Original Article

Ascitic calprotectin and lactoferrin for detection of spontaneous bacterial peritonitis: a systematic review and meta-analysis

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Background: Spontaneous bacterial peritonitis (SBP) is a common bacterial infection in cirrhotic patients associated with a high mortality rate. Prompt diagnosis and early antibiotic administration are crucial in minimizing adverse outcomes. Although detection of ≥250 polymorphonuclear leukocytes (PMN) in ascitic fluid is the current gold standard to diagnose SBP, consideration for rapid detection with biomarkers is warranted.

Methods: A literature search for studies evaluating ascitic calprotectin and lactoferrin for detection of SBP was performed using PubMed, Embase, Scopus, Google Scholar, Cochrane library, and Clinical Trial Registries. Summary sensitivity, specificity, log diagnostic odds ratio (LDOR), and area under the summary receiver operating curve (AUC) were calculated.

Results: In total, 12 and 13 studies evaluated ascitic calprotectin and lactoferrin, respectively, for detection of SBP. Summary sensitivity, specificity, and LDOR for calprotectin were 0.942 (95% CI, 0.916, 0.967), 0.860 (95% CI, 0.799, 0.935), and 4.250 (95% CI, 3.504, 4.990), respectively. AUC for calprotectin was 0.91. Summary sensitivity, specificity, and LDOR for lactoferrin were 0.954 (95% CI, 0.930, 0.979), 0.890 (95% CI, 0.836, 0.945), and 4.630 (95% CI, 3.800, 5.452), respectively. AUC for lactoferrin was 0.958.

Conclusions: The overall performance of ascitic calprotectin and lactoferrin was substantial, potentially serving as a screening tool or an alternative to manual cell count. However, a variety of manufacturers, cut-off values, and significant heterogeneity between studies should be noted. Point-of-care testing for calprotectin and lactoferrin may resolve disadvantages associated with the current methods. Future studies on this topic are, therefore, needed.

Keywords: Lactoferrin; calprotectin; ascites; spontaneous bacterial peritonitis (SBP); cirrhosis

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Introduction

A diagnosis of spontaneous bacterial peritonitis (SBP) is essential for cirrhotic patients considering significant associated morbidity and mortality. SBP is the most common bacterial infection among cirrhotic patients accounting for approximately 10–30% of all bacterial infections in hospitalized cirrhotic patients (1). Most importantly, patients with SBP are at risk of acute kidney injury and acute on chronic liver failure, which significantly increases risk of mortality (2). With a rise in multi-drug resistant organisms, the management of SBP more heavily relies on the administration of appropriate empiric antibiotic therapies. Piano *et al*. investigated infections in patient with cirrhosis via an intercontinental study, noting that SBP was the most common bacterial infection, with 27% of cases, followed by urinary tract infections (22%) and pneumonia (19%). Additionally, there was a higher prevalence of SBP detected in American and European centers compared to Asian centers (3). The hospital mortality of SBP was previously estimated to be between 10–50% for first episodes, and 31–93% for subsequent episodes; with recent studies suggesting a one-month mortalities greater than 20%. Furthermore, third-generation cephalosporins are still effective for community-acquired SBP but were thought to be as low as 40% effective in nosocomial infections (4). A study by Kim *et al*. also demonstrated a 2.7-fold increase in mortality when a diagnosis is delayed (5). For these reasons, prompt diagnosis and early antibiotic treatment are crucial in successful treatment and minimizing these adverse outcomes.

Currently, the diagnosis of SBP is established when polymorphonuclear (PMN) counts are ≥250 cells/mm^3 in the ascitic fluid (1,2,6). The laboratory process is generally performed by manual cell count using an optical microscope. However, several steps during this process are subject to deficiency. Lysis of PMNs during transport can occur, leading to false-negative results. Additionally, the manual cell count is subject to human error, and laboratory processing time can take several hours to result (7). Although automated techniques have become increasingly popular over the manual cell count, the availability of automated cell count remains limited, especially in a rural area or small facilities (8). As a delay in diagnosing SBP significantly contributes to a worse prognosis, efficient alternative diagnostic methods are crucial.

In an effort to expedite the detection of SBP, biochemical markers of PMNs, such as ascitic calprotectin and lactoferrin, have been studied. Calprotectin is a calcium-binding antimicrobial protein found almost exclusively in neutrophil cytosol, whereas lactoferrin is a glycoprotein found in granules of PMNs (9-11). Studies have suggested the potential for a faster turnaround time and even bedside point of care testing when compared to the manual count; laboratory capacity and hours of operation, including overnight and on weekends, can affect detection and delay antibiotic administration. Though non-specific, biomarkers such as calprotectin act as surrogate markers for neutrophilic turnover in the presence of inflammation. Calprotectin and lactoferrin have been extensively studied in other inflammatory or infectious conditions such as inflammatory bowel disease and urinary tract infection. Similarly, both of these markers can be measured in the ascitic fluid by the enzyme-linked immunosorbent assay (ELISA) method. Notably, calprotectin and lactoferrin are extremely stable and not subject to error from cell lysis (12,13). Early studies have also demonstrated a linear relationship between the level of ascitic calprotectin and lactoferrin and ascitic neutrophil count (14,15). Therefore, detection of calprotectin and lactoferrin in an ascitic fluid may potentially serve as a diagnostic tool for SBP. However, the performance of calprotectin and lactoferrin appeared to vary due to differences in the study population and manufacturers. Hence, we conducted this meta-analysis to examine the performance of ascitic calprotectin and lactoferrin for detection of SBP by following the PRISMA and Cochrane guidelines. We present the following article in accordance with the PRISMA reporting checklist (available at https://tgh.amegroups.com/article/view/10.21037/tgh-20-323/rc).

