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ASCITIC FLUID MARKERS FOR DIAGNOSING SPONTANEOUS BACTERIAL PERITONITIS IN DECOMPENSATED CIRRHOSIS

MARKERII LICHIDULUI ASCITIC ÎN DIAGNOSTICUL PERITONITEI BACTERIENE SPONTANE ÎN CIROZA DECOMPENSATĂ

Sergiu Pisarenco^{1*}, Tatiana Zugrav^{1,2}, Gheorghe Anghelici^{1,2}, Ana Otgon²

¹ Department of Surgery No. 2, "Nicolae Testemițanu" State University of Medicine and Pharmacy, Chișinău, Republic of Moldova;

² General Surgery Department No. 2, "St. Trinity" Municipal Clinical Hospital, Chișinău, Republic of Moldova.

* Corresponding author: sergiu.pisarenco@usmf.md

ABSTRACT

Objectives. To synthesize the evidence on the diagnostic value of ascitic fluid markers for spontaneous bacterial peritonitis in decompensated liver cirrhosis and to define their role relative to the current diagnostic criterion.

Methods. Critical narrative review based on a structured search of PubMed/MEDLINE, supplemented by the reference lists of the European, American, British and Korean guidelines. The review had no registered protocol, no duplicate selection, no formal risk-of-bias assessment and no original meta-analysis.

Results. An ascitic polymorphonuclear neutrophil count ≥ 250 cells/ μ L remains the diagnostic criterion for spontaneous bacterial peritonitis, irrespective of culture result and provided a secondary intra-abdominal source is excluded. The serum-ascites albumin gradient characterizes the mechanism of ascites and low ascitic protein is a risk factor; neither diagnoses infection. Leukocyte esterase reagent strips perform variably. Ascitic calprotectin and lactoferrin have the most extensive, but inconsistent, evidence base: in a meta-analysis pooling 12 and 13 studies, respectively, summary sensitivity and specificity were 94.2% and 86.0% for calprotectin and 95.4% and 89.0% for lactoferrin. Specificity is highly heterogeneous, thresholds and platforms differ, no universally validated threshold exists, and a recent prospective study did not reproduce the discriminative capacity of ascitic calprotectin. The remaining markers are exploratory, and molecular technologies increase the yield of pathogen identification without replacing the cellular criterion.

Conclusions. No investigational ascitic fluid biomarker can currently replace the polymorphonuclear neutrophil count, and no externally validated universal threshold is available. Calprotectin and lactoferrin remain investigational biomarkers, not recommended by current guidelines for routine triage or treatment decisions. Prospective multicenter validation, assay standardization and platform-specific thresholds are required.

Keywords: spontaneous bacterial peritonitis, liver cirrhosis, ascitic fluid, calprotectin, lactoferrin, diagnostic accuracy

REZUMAT

Obiective. Sintetizarea dovezilor privind valoarea diagnostică a markerilor lichidului ascitic pentru peritonita bacteriană spontană în ciroza hepatică decompensată și delimitarea rolului lor față de criteriul diagnostic actual.

Metode. Revizuire narativă critică, bazată pe o căutare structurată în PubMed/MEDLINE, completată prin listele de referințe ale ghidurilor europene, americane, britanice și coreene. Lucrarea nu a avut protocol înregistrat, selecție în duplicat, evaluare formală a riscului de bias sau meta-analiză proprie.

Rezultate. Numărul de polimorfonucleare ≥ 250 celule/ μ L rămâne criteriul diagnostic al peritonitei bacteriene spontane, indiferent de cultură și cu condiția excluderii unei surse intraabdominale secundare. Gradientul seroascitic al albuminei caracterizează mecanismul ascitei, iar proteina ascitică scăzută este un factor de risc; niciunul nu diagnostichează infecția. Bandedelele cu esterază leucocitară au performanțe variabile. Calprotectina și lactoferina ascitică dispun de cea mai extinsă bază de dovezi, dar neuniformă: în meta-analiza care a inclus 12, respectiv 13 studii, sensibilitatea și specificitatea sumare au fost de 94,2% și 86,0% pentru calprotectină și de 95,4% și 89,0% pentru lactoferină. Heterogenitatea specificității este mare, pragurile și platformele diferă, nu există un prag universal validat, iar un studiu prospectiv recent nu a regăsit capacitatea discriminativă a calprotectinei. Ceilalți markeri rămân exploratorii, iar tehnologiile moleculare cresc randamentul identificării agentului etiologic fără a substitui criteriul celular.

