likelihood of FRI. Only one study assessed the combination CRP, LC, ESR, and clinical parameters predictive of FRI, and reported a limited added value of these inflammatory markers.[26] The other articles reported increased diagnostic performance when combining

markers.[34,36,37] However, the diagnostic performance remains insufficient in most articles.

We recommend that international laboratory protocols for serum inflammatory markers become standardized in order to compare articles in a more reliable way and improve the diagnosis of late FRI in a clinical setting. Furthermore, uniform definitions and diagnostic criteria, as recently published in the FRI Consensus Definition,[13] should be implemented in both clinical practice and research.

This review has some limitations. Most articles on this topic suffer from small and heterogeneous patient populations, under reporting regarding laboratory techniques, different thresholds used and lack of a reference standard. Therefore, only six articles could be included. Furthermore, slight differences existed in the reference tests used by the included articles. Finally, it needs to be mentioned that a cut-off, time-based division between early and late infections remains arbitrary and therefore subject to on-going discussion.[13]

In conclusion, the serum inflammatory markers CRP, LC and ESR are insufficiently accurate to diagnose late FRI. These markers cannot confirm or rule out the presence of FRI, and should therefore be used as a suggestive sign in the diagnosis of late FRI.

Take home message

- The diagnostic accuracy of the serum inflammatory markers C-reactive protein, leucocyte count, and erythrocyte sedimentation rate is insufficient to diagnose or exclude late fracture-related infection. These markers should therefore be used only as a suggestive sign in the diagnostic work-up of suspected late fracture-related infection.

Supplementary material (available online)

Search strings for PubMed and Embase.

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Funding statement:
No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

J. van den Kieboom and P. Bosch are co-first authors.

This article was primary edited by G. Scott.