Methods

This meta-analysis was performed in accordance to Cochrane's manual of diagnostic test accuracy as outlined by the preferred reporting items for systematic reviews and meta-analysis of diagnostic test accuracy (PRISMA-DTA) guidelines (16,17). A literature search of PubMed, Embase, Scopus, Google Scholar, Cochrane, ClinicalTrials.gov, and European Clinical Trial Registry was performed through March 2020 by a librarian (C.S.) specialized in a systemic review. Search terms included: (I) SBP; (II) calprotectin; and (III) lactoferrin. The detail regarding search terms is shown in the supplementary document. SBP was defined by a PMN ≥250* cells/mm^3 regardless of ascitic fluid culture. Calprotectin and lactoferrin were measured on ascitic fluid. The titles and abstracts obtained through the searching and screening process were reviewed by two independent

authors (P.M.K. and J.P.G.). Discrepancies were carefully resolved amongst the two independent authors and a senior author (W.M.). The independent authors extracted and compiled data from each study, which consisted of study characteristics and results such as author, year of publication, start and end dates for data collection, country, and type of study design. Study population characteristics include the number of patients, number of paracenteses performed, mean age, number of inpatients, number of outpatients, Child-Pugh score, and criteria for the diagnosis of SBP. Exclusion criteria included secondary causes of other causes of neutrocytic ascites, such as malignancy, other intra-abdominal infection(s), recent abdominal surgeries, or recent exposure to antibiotics. Abstracted data include the prevalence of SBP, method of detection, the cut-off level used, sensitivity, specificity, true positive, false positive, false negative, and true negative. This information was extracted from the study itself or calculated utilizing other information. The primary outcome of the study was the overall performance of ascitic calprotectin and lactoferrin in the detection of SBP as determined by summary sensitivity, specificity, log diagnostic odds ratio (LDOR), and the area under summary receiver operating characteristic (SROC) curves (AUC). The secondary outcomes are summary statistics from the subgroup analyses performed. Quality assessment for each individual study for use in this meta-analysis was performed using QUADAS-2 by the same two independent authors (P.M.K. and J.P.G.). Any discrepancies during the process were again resolved following discussion with the senior author (W.M.).

Statistical analysis

R version 3.2.4 (R Core team 2013) with Metafor and Mada packages was used for the statistical analysis in this study (18,19). By using Cohen's Kappa coefficient, an inter-observer agreement was evaluated. Summary sensitivity, specificity, and LDOR were calculated by bivariate meta-analysis as described by Reitsma (20). The hierarchical summary receiver operating characteristic model was utilized to calculate the summary receiver operating characteristic (SROC) as described by Rutter and Gatsonis (21). AUC was then calculated. Sensitivity analysis was performed by conducting subgroup analyses based on the method of detection, the setting of paracenteses (inpatient), and manufacturers. A P value <0.05 was considered statistically significant. Study heterogeneity was evaluated by the I^2 statistic. I^2 of 0–40%, 50–90%, 30–60%, and 75–100% were considered low, moderate, substantial, and considerable (22). Publication biases were assessed by Deeks' funnel plot where a P value <0.1 suggests evidence of a publication bias (23).

Results

Figure 1 highlights a flow diagram of the screening and study selection process performed for this analysis. Following the removal of duplicate studies, a total of 247 articles were found using the systematic search criteria. Of these, 32 articles were noted to be relevant. Ultimately, 23 studies were included in this meta-analysis, including one abstract and 22 full articles. Specifically, 12 of the 23 studies investigated the performance of calprotectin, and 13 of the 23 studies investigated the performance of lactoferrin. Characteristics of calprotectin and lactoferrin ELISA kit manufacturers used in each study are shown in Table S1.

Study characteristics

Table 1 demonstrates the characteristics of each study evaluating calprotectin for the detection of SBP, whereas Table S2 demonstrates abstracted data. Among studies evaluating calprotectin, there were 1,046 patients with a total of 1,191 paracenteses performed. The prevalence of SBP was 51.22% ranging from 15.25% to 71.43%. All studies utilized ELISA-based techniques, whereas one study utilized point-of-care testing. Five studies included only inpatient data, whereas only one study included outpatient data exclusively. Six studies in total did not specify the setting in which samples were collected. The cut-off values for ascitic calprotectin range from 0.002 μg/mL to 2.89 ng/mL.

Table 1 also demonstrates the characteristics of each study evaluating lactoferrin for the detection of SBP, whereas Table S3 demonstrates abstracted data. Among studies evaluating lactoferrin, there were 1,291 patients with a total of 1,457 paracenteses performed. The prevalence of SBP was 42.03% ranging from 10.09% to 71.43%. Three studies did not report laboratory techniques for the detection of lactoferrin, whereas the remainder used ELISA-based techniques. A total of eight studies included only inpatient data, whereas five studies did not specify the setting in which samples were collected. The cut-off values for ascitic lactoferrin range from 46.1 to 300 ng/mL.