Concluzii. Niciun biomarker investigațional al lichidului ascitic nu poate înlocui în prezent numărarea polimorfo-

nuclearelor și niciun prag universal validat extern nu este disponibil. Calprotectina și lactoferina rămân biomarkeri investigaționali, nerecomandați de ghiduri pentru triaj sau decizii terapeutice de rutină. Sunt necesare validarea multicentrică prospectivă, standardizarea dozării și praguri specifice platformei.

Cuvinte-cheie: peritonită bacteriană spontană, ciroză hepatică, lichid ascitic, calprotectină, lactoferină, acuratețe diagnostică

Introduction

Ascites is the most frequent complication of decompensated cirrhosis, and its onset marks a major deterioration in prognosis [1]. Spontaneous bacterial peritonitis (SBP) is an infection of the ascitic fluid occurring in the absence of a surgically treatable intra-abdominal source and is frequently associated with acute kidney injury, encephalopathy and hepatic decompensation [1, 2].

Antimicrobial resistance adds a further dimension: in an intercontinental study of 1,302 patients hospitalized with cirrhosis and bacterial or fungal infection, the prevalence of multidrug-resistant bacteria was 34% (95% confidence interval [CI] 31–37), with significant regional differences and higher in-hospital mortality [3].

In observational studies, diagnostic paracentesis has been associated with lower in-hospital mortality. In an analysis of 31,614 non-elective admissions of patients with cirrhosis and ascites, mortality was 6.3% with paracentesis versus 8.9% without ($P < 0.001$), with 1.83-fold higher odds of death in the absence of the procedure (95% CI 1.66–2.02) [4]. In a two-center study of 239 patients with SBP, paracentesis performed ≥ 12 hours after admission was associated with a mortality of 27% versus 13% ($P = 0.007$), each hour of delay being associated with a 3.3% increase in mortality (95% CI 1.3–5.4) after adjustment for the Model for End-Stage Liver Disease (MELD) score and creatinine [5]. Both associations are observational.

These data explain the interest in ascitic markers that could allow a more rapid diagnosis. This review synthesizes the available evidence and delineates the functional categories of these parameters: diagnostic criterion, risk factor, test for differentiating secondary peritonitis, and investigational biomarker.

Materials and Methods

The present work is a critical narrative review based on a structured search of PubMed/MEDLINE, with full texts consulted through PubMed Central and publishers' websites. Separate queries were run for each category of markers, combining the terms "spontaneous bacterial peritonitis", "neutrocytic ascites", "liver cirrhosis" and "ascites" with category-specific terms using the AND operator (manual and automated cell counting, culture and molecular microbiological diagnosis, leukocyte esterase, calprotectin, lactoferrin, lactate and pH, glucose, protein, lactate dehydrogenase, ascitic cytokines, endocan, neutrophil gelatinase-associated lipocalin [NGAL, lipocalin-2], sepsis peptides, molecular markers), supplemented by the reference

lists of the European Association for the Study of the Liver (EASL, 2018), American Association for the Study of Liver Diseases (AASLD, 2021), British Society of Gastroenterology/ British Association for the Study of the Liver (BSG/BASL, 2021) and Korean Association for the Study of the Liver (KASL, 2026) guidelines [1, 2, 6, 7]. Scopus, Web of Science and the Cochrane Library were not searched; the sources retained date from 1983 to 2026.

Professional guidelines, systematic reviews with meta-analysis and primary accuracy studies in adults with ascites, with measurement performed in ascitic fluid, were included. For clinical context, observational studies on prognosis and paracentesis were also used, as were systematic reviews without meta-analysis. Some cohorts were mixed and also included ascites of other etiologies; in these cases the estimates are reported for the overall sample, and the composition of the sample is specified in the text and in Table 1. Preanalytical studies were used exclusively in the section on heterogeneity. Pediatric studies, animal model studies, case reports, editorials and works whose values or population could not be verified in the original publication were excluded.

For every numerical value in the text and in the tables, the original article was consulted; parameters that were not reported are marked as such, with no derived estimates. The last verification was performed on 10 September 2026. The pivotal studies are presented in Table 1.

The review had no registered protocol, no duplicate study selection or data extraction, no formal risk-of-bias assessment, and no original meta-analysis. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram is not provided. These are the principal methodological limitations of the review.