Performance of ascitic calprotectin for detection of SBP

For ascitic calprotectin, summary sensitivity, specificity,

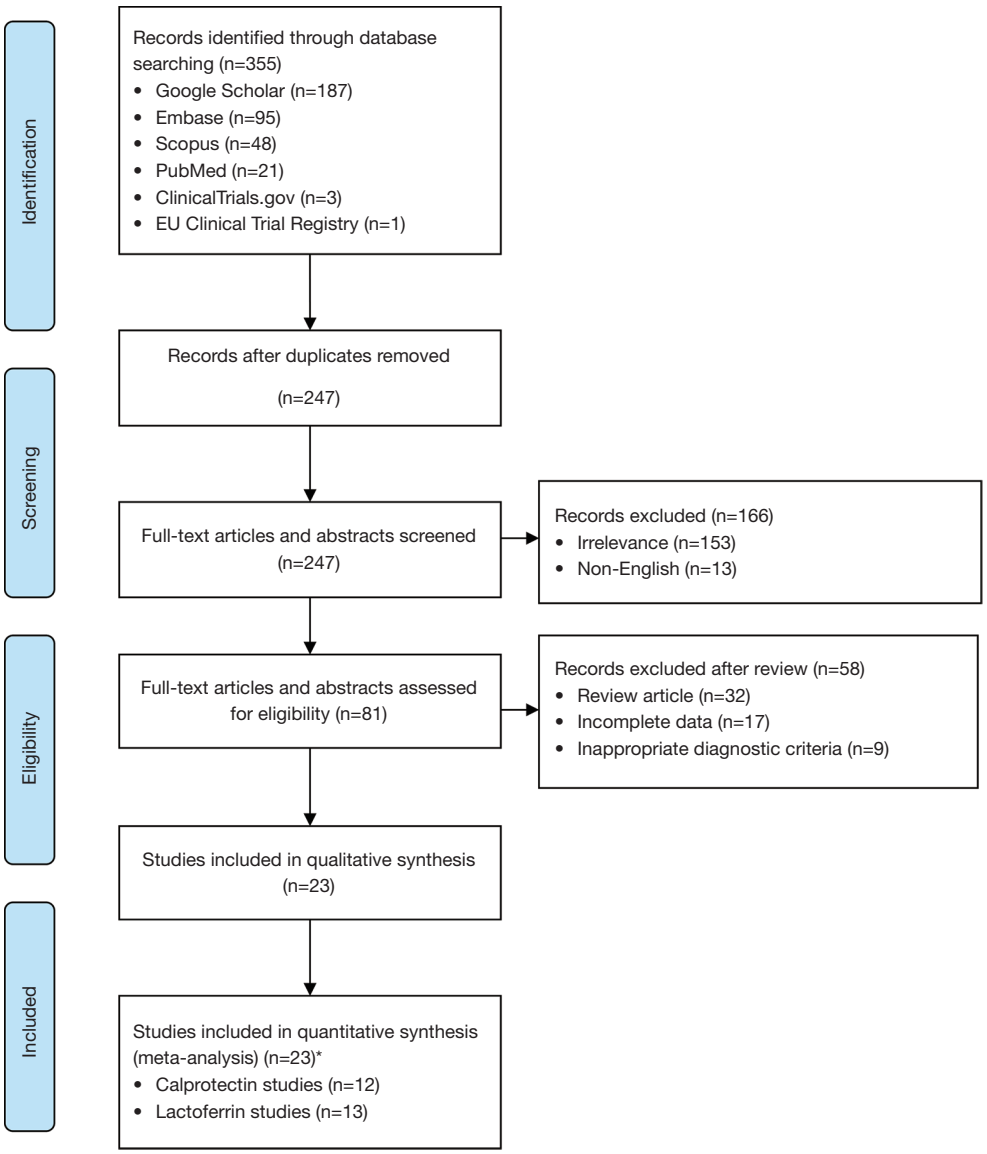

Figure 1 A flowchart demonstrating the study search and selection process for this meta-analysis according to the PRISMA statement. (* two studies evaluated both ascites calprotectin and lactoferrin for the detection of SBP). SBP, spontaneous bacterial peritonitis.

LDOR were 0.942 (95% CI, 0.916, 0.967), 0.867 (95% CI, 0.799, 0.935), and 4.250 (95% CI, 3.504, 4.990), respectively (see *Table 2*). The level of heterogeneity for summary sensitivity, specificity, and LDOR was moderate (43.04%), considerable (89.70%), and low (12.46%), respectively. *Figure 2A,2B* demonstrated a graphical representation of the summary sensitivity and specificity of calprotectin. SROC is shown in Figure S1A (AUC =0.91). Subgroup analyses, according to the manufacturers and method of calprotectin detection, were not possible due to an inadequate amount of data. Of the five studies evaluating inpatient solely, the summary sensitivity, specificity, LDOR were 0.957 (95% CI, 0.922, 0.993), 0.830 (95% CI, 0.676, 0.984), and 4.360 (95% CI, 2.774, 5.950) with similar levels of heterogeneity as the overall performance.

Performance of ascitic lactoferrin for detection of SBP

For ascitic lactoferrin, summary sensitivity, specificity, and LDOR were 0.954 (95% CI, 0.930, 0.979), 0.890 (95% CI,

Table 1 Characteristics of studies evaluating ascitic calprotectin and lactoferrin for detection of SBP

Study	Type	Country/ Region	Study type	Method	Start date	End date	Mean age (years)	Sample size (n)	Outpatient *vs*. inpatient	Child-Pugh score		
										A (n)	B (n)	C (n)
Calprotectin												
Abdel Rahman *et al*. (24)	Full paper	Egypt	NR	ELISA	NR	NR	55±8	80	Outpatient	0	16	64
Abdel-Razik *et al*. (25)	Full paper	Egypt	Prospective	ELISA	Apr 2013	May 2014	58	79	NR	0	20	59
Ali *et al*. (26)	Full paper	Egypt	NR	ELISA	May 2017	Apr 2018	52±5	72	Inpatient	0	18	54
El-Baz *et al*. (27)	Full paper	Egypt	Prospective	ELISA	Aug 2016	Dec 2017	53±8	88	Inpatient	0	33	54
Fernades *et al*. (9)	Full paper	Portugal	Prospective	POC	NR	NR	62±12	88	NR	3	46	39
Gad *et al*. (28)	Full paper	Egypt	Prospective	ELISA	Apr 2014	Oct 2014	57±8	80	Inpatient	NR	NR	NR
Heikl *et al*. (29)	Full paper	Egypt	Cross-sectional	ELISA	NR	NR	52±5	70	NR	NR	NR	NR
Kassem *et al*. (30)	Full paper	Egypt	Prospective	ELISA	Aug 2016	Dec 2017	53±6	90	Inpatient	20	35	35
Makhlouf *et al*. (31)	Full paper	Egypt	Cross-sectional	ELISA	Apr 2015	Sep 2015	52	87	Inpatient	0	10	77
Mohammed *et al*. (32)	Full paper	Egypt	Cross-sectional	ELISA	NR	NR	56±8	60	NR	0	33	27
Rizk *et al*. (14)	Full paper	Egypt	Prospective	ELISA	Oct 2012	Mar 2013	NR	124	NR	0	88	36
Weil *et al*. (33)	Full paper	France	Prospective	ELISA	May 2016	May 2017	62±11	128	NR	2	42	75
Lactoferrin												
Abuelfadi *et al*. (34)	Full paper	Egypt	Cross-sectional	ELISA	July 2016	Feb 2017	64±8	150	NR	NR	NR	NR
Al Sawaf *et al*. (35)	Full paper	Egypt	Prospective	ELISA	Jan 2010	Dec 2012	51±11	168	NR	0	16	152
Ali *et al*. (36)	Full paper	Egypt	NR	ELISA	Mar 2009	Sep 2009	53±9	96	Inpatient	NR	NR	NR
Chen *et al*. (37)	Full paper	Taiwan	Prospective	ELISA	Jan 2010	Dec 2010	60	66	Inpatient	1	43	67
El-Baz *et al*. (27)	Full paper	Egypt	Prospective	ELISA	Aug 2016	Dec 2017	53±8	88	Inpatient	0	33	54
Khalifa *et al*. (15)	Full paper	Egypt	Prospective	ELISA	NR	NR	53.5	70	Inpatient	NR	NR	NR
Kumar *et al*. (38)	Abstract	NR	Prospective	NR	NR	NR	NR	115	NR	0	94	21
Lee *et al*. (39)	Full paper	South Korea	Prospective	ELISA	Dec 2008	Dec 2011	54.5	102	NR	NR	NR	NR
Liang *et al*. (40)	Full paper	China	NR	NR	May 2011	Dec 2011	NR	66	Inpatient	NR	NR	NR
Makhlouf *et al*. (31)	Full paper	Egypt	Cross-sectional	ELISA	Apr 2015	Sep 2015	52	87	Inpatient	0	10	77
Mohammad *et al*. (41)	Full paper	Egypt	NR	ELISA	Dec 2013	Feb 2014	NR	84	Inpatient	NR	NR	NR
Parsi *et al*. (7)	Full paper	USA	Prospective	ELISA	NR	NR	NR	148	NR	NR	NR	NR
Salman *et al*. (42)	Full paper	Egypt	NR	NR	Mar 2010	Mar 2010	NR	51	Inpatient	NR	NR	NR