Results

The current diagnostic criterion for spontaneous bacterial peritonitis

The diagnosis of SBP is established on the basis of an ascitic polymorphonuclear (PMN) cell count ≥ 250 cells/ μL (≥ 250 cells/ mm^3); in blood-contaminated ascites, one PMN is subtracted for every 250 red blood cells/ mm^3 [7]. The culture may be positive or negative, and a negative result does not rule out the diagnosis. Exclusion of a secondary, surgically treatable intra-abdominal source is also required [1, 2, 6].

The terminology distinguishes four entities that should not be confused:

- culture-positive SBP — PMN $\geq 250/\mu\text{L}$ and a positive culture, usually monomicrobial;
- culture-negative neutrocytic ascites — PMN $\geq 250/\mu\text{L}$ and a negative culture; it is managed in the same way as

Table 1. *Selected pivotal studies on ascitic fluid markers*

Study (year)	Design	N; cases	Population	Index test	Reference standard	PMID
Nousbaum et al. (2007) [8]	Prospective, 70 centers	2,123 samples / 1,041 patients; 117 samples PMN $\geq 250/\mu\text{L}$	France	Multistix 8 SG	PMN $\geq 250/\mu\text{L}$	17464969
Mwinyi et al. (2026) [9]	Prospective	269 patients; 51 SBP (19.0%)	Tanzania	Leukocyte esterase	PMN $\geq 250/\text{mm}^3$	42676743
Abdel-Razik et al. (2016) [10]	Prospective, two centers	79 patients; 52 SBP	Egypt	Calprotectin (ELISA)	PMN $\geq 250/\mu\text{L}$	26601826
Burri et al. (2013) [11]	Prospective, two centers	130 samples / 71 patients (54 with cirrhosis); 19 samples PMN $> 250/\mu\text{L}$	Switzerland; mixed ascites	Calprotectin (ELISA; POC)	PMN $> 250/\mu\text{L}$	23599621
Hadjivasilis et al. (2021) [12]	Meta-analysis	10 studies	Cirrhotic patients	Calprotectin (various methods)	PMN $\geq 250/\text{mm}^3$	32541235
Patel et al. (2022) [13]	Meta-analysis	12 calprotectin studies; 13 lactoferrin studies	Cirrhotic patients	Calprotectin and lactoferrin (various kits)	PMN $\geq 250/\text{mm}^3$	36300150
Sbeit et al. (2024) [14]	Proof-of-concept	31 patients; 8 SBP	Israel	Calprotectin (ELISA)	PMN $\geq 250/\text{mm}^3$	38281236
Bhatia et al. (2026) [15]	Prospective, single-center	137 patients; 55 SBP (40.1%)	India	Ascitic calprotectin (ELISA)	PMN $\geq 250/\text{mm}^3$	41746298
Parsi et al. (2008) [16]	Prospective, two centers	218 samples / 148 patients; 22 samples (10.1%)	USA	Lactoferrin (ELISA)	PMN $\geq 250/\mu\text{L}$	18590731
Lee SS et al. (2016) [17]	Prospective, single-center	102 patients; 24 SBP	South Korea	Lactoferrin (ELISA)	PMN $\geq 250/\mu\text{L}$	27733127
Guyton and Achord (1983) [18]	Prospective, single-center	45 patients; 7 SBP	Mixed ascites	L-lactate (rapid kit)	Clinical diagnosis	6837548

SBP – spontaneous bacterial peritonitis; PMN – polymorphonuclear cells; ELISA – enzyme-linked immunosorbent assay; POC – point-of-care. The DOIs are given in the reference list. Samples marked “mixed ascites” also comprise ascites of an etiology other than cirrhosis, the estimates being reported for the overall sample. “Not reported” – parameter not provided in the original source. Numbers in square brackets refer to the reference list.

culture-positive SBP;

- monomicrobial bacterascites — PMN $< 250/\mu\text{L}$ and a positive culture. The guidelines do not propose an identical algorithm: in the symptomatic patient, empirical antibiotic therapy is initiated, whereas in the asymptomatic patient paracentesis is repeated under clinical monitoring; according to EASL, persistence of a positive culture justifies treatment, irrespective of the PMN count [1, 2, 6];
- secondary bacterial peritonitis — infection of the ascitic fluid arising from an intra-abdominal source, which requires imaging assessment and, frequently, surgical treatment [1, 2,

6, 19].