ELISA, enzyme-linked immunosorbent assay; NR, not reported; PMN, polymorphonuclear leukocytes; SBP, spontaneous bacterial peritonitis.

Table 2 The results of the meta-analysis of studies evaluating ascitic calprotectin and lactoferrin for the detection of SBP

	Number of studies (n)	Sensitivity (95% CI)	I^2 (%)	Specificity (95% CI)	I^2 (%)	LDOR (95% CI)	I^2 (%)	AUC
Calprotectin								
Overall	12	0.942 (0.916, 0.967)	43.04	0.860 (0.799, 0.935)	89.70	4.250 (3.504, 4.990)	12.56	0.91
Study characteristics: inpatient	5	0.957 (0.922, 0.993)	40.52	0.830 (0.676, 0.984)	94.38	4.360 (2.774, 5.950)	28.77	0.949
Lactoferrin								
Overall	13	0.954 (0.930, 0.979)	65.51	0.890 (0.836, 0.945)	91.04	4.630 (3.800, 5.452)	15.24	0.958
Study characteristics: inpatient	8	0.952 (0.920, 0.983)	54.59	0.899 (0.830, 0.968)	85.52	4.623 (3.579, 5.668)	2.18	0.957

I^2, study heterogeneity; AUC, area under the summary receiver operating curve; CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; LDOR, log diagnostic odds ratio; SBP, spontaneous bacterial peritonitis.

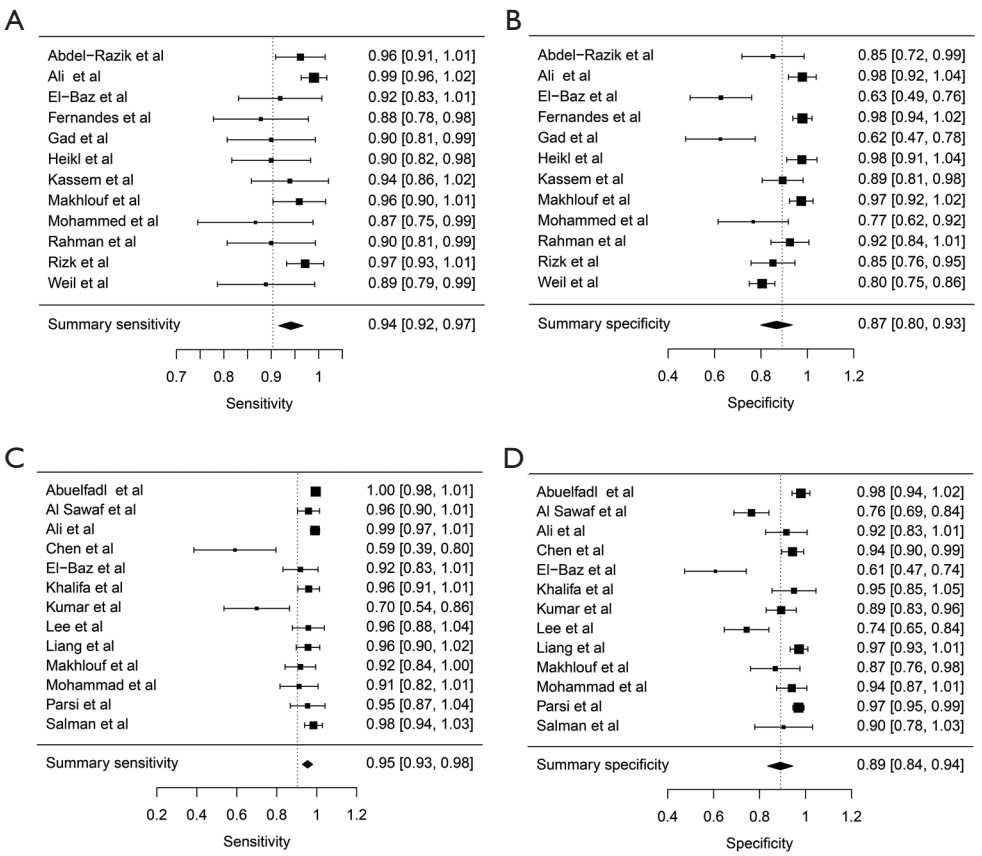

Figure 2 Forest plots demonstrating individual and summary sensitivity and specificity of each study evaluating ascitic calprotectin and lactoferrin for the detection of SBP: sensitivity of calprotectin (A), specificity of calprotectin (B), sensitivity of lactoferrin (C), and specificity of lactoferrin (D). SBP, spontaneous bacterial peritonitis.

0.836, 0.945), and 4.630 (95% CI, 3.800, 5.452), respectively (see *Table 2*). The level of heterogeneity for summary sensitivity, specificity, and LDOR were substantial (65.51%), considerable (91.04%), and low (15.24%), respectively.

Figure 2C,2D demonstrated a graphical representation of the summary sensitivity and specificity of lactoferrin. SROC is shown in Figure S1B (AUC =0.958). Subgroup analysis, according to manufacturers and method of lactoferrin

detection, was not possible due to an inadequate amount of information. Of the eight studies evaluating inpatient solely, the summary sensitivity, specificity, LDOR were 0.952 (95% CI, 0.920, 0.983), 0.899 (95% CI, 0.830, 0.968), and 4.623 (95% CI, 3.579, 5.668) with similar levels of heterogeneity as the overall performance.