Isolation of a polymicrobial flora is not typical of SBP and raises the suspicion of secondary peritonitis or of inadvertent bowel puncture [1, 2, 19].

Diagnostic paracentesis is indicated in new-onset ascites amenable to puncture and at every non-elective admission of a patient with cirrhosis and ascites, even in the absence of signs of infection, as well as in the presence of fever or systemic inflammation, shock, gastrointestinal symptoms, gastrointestinal bleeding, encephalopathy, or worsening hepatic or renal function [1, 2, 6].

Sampling, PMN counting and microbiological examination

The sensitivity of the microbiological examination depends critically on the sampling technique: conventional culture identified bacteria in 13 of 30 episodes of neutrocytic ascites (43%), compared with 28 of 30 (93%; $P < 0.0001$) with bedside inoculation into blood culture bottles, a difference explained by the very low bacterial concentration (median, one microorganism per milliliter) [20]. The guidelines therefore recommend inoculating approximately 10 mL into each of the aerobic and anaerobic blood culture bottles, at the bedside and before antibiotic therapy, with simultaneous blood cultures [1, 2, 6].

The diagnostic criterion is the PMN count, determined manually or by validated automated methods. Manual counting is time-consuming and subject to human error, and lysis of polymorphonuclear cells during transport may produce false-negative results. Automated counters have given non-uniform results across instruments: a sensitivity of 100% and a specificity of 97.7% compared with manual counting, in 112 samples from 52 cirrhotic patients [21], but a specificity of only 65% for another instrument, versus 100% for flow cytometry [22]. In a retrospective analysis of two cohorts (137 cases with 5 episodes of SBP and 85 cases with 33), with positive culture associated with clinical signs as the reference standard, assessment of the 74 samples with both determinations available from the second cohort showed a sensitivity of 80% for the automated method and of 52% for the manual method ($P = 0.02$), using thresholds of 200 and 250 PMN/mm³, respectively; the specificities were 96% and 100% [23]. The threshold proposed by the authors, $\geq 0.2 \times 10^9$ PMN/L (200 cells/mm³), has not been adopted by the guidelines. Local validation remains necessary; these practical limitations justify the development of rapid tests but do not imply that the criterion itself lacks sensitivity.

Urine reagent strips, which detect leukocyte esterase through a colorimetric reaction, have been proposed as a rapid diagnostic solution. The largest prospective multicenter study — 2,123 paracenteses in 1,041 patients from 70 centers — reported, at the 2+ threshold, a sensitivity of 45.3% and a specificity of 99.2%, and the authors concluded that the strip had no diagnostic efficacy [8]. A meta-analysis of 31 studies reported estimates that vary substantially according to manufacturer: sensitivity 0.806–0.962, specificity 0.672–0.974 [24]. A 2026 study of 269 adults with cirrhosis and ascites in a resource-limited setting (SBP prevalence 19.0%) reported, for the 2+ colorimetric category, a sensitivity of 80.4% and a specificity of 99.1%, the authors proposing the strip as a possible ancillary screening test rather than as a substitute for standard assessment [9] (Table 2). Sensitivity remains insufficient to substitute for PMN determination, and the guidelines do not recommend the strips for the rapid diagnosis of SBP [1].

Distinguishing risk factors from diagnostic markers

A frequent source of confusion is the treatment of prognostic or etiological parameters as diagnostic tests.

A serum-ascites albumin gradient (SAAG) ≥ 1.1 g/dL indicates ascites associated with portal hypertension; in 901 paired samples, SAAG correctly classified the cause of ascites in 96.7% of cases, compared with 55.6% for the exudate–transudate concept [25]. It is a test of the mechanism of ascites formation and provides no information on infection.

A low ascitic total protein identifies patients at increased risk of SBP and contributes to the indication for primary prophylaxis, without in itself constituting a universal indication: EASL and AASLD associate it with advanced hepatic failure and/or with renal dysfunction or hyponatremia, whereas BSG/BASL issue a weaker recommendation, acknowledging the uncertainty of the evidence [1, 2, 6]. It is a risk factor, not a test that confirms or rules out infection. Multiparametric models based predominantly on serum variables are not ascitic markers and fall outside the scope of this review.

Differentiating SBP from secondary bacterial peritonitis

Identification of secondary bacterial peritonitis has immediate therapeutic consequences: unlike SBP, it requires imaging investigation and, often, surgical intervention. The classic criteria derive from a series that compared six patients with gastrointestinal perforation and ascites with 33 episodes of SBP: all patients with perforation met at least two of three criteria (total protein >1 g/dL, glucose <50 mg/dL and lactate dehydrogenase >225 mU/mL), compared with two of the 33 SBP episodes [19] (Table 3).

The Runyon biochemical criteria are of historical value and are indicative only, having been developed in a very small series and subsequently evaluated retrospectively. The guidelines reviewed recommend prompt investigation of a secondary source in the presence of localized clinical signs, polymicrobial culture, a very high PMN count, elevated ascitic protein or inadequate therapeutic response, but do not uniformly reproduce the “at least two of three” rule [1, 2, 6]. KASL 2026 explicitly lists, as features of secondary peritonitis, ascitic protein >1.0 g/dL, glucose ≤ 50 mg/dL, ascitic lactate dehydrogenase above the upper limit of the serum reference range, and the absence of a decrease in PMN at repeat paracentesis after 48 hours of adequate antibiotic therapy [7].

The criteria were evaluated in a retrospective study that compared 24 cirrhotic patients with secondary peritonitis with 106 episodes of SBP. Secondary peritonitis accounted for 4.5% of all episodes of peritonitis recorded in cirrhotic patients during the study period, a percentage that refers to this total and not to the 24 versus 106 episodes of comparison. The criteria had a sensitivity of 66.6% and a specificity of 89.7%; the criteria and/or a polymicrobial culture were present in 95.6% of patients, and computed tomography was diagnostic in 85% of those with a surgically or post-mortem confirmed diagnosis [26].

Elevated lactate dehydrogenase values reflect peritoneal inflammation but are not specific — they also occur in malignant, tuberculous or pancreatic ascites — so that the parameter cannot be used in isolation [1, 19].

Table 2. Diagnostic performance reported in the verified sources

Study (year)	Index test and threshold	Se % (95% CI)	Sp % (95% CI)	AUROC (95% CI)	Key limitation
Nousbaum et al. (2007) [8]	Multistix 8 SG, $\geq 2+$	45.3	99.2	Not reported	Sensitivity insufficient for exclusion
Mwinyi et al. (2026) [9]	Leukocyte esterase, 2+ category	80.4 (67.6–89.8)	99.1 (95.7–99.9)	Not reported	Proposed as an ancillary screening test, not as a substitute for PMN
Abdel-Razik et al. (2016) [10]	Calprotectin, 445 ng/mL	95.4	85.2	0.921	NPV and PPV cannot be reconciled with the sample; prevalence 65.8%; threshold derived in the same sample
Burri et al. (2013) [11]	Calprotectin, ELISA, $>0.63 \mu\text{g/mL}$	94.8	89.2	0.977 (0.933–0.995)	NPV 99.0%; target condition PMN $>250/\mu\text{L}$, not the clinical diagnosis; multiple samples per patient; threshold optimized in the same sample
Burri et al. (2013) [11]	Calprotectin, POC, $>0.51 \mu\text{g/mL}$	100	84.7	0.982 (0.942–0.997)	Same limitations; measurements in a central laboratory; difference versus ELISA not statistically significant ($P = 0.246$)
Hadjivasilis et al. (2021) [12] – meta-analysis	Calprotectin, various thresholds	93 (90–95)	89 (80–95)	Not reported	10 studies, overlapping with the meta-analysis by Patel et al.
Sbeit et al. (2024) [14]	Calprotectin, ELISA, $21 \mu\text{g/mL}$	85.7	89.5	0.947 (0.783–0.997)	8 cases, 23 controls; the published values cannot be reconstructed
Bhatia et al. (2026) [15]	Ascitic calprotectin, $>0.63 \mu\text{g/mL}$	45.5 (32.4–59.3)	56.1 (44.6–67.1)	0.453 (0.346–0.560)	No discriminative capacity; the 95% CI includes 0.50
Parsi et al. (2008) [16]	Lactoferrin, 242 ng/mL	95.5	97.0	0.98	1–8 samples per patient; threshold derived in the same sample
Lee SS et al. (2016) [17]	Lactoferrin, 51.4 ng/mL	95.8	74.4	0.898 (0.839–0.957)	Much lower specificity at a fivefold lower threshold
Patel et al. (2022) [13] – meta-analysis	Calprotectin, various thresholds	94.2 (91.6–96.7)	86.0 (79.9–93.5)	0.91	12 studies; $I^2 = 43.04\%$ (Se) and 89.70% (Sp); different kits and thresholds
Patel et al. (2022) [13] – meta-analysis	Lactoferrin, various thresholds ($46.1–300 \text{ ng/mL}$)	95.4 (93.0–97.9)	89.0 (83.6–94.5)	0.958	13 studies; $I^2 = 65.51\%$ (Se) and 91.04% (Sp); no external validation