Quality assessment and publication bias

During the screening process performed, our independent authors demonstrated a high degree of agreement, as supported by Cohen's kappa coefficient of 0.95. Simplified QUADAS-2 for studies investigating ascitic fluid calprotectin and lactoferrin are shown in *Table 3*, whereas an in-depth QUADAS-2 is shown as Table S4. In general, the overall concern for a patient selection bias, applicability of findings, conduct, or interpretation of the index test was found to be low. Utilizing Deeks' funnel plot, no publication bias was found among studies evaluating calprotectin and lactoferrin for the detection of SBP (P=0.325 and 0.956, respectively) (*Figures 3*,*4*).

Discussion

Our meta-analysis demonstrated a considerable sensitivity and good specificity for both ascitic calprotectin and lactoferrin for the detection of SBP. Although the performance of ascitic lactoferrin appeared to be slightly better than calprotectin, this was not statistically significant. SBP was previously diagnosed by the presence of ≥250 PMNs in an ascitic fluid along with positive ascitic fluid culture; however, patients with culture-negative neutrocytic ascites carried similar morbidity and mortality, and, therefore, PMNs count became the standard for diagnosis of SBP regardless of the culture (43). Currently, the manual cell count remains the gold standard for obtaining a PMN count; however, this generally takes several hours to result. Additionally, the manual cell count cannot be performed in various settings, such as rural sites, small medical facilities, and developing countries.

In the past decade, several inflammatory markers have been shown to be associated with SBP, including tumor necrosis factor-α, interleukin-6, C-reactive protein, procalcitonin, leukocyte esterase, calprotectin, and lactoferrin (7,9,10,44,45). The stability of biochemical markers is thought to exceed that of PMNs; for example, lactoferrin was noted to be more resistant and stable when left at room temperature for several hours (7). Leukocyte esterase testing, in the form of reagent test strips, has also drawn interest as the results could be interpreted at the bedside and potentially allow for more rapid detection of SBP without the need for laboratory testing. Calprotectin and lactoferrin should be used with caution in patients with secondary causes of peritonitis, such as inflammation secondary to malignancy, other infections, which may result in false positives. Likewise, an impaired immune response or conditions such as granulocytopenia may potentially result in false negative results.

In the previous studies, the performance of ascitic calprotectin and lactoferrin in the detection of SBP appeared promising but has often varied, which may be in part due to the variable cut-off values or prevalence of SBP noted in each study. For example, studies by Ali *et al*. and Heikl *et al*. suggested that the prevalence of SBP in their findings were 69.44% and 71.43%, respectively, but both demonstrated the specificity of 100% despite varying cut-off values (0.372 versus 0.783 μg/mL). In addition, Abdel-Razik *et al*. had a comparable prevalence and cut-off value to Ali *et al*. (65.82% and cut-off 0.445 ug/mL versus 69.44% and cut-off 0.372 μg/mL); however, their specificities were inconsistent (85.2% versus 100%).

In this meta-analysis, both ascitic calprotectin and lactoferrin had an excellent overall performance as reflected by AUC of 0.91 and 0.958, respectively. Our data suggested that both ascitic calprotectin and lactoferrin could potentially be utilized as a screening to SBP given a notable sensitivity (0.942 and 0.954, respectively). The advantages of calprotectin and lactoferrin include a more rapid turnaround time and less human error as compared with manual cell count. In theory, these methods can minimize delays in the detection of SBP and decrease utilization of unnecessary empirical antibiotics, ultimately decreasing patients' risk for Clostridium Difficile infection, multi-drug resistance bacteria, and various other side effects of antibiotic use.

Despite several advantages and potential clinical use of calprotectin and lactoferrin, these markers also are subject to disadvantages. The main disadvantage is the lack of standardization in regard to cut-off values, processing techniques, and ELISA kit manufacturers. For example, the cut-off values in studies utilizing ELISA kit for Immunodiagnostik were 0.270, 0.372, and 0.445 ug/mL, whereas cut-off values for Sunred-bio kits were 2.89 ng/mL, 0.950 μg/mL, and 0.620 μg/mL. We hypothesized that these could be the explanation to a higher level of heterogeneity of specificity for both ascitic calprotectin and lactoferrin;

Table 3 Simplified QUADAS form of studies evaluating ascitic calprotectin and lactoferrin for the detection of SBP

Study	Patient selection		Index test		Reference standard		Flow and timing
	Could the selection of patients have introduced bias?	Is there concern the included patients do not match the review question?	Could the conduct or interpretation of the index test have introduced bias?	Is there concern that the index test, its conduct, or interpretation differ from the review question?	Could the reference standard, its conduct, or its, interpretation have introduced bias?	Is there concern the target condition as defined by the reference standard does not match the review question?	Could the patient flow have introduced bias?
Calprotectin							
Abdel Rahman *et al*. (24)	Low	Low	Low	Low	Low	Low	Low
Abdel-Razik *et al*. (25)	Low	Low	Low	Low	Low	Low	Low
Ali *et al*. (26)	Low	Low	Low	Low	Low	Low	Low
El-Baz *et al*. (27)	High	Low	Low	Low	Low	Low	Low
Fernades *et al*. (9)	Low	Low	Low	Low	Low	Low	Low
Gad *et al*. (28)	High	Low	Low	Low	Low	Low	Low
Heikl *et al*. (29)	High	Low	Low	Low	Low	Low	Low
Kassem *et al*. (30)	High	Low	Low	Low	Low	Low	Low
Makhlouf *et al*. (31)	Low	Low	Low	Low	Low	Low	Low
Mohammed *et al*. (32)	High	Low	Low	Low	Low	Low	Low
Rizk *et al*. (14)	Low	Low	Low	Low	Low	Low	Low
Weil *et al*. (33)	Low	Low	Low	Low	Low	Low	Low
Lactoferrin							
Abuelfadi *et al*. (34)	High	Low	Low	Low	Low	Low	Low
Al Sawaf *et al*. (35)	Low	Low	Low	Low	Low	Low	Low
Ali *et al*. (36)	Low	Low	Low	Low	Low	Low	Low
Chen *et al*. (37)	Low	Low	Low	Low	Low	Low	Low
El-Baz *et al*. (27)	High	Low	Low	Low	Low	Low	Low
Khalifa *et al*. (15)	High	Low	Low	Low	Low	Low	Low
Kumar *et al*. (38)	Low	Low	Low	Low	Low	Low	Low
Lee *et al*. (39)	Low	Low	Low	Low	Low	Low	Low
Liang *et al*. (40)	High	Low	Low	Low	Low	Low	Low
Makhlouf *et al*. (31)	Low	Low	Low	Low	Low	Low	Low
Mohammad *et al*. (41)	Low	Low	Low	Low	Low	Low	Low
Parsi *et al*. (7)	Low	Low	Low	Low	Low	Low	Low
Salman *et al*. (42)	Low	Low	Low	Low	Low	Low	Low

QUADAS, quality assessment of diagnostic accuracy studies; SBP, spontaneous bacterial peritonitis.

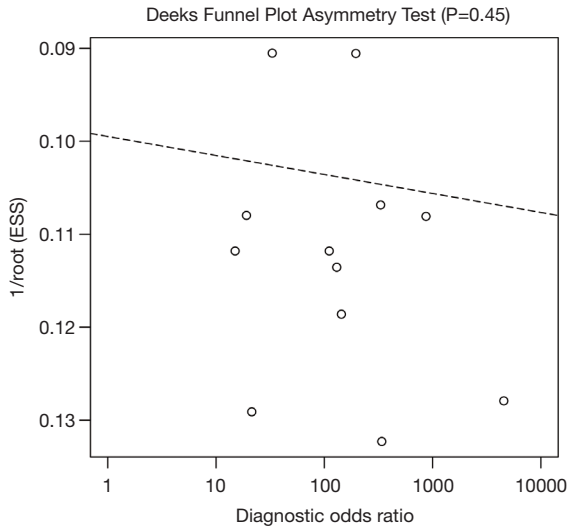

Figure 3 Deeks' funnel plot of studies evaluating ascitic calprotectin for the detection of SBP. ESS, effective sample size; SBP, spontaneous bacterial peritonitis.

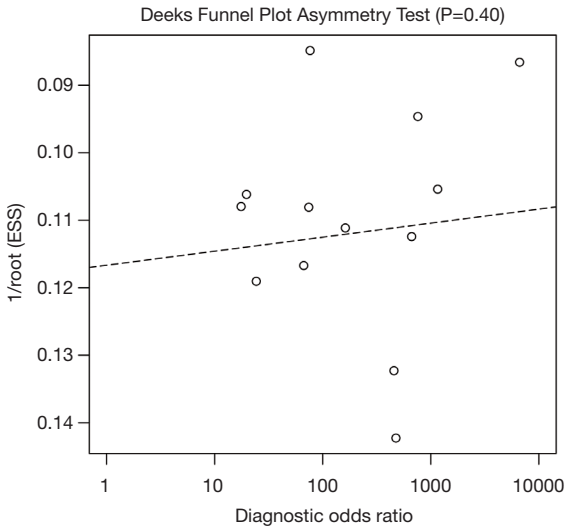

Figure 4 Deeks' funnel plot of studies evaluating ascitic lactoferrin for the detection of SBP. ESS, effective sample size; SBP, spontaneous bacterial peritonitis.

however, we were unable to confirm this due to inadequate studies for the subgroup analyses.

Recently, point-of-care-testing (POCT) for calprotectin and lactoferrin has been developed. These methods have a very rapid turnaround time, typically within an hour, and often have more consistent processing techniques due to dedicated analyzers. Therefore, POCT testing could potentially resolve all of the disadvantages present in the current ELISA methods, resulting in a standardized approach with consistent cut-off values. A few studies evaluating POCT detection of calprotectin and lactoferrin have recently been published, however, the number of studies were not adequate for inclusion in this meta-analysis. Nevertheless, these new methods remain expensive and are still under investigation. Our findings, therefore, emphasize the need for future studies to evaluate these POCT methods to diagnose SBP.

Despite a notable performance of calprotectin and lactoferrin, as seen in this study, several limitations were evident and should be considered. A major limitation includes the wide range of cut-off values used in each study; the cut-off values for both calprotectin and lactoferrin varied widely despite being further classified by subgroups. This is most likely attributable to differences in laboratory techniques and ELISA kit manufacturers. Though limited in this analysis, studies utilizing the same ELISA manufacturers supported the notion of varying cut-off values. Again, this emphasizes the need for standardization among ELISA-based methods for detection of calprotectin and lactoferrin. It is notable that a majority of the studies included in this meta-analysis performed paracenteses in the inpatient setting. Some studies also demonstrated a very high incidence of SBP. Lastly, the corresponding values/stages of heterogeneity for summary sensitivity and specificity of calprotectin studies were 43.04% (moderate), 89.70% (considerable) whereas the corresponding values/stages of heterogeneity for summary sensitivity and specificity of lactoferrin were 65.51% (substantial), 91.04% (considerable). Therefore, readers and clinicians alike, should take these factors into consideration during the interpretation of this data.

In summary, our data demonstrated notable overall performance of ascitic calprotectin and lactoferrin for the detection of SBP. Calprotectin and lactoferrin have the potential to become a rapid screening tool. The clinical significance of such methods lies in the fact that rapid and reliable diagnostic tests for SBP can serve to decrease time to diagnosis and initiation of antibiotic therapy. Standardization and agreement on cut-off values are necessary. Future studies evaluating POCT for ascitic calprotectin and lactoferrin are crucial and could be promising.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://tgh.amegroups.com/article/view/10.21037/tgh-20-323/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tgh.amegroups.com/article/view/10.21037/tgh-20-323/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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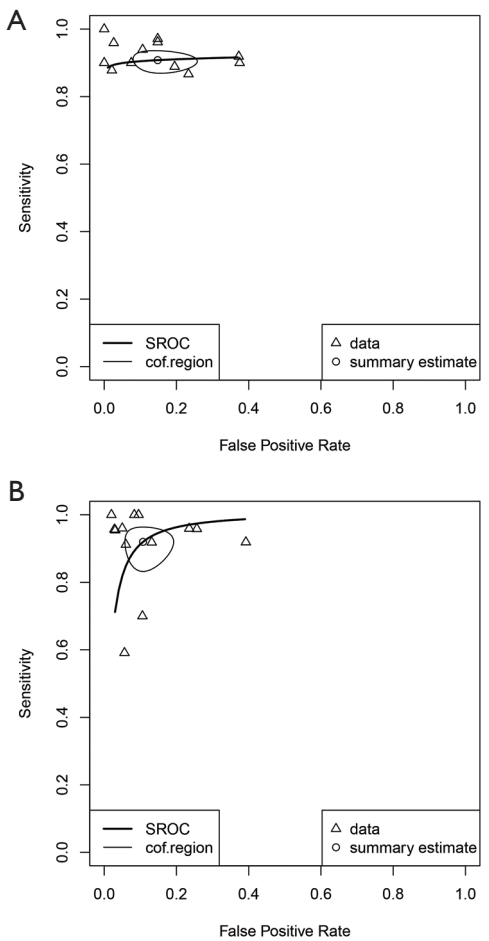

Figure S1 Summary receiver operating characteristic (SROC) curves of studies evaluating ascitic calprotectin (A) and lactoferrin (B) for the detection of SBP.