Se – sensitivity; Sp – specificity; AUROC – area under the ROC curve; 95% CI – 95% confidence interval; PMN – polymorphonuclear cells; POC – point-of-care; NPV/PPV – negative/positive predictive value; I^2 – heterogeneity index. The design and the population are given in Table 1. The absence of a 95% CI and the entry “Not reported” indicate parameters not provided in the original source. The series by Guyton and Achord (1983) [18] does not appear here, as it does not report sensitivity and specificity separately for its own cohort. Numbers in square brackets refer to the reference list.

Table 3. Features raising the suspicion of secondary bacterial peritonitis

Feature	Value / specification
Ascitic total protein	>1 g/dL (historical Runyon series)
Ascitic glucose	<50 mg/dL (historical Runyon series)
Ascitic lactate dehydrogenase	>225 mU/mL (historical Runyon series), corresponding to the reference limits of that particular laboratory; it is not a current universal threshold
“Positive” Runyon result	At least two of the three biochemical criteria above, met concurrently
Other features recognized by the current guidelines	Localized abdominal signs or symptoms; polymicrobial culture; a very high PMN count; elevated ascitic protein; inadequate therapeutic response [1, 2, 6]; absence of a decrease in PMN at repeat paracentesis after 48 hours of adequate antibiotic therapy [7]
Interpretation	These features are to be interpreted in the clinical context. Suspicion of secondary peritonitis requires prompt imaging assessment [1, 2, 6]; no isolated biochemical parameter establishes the diagnosis.

PMN – polymorphonuclear cells. The biochemical criteria are adapted from Runyon and Hoefs [19], are of historical value, are indicative only, and derive from a very small series, subsequently evaluated retrospectively [26]. The guidelines reviewed do not uniformly reproduce the “at least two of three” rule. The biochemical values in the table are those of the historical Runyon series [19] and should not be confused with current universal thresholds. The other features are compiled from the European, American, British and Korean guidelines [1, 2, 6, 7].

Calprotectin in ascitic fluid

Calprotectin is a calcium- and zinc-binding protein predominantly located in the neutrophil cytosol; its concentration reflects neutrophil influx, which could allow a rapid estimation of the ascitic neutrophil load [13].

In a prospective two-center Egyptian study of 79 cirrhotic patients (52 with SBP), ascitic calprotectin measured by enzyme-linked immunosorbent assay (ELISA) had, at a threshold of 445 ng/mL, a sensitivity of 95.4% and a specificity of 85.2% (area under the receiver operating characteristic curve [AUROC] 0.921) [10]. The predictive values reported cannot be reconciled with the composition of the sample and with the published sensitivity and specificity; for this reason they are not reproduced and are not used in the argument.

A prospective two-center Swiss study analyzed 130 samples from 71 consecutive patients referred for paracentesis, 54 of whom had cirrhosis. The target condition was PMN >250/μL, met by 19 samples (14.6%), whereas a clinical diagnosis of SBP was established in 4 of the 71 patients (5.6%). At the ELISA threshold of >0.63 μg/mL, sensitivity was 94.8%, specificity 89.2% and the negative predictive value 99.0% (AUROC 0.977; 95% CI 0.933–0.995); the point-of-care (POC) platform, at >0.51 μg/mL, had a sensitivity of 100% and a specificity of 84.7% (AUROC 0.982; 95% CI 0.942–0.997); the difference between the AUROCs was not statistically significant ($P = 0.246$) [11]. The measurements were performed in a central laboratory, after centrifugation and storage; only a random subgroup of 17 samples was measured immediately, unprocessed, at the bedside, and for this subgroup only the correlation with the laboratory determination is reported, not a diagnostic validation [11].