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Table S1 Characteristics calprotectin and lactoferrin ELISA kit manufacturers in each study

Author	Name of the tests	Company	City/state	Country
Calprotectin				
Abdel Rahman *et al*. (24)	NR	Assay Kit Co.	NR	USA
Abdel-Razik *et al*. (25)	NR	Immundiagnostik AG	Bensheim	Germany
Ali *et al*. (26)	NR	Immundiagnostik AG	Bensheim	Germany
El-Baz *et al*. (27)	DEH 325 Calprotectin human ELISA kit	Demeditech Diagnostics	Kiel	Germany
Fernades *et al*. (9)	point-of-care High-range-Quantum-Blue	Bühlmann Laboratories AG	Schönenbuch	Switzerland
Gad *et al*. (28)	Sunred Human ELISA kit	Sunred-bio	Shanghai	China
Heikl *et al*. (29)	NR	Epitope Diagnostics	California	USA
Kassem *et al*. (30)	Sunred Human ELISA kit	Sunred-bio	Shanghai	China
Makhlouf *et al*. (31)	RD 191217100R	BioVendor Laboratorni medicina	Brno	Czech Republic
Mohammed *et al*. (32)	NR	NR	NR	NR
Rizk *et al*. (14)	NR	Immundiagnostik AG	Bensheim	Germany
Weil *et al*. (33)	Quantum Blue Calprotectin Ascites	Bühlmann Laboratories AG	Schönenbuch	Switzerland
Lactoferrin				
Abuelfadi *et al*. (34)	Human Lactoferrin ELISA kit	Bethyl Laboratories Inc	Texas	USA
Al Sawaf *et al*. (35)	NR	NR	NR	NR
Ali *et al*. (36)	NR	Bioxytech	Paris	France
Chen *et al*. (37)	NR	NR	NR	NR
El-Baz *et al*. (27)	Assay Max Hu-man Lactoferrin ELISA Kit	AssayPro	Missouri	USA
Khalifa *et al*. (15)	Assay Max Human Lactoferrin ELISA Kit	Endomedix	New Jersey	USA
Kumar *et al*. (38)	NR	NR	NR	NR
Lee *et al*. (39)	Human lactoferrin ELISA kit	Bethyl Laboratories Inc	Tokyo	Japan
Liang *et al*. (40)	NR	NR	NR	NR
Makhlouf *et al*. (31)	Human lactoferrin ELISA kit	BioVendor Laboratoni Medicina	Brno	Czech Republic
Mohammad *et al*. (41)	NR	NR	NR	NR
Parsi *et al*. (7)	NR	NR	NR	NR
Salman *et al*. (42)	NR	NR	NR	NR

ELISA, enzyme-linked immunosorbent assay; NR, not reported.

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Table S2 Extracted data from studies evaluating ascitic calprotectin for detection of SBP

Study	Number of paracenteses (n)	Prevalence of SBP (%)	Cut-off value	Unit	Sensitivity (%)	Specificity (%)	TP (n)	FP (n)	FN (n)	TN (n)
Abdel Rahman *et al*. (24)	80	50	0.002	ug/mL	90	92.5	36	3	4	37
Abdel-Razik *et al*. (25)	79	65.82	0.445	ug/mL	95.4	85.2	50	4	2	23
Ali *et al*. (26)	72	69.44	0.372	ug/mL	100	100	50	0	0	22
El-Baz *et al*. (27)	88	42.05	0.048	ug/mL	91.7	62.7	34	19	3	32
Fernades *et al*. (9)	88	46.59	1.570	ug/mL	87.8	97.9	36	1	5	46
Gad *et al*. (28)	80	50	2.89	ng/mL	90	62.5	36	15	4	25
Heikl et al. (29)	70	71.43	0.783	ug/mL	90	100	45	0	5	20
Kassem *et al*. (30)	90	41.25	0.950	ug/mL	95	89.2	31	5	2	42
Makhlouf *et al*. (31)	87	56.32	0.710	ug/mL	95.9	97.4	47	1	2	37
Mohammed *et al*. (32)	60	50	0.096	ug/mL	86.7	76.7	26	7	4	23
Rizk *et al*. (14)	124	56.45	0.270	ug/mL	97.5	86	68	8	2	46
Weil *et al*. (33)	273	15.25	0.680	ug/mL	88.9	80.5	32	39	4	161

FN, false negative; FP, false positive; mL, milliliter; SBP, spontaneous bacterial peritonitis; TN, true negative; TP, true positive; ug, microgram.

Table S3 Extracted data from studies evaluating ascitic lactoferrin for detection of SBP

Study	Number of paracenteses (n)	Prevalence of SBP (%)	Cut-off value	Unit	Sensitivity (%)	Specificity (%)	TP (n)	FP (n)	FN (n)	TN (n)
Abuelfadi *et al*. (34)	150	66.67	75.55	ng/mL	100	98	100	1	0	49
Al Sawaf *et al*. (35)	168	29.17	100	ng/mL	95.9	76.5	47	28	2	91
Ali *et al*. (36)	96	62.5	88	ng/mL	100	91.7	60	3	0	33
Chen *et al*. (37)	111	19.82	46.1	ng/mL	59.1	94.8	13	5	9	84
El-Baz *et al*. (27)	88	42.05	189.9	ng/mL	91.9	60.8	34	20	3	31
Khalifa *et al*. (15)	70	71.43	270	ng/mL	96	95	48	1	2	19
Kumar *et al*. (38)	115	26.09	300	ng/mL	70	89.3	21	9	9	76
Lee *et al*. (39)	102	23.53	51.4	ng/mL	95.8	74.4	23	20	1	58
Liang *et al*. (40)	117	39.39	233	ng/mL	96.2	97.5	44	2	2	69
Makhlouf *et al*. (31)	87	56.32	118.2	ng/mL	91.5	86.1	45	5	4	33
Mohammad *et al*. (41)	84	40.48	83	ng/mL	91	94	31	3	3	47
Parsi *et al*. (7)	218	10.09	242	ng/mL	95.5	97	21	6	1	190
Salman *et al*. (42)	51	58.82	255	ng/mL	100	90.3	30	2	0	19

FN, false negative; FP, false positive; mL, milliliter; ng, nanogram; SBP, spontaneous bacterial peritonitis; TN, true negative; TP, true positive.