Rapid platforms were evaluated in two further cohorts: a French two-center study of 236 samples from 119 patients

(prevalence 15.2%), with a sensitivity of 86.1% and a specificity of 92.0% at 1.51 μg/mL [27], and a Portuguese study of 88 patients (prevalence 46.6%), with 87.8% and 97.9% at 1.57 μg/mL [28]. Both studies are included in the meta-analysis discussed below; their results therefore do not represent additional independent evidence beyond the pooled estimate.

The largest meta-analysis pooled 12 studies, with a summary sensitivity of 94.2% (95% CI 91.6–96.7), a specificity of 86.0% (95% CI 79.9–93.5) and a summary AUROC of 0.91 [13]. A second meta-analysis, based largely on overlapping primary studies, reported concordant values across 10 studies [12] but does not constitute an independent confirmation. A proof-of-concept study of 31 patients (8 with SBP) reported, at 21 μg/mL, values that cannot be reconstructed from the published denominators [14] (Table 2).

The evidence is not, however, unequivocal. A recent prospective accuracy study included 137 consecutive patients with cirrhosis and ascites, 55 of whom had SBP defined by PMN ≥ 250 cells/mm³. Ascitic calprotectin did not differ significantly between the groups (medians 506.42 versus 562.99 ng/mL; $P = 0.378$) and had an AUROC of 0.453 (95% CI 0.346–0.560), indicating no demonstrated discriminative capacity, as the confidence interval included 0.50; at >0.63 μg/mL, sensitivity was 45.5% and specificity 56.1% [15]. The authors proposed dilution and proteolytic degradation as possible explanations. A systematic review of 26 observational studies, 14 of which measured ascitic calprotectin, found that thresholds had been proposed in only nine, with no convergence across platforms [29].

Lactoferrin in ascitic fluid

Lactoferrin is an iron-binding glycoprotein released upon degranulation of polymorphonuclear cells; unlike PMN, it is described as stable at room temperature for several hours,

which makes it attractive for a rapid test [13].

The reference study analyzed 218 samples from 148 patients with cirrhosis in two tertiary centers; 22 samples (10.1%) met the criteria for SBP. At 242 ng/mL, sensitivity was 95.5% and specificity 97% (AUROC 0.98) [16]; confidence intervals are lacking, and the collection of 1–8 samples from the same patient introduces unadjusted dependence. A South Korean study of 102 patients reported, at 51.4 ng/mL, a sensitivity of 95.8% but a specificity of only 74.4% (AUROC 0.898; 95% CI 0.839–0.957) [17], illustrating the dependence of performance on the threshold and on the study sample.

In the meta-analysis of 13 studies, the summary sensitivity was 95.4% (95% CI 93.0–97.9), the specificity 89.0% (95% CI 83.6–94.5) and the summary AUROC 0.958 [13]. Thresholds in the primary studies ranged from 46.1 to 300 ng/mL, reflecting different kits and derivation in samples with widely differing prevalences. No validation studies of a rapid device comparable to those for calprotectin were identified.

Other investigational markers

Ascitic lactate and pH have been studied since the 1980s. In a prospective study of 45 patients admitted with ascites, 7 of whom had SBP, an L-lactate above 33 mg/dL was present in all 7, and PMN exceeded 250/mm³ in 6 [18]; the sensitivity of 100% and the specificity of 96% published there derive from pooling with an earlier series and cannot be attributed to this cohort. Subsequent evaluations did not confirm a sensitivity sufficient for their use as independent tests: in 109 consecutive patients with ascites (10 with SBP), a pH below 7.31 and a lactate above 33 mg/dL were found in only 3 of those with SBP, the same changes also occurring in hemorrhagic or malignant ascites [30]; in 285 patients, neither the optimal thresholds for pH (<7.32) and lactate (>32 mg/dL) nor the blood–ascitic fluid gradients were more reliable than PMN, because of the altered values found in malignant, tuberculous and pancreatic ascites [31]; in a cohort with hepatitis B virus-related cirrhosis, sensitivity was 29% for pH ≤7.35 and 52% for lactate ≥32 mg/dL, versus 100% for PMN ≥250 cells/mm³ [32]. Both parameters have historical value and cannot replace the PMN count.