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Table S4 Detailed QUADAS form of studies evaluating ascitic calprotectin and lactoferrin for the detection of SBP

Study	Patient selection					Index test				Reference standard				Flow and timing				
	Was a consecutive or random sample of patients enrolled?	Was a case-control design avoided?	Did the study avoid inappropriate exclusions?	Could the selection of patients have introduced bias?	Is there concern the included patients do not match the review question?	Were the index test results interpreted without knowledge of the results of the reference standard?	If a threshold was used, was it pre-specified?	Could the conduct or interpretation of the index test have introduced bias?	Is there concern that the index test, its conduct, or interpretation differ from the review question?	Is the reference standard likely to correctly classify the target condition?	Were the reference standard results interpreted without knowledge of the results of the index test?	Could the reference standard, its conduct, or its, interpretation have introduced bias?	Is there concern the target condition as defined by the reference standard does not match the review question?	Was there an appropriate interval between index tests and reference standard?	Did all patients receive a reference standard?	Did patients receive the same reference standard?	Were all patients included in the analysis?	Could the patient flow have introduced bias?
Calprotectin																		
Abdel Rahman *et al*. (24)	Unclear	Yes	Yes	Low	Low	Unclear	No	Low	Low	Yes	No	Low	Low	Yes	Yes	Yes	No	Low
Abdel-Razik *et al*. (25)	Yes	Yes	Yes	Low	Low	Yes	No	Low	Low	Yes	No	Low	Low	Yes	Yes	Yes	No	Low
Ali *et al*. (26)	Unclear	Unclear	Yes	Low	Low	Unclear	No	Low	Low	Yes	No	Low	Low	Yes	Yes	Yes	Yes	Low
El-Baz *et al*. (27)	Unclear	No	Yes	High	Low	Unclear	No	Low	Low	Yes	No	Low	Low	Yes	Yes	Yes	Yes	Low
Fernades *et al*. (9)	Yes	Yes	Yes	Low	Low	Yes	No	Low	Low	Yes	No	Low	Low	Yes	Yes	Yes	Yes	Low
Gad *et al*. (28)	No	No	Yes	High	Low	Unclear	No	Low	Low	Yes	No	Low	Low	Yes	Yes	Yes	Yes	Low
Heikl *et al*. (29)	No	No	Yes	High	Low	Unclear	No	Low	Low	Yes	No	Low	Low	Yes	Yes	Yes	Yes	Low
Kassem *et al*. (30)	Yes	No	Yes	High	Low	Unclear	No	Low	Low	Yes	No	Low	Low	Yes	Yes	Yes	Yes	Low
Makhlouf *et al*. (31)	Yes	Yes	Yes	Low	Low	Yes	No	Low	Low	Yes	No	Low	Low	Yes	Yes	Yes	Yes	Low
Mohammed *et al*. (32)	No	No	Yes	High	Low	Unclear	No	Low	Low	Yes	No	Low	Low	Yes	Yes	Yes	Yes	Low
Rizk *et al*. (14)	Yes	Yes	Yes	Low	Low	Yes	No	Low	Low	Yes	No	Low	Low	Yes	Yes	Yes	No	Low
Weil *et al*. (33)	Yes	Yes	Yes	Low	Low	Yes	No	Low	Low	Yes	No	Low	Low	Yes	Yes	Yes	Yes	Low
Lactoferrin																		
Abuelfadi *et al*. (34)	Unclear	No	Yes	High	Low	Unclear	No	Low	Low	Yes	No	Low	Low	Yes	Yes	Yes	Yes	Low
Al Sawaf *et al*. (35)	Yes	Yes	Yes	Low	Low	Yes	No	Low	Low	Yes	Unclear	Low	Low	Yes	Yes	Yes	Yes	Low
Ali *et al*. (36)	Unclear	Unclear	Yes	Low	Low	No	No	Low	Low	Yes	No	Low	Low	Yes	Yes	Yes	Yes	Low
Chen *et al*. (37)	Yes	Yes	Yes	Low	Low	Yes	No	Low	Low	Yes	Yes	Low	Low	Yes	Yes	Yes	Yes	Low
El-Baz *et al*. (27)	Unclear	No	Yes	High	Low	No	No	Low	Low	Yes	Yes	Low	Low	Yes	Yes	Yes	Yes	Low
Khalifa *et al*. (15)	Yes	No	Yes	High	Low	Unclear	No	Low	Low	Yes	Unclear	Low	Low	Yes	Yes	Yes	Yes	Low
Kumar *et al*. (38)	Yes	Yes	Unclear	Low	Low	Yes	No	Low	Low	Yes	No	Low	Low	Yes	Yes	Yes	Yes	Low
Lee *et al*. (39)	Yes	Yes	Yes	Low	Low	Yes	No	Low	Low	Yes	Yes	Low	Low	Yes	Yes	Yes	No	Low
Liang *et al*. (40)	Unclear	Yes	Unclear	High	Low	Unclear	No	Low	Low	Yes	Unclear	Low	Low	Yes	Yes	Yes	Yes	Low
Makhlouf *et al*. (31)	Yes	Yes	Yes	Low	Low	Yes	No	Low	Low	Yes	Yes	Low	Low	Yes	Yes	Yes	Yes	Low
Mohammad *et al*. (41)	Yes	Yes	Unclear	Low	Low	Yes	No	Low	Low	Yes	No	Low	Low	Yes	Yes	Yes	Yes	Low
Parsi *et al*. (7)	Yes	Yes	Yes	Low	Low	Unclear	No	Low	Low	Yes	Unclear	Low	Low	Yes	Yes	Yes	Yes	Low
Salman *et al*. (42)	Yes	Yes	Yes	Low	Low	Yes	No	Low	Low	Yes	No	Low	Low	Yes	Yes	Yes	Yes	Low

QUADAS, quality assessment of diagnostic accuracy studies; SBP, spontaneous bacterial peritonitis.

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