NGAL (lipocalin-2) originates from the secondary granules of polymorphonuclear cells. In 146 patients hospitalized with cirrhosis and ascites, 29 of whom had SBP (20%), the ascitic concentration was significantly higher in the SBP group (medians 221.3 versus 139.2 ng/mL; $P < 0.01$), and the marker remained an independent predictor of in-hospital mortality [33]; a study of 204 patients with decompensated cirrhosis found the same difference (111 versus 48 ng/mL; $P < 0.001$) [34]. A meta-analysis of 10 studies (573 cases, 833 controls) reported a summary sensitivity of 0.95 (95% CI 0.90–0.97) and a specificity of 0.86 (95% CI 0.70–0.94), but with a prediction interval for specificity of 0.23–0.99 and evidence of a small-study effect, the authors recommending it exclusively as an adjunctive test [35]. The pooled cohorts also include peritoneal dialysis-associated peritonitis, not only cirrhotic ascites.

Ascitic inflammatory markers: endocan, interleukin-6

and TNF- α

Endocan is a proteoglycan secreted by activated endothelial cells. A prospective Chinese study of 167 patients with decompensated cirrhosis, 39 of whom had SBP, measured ascitic endocan, tumor necrosis factor α (TNF- α) and interleukin-6 by ELISA; all three were significantly higher in the SBP group ($P < 0.001$), and endocan had an AUROC of 0.805, with a sensitivity of 82.1% and a specificity of 73.4% at approximately 295 pg/mL [36]. The threshold was derived in the same sample, without external validation. The estimates for endocan were lower than those pooled for calprotectin and lactoferrin, but, in the absence of a direct comparison, statistical inferiority cannot be established. No validated point-of-care devices were identified for these markers in ascitic fluid.

Sepsis peptides: MR-proadrenomedullin and ascitic procalcitonin

Mid-regional pro-adrenomedullin (MR-proADM) is a stable fragment of the adrenomedullin precursor that can be measured rapidly. In a French derivation and validation study, in the derivation cohort (236 visits, 22 with bacteriologically confirmed SBP) the ascitic concentration was higher in patients with SBP (3.14 versus 1.91 nmol/L; $P = 0.0002$), and as a continuous variable the marker had an AUROC of 0.746 (95% CI 0.685–0.801); at ≥2.50 nmol/L, sensitivity was 76%, specificity 69%, the positive predictive value 20% and the negative predictive value 97%. Ascitic procalcitonin had poor discriminative capacity. In a temporal cohort of 85 visits, the criterion MR-proADM ≥2.5 nmol/L had an AUROC of 0.958 (95% CI 0.876–0.993) [37]; the validation, however, came from the same center and used a different reference standard — PMN ≥250 cells/mm³, as opposed to the composite bacteriological criterion used in the derivation — and is therefore not an external multicenter validation. The composite score reported (AUROC 0.993) includes PMN ≥250 cells/mm³ both as a variable of the model and as the reference standard, so that it cannot be interpreted as the diagnostic performance of the marker.

Molecular markers and ascitic amyloid A

An Egyptian observational study of 103 patients with ascites, 64 of whom had SBP, reported for ascitic microRNA-155 a sensitivity of 95.3%, a specificity of 97.4% and an AUROC of 0.95 [38]. The high proportion of patients with SBP (62%) limits the extrapolation of the predictive values to populations with a lower prevalence, the threshold has not been externally validated, and the assay requires molecular techniques that are not routinely available for urgent decision-making; CD64, evaluated in the same study, was measured in blood. Ascitic amyloid A was measured in 37 patients (22 with SBP), with a sensitivity of approximately 90% and a specificity of 60% reported at 2.85 μ g/mL [39]. The small sample size and the modest specificity limit the interpretation and the clinical use of the result.

For most of these markers, no independent external validations, harmonized thresholds or clinical impact studies were identified; for MR-proADM there is only a temporal

validation in the same center.

Emerging microbiological technologies

Molecular methods and modifications of the culture technique target identification of the causative agent, not the cellular criterion. Metagenomic next-generation sequencing had, in 109 patients with cirrhotic ascites, a positivity rate of 73.4% versus 28.4% for conventional culture ($P < 0.001$) [40]. An integrated centrifugation–washing–lysis method increased culture positivity from 13.8% to 30.6% in 160 samples and reduced the mean time to detection from 2.3 to 1.0 days ($P < 0.001$) [41].

In a cohort with ascites of multiple etiologies, nanopore-targeted sequencing identified pathogens in 81.0% of the 616 samples assessed comparatively, versus 16.8% by culture. In the subgroup of patients with chronic renal failure who met the cellular criterion for SBP ($n = 56$), the detection rates were 82% by sequencing and 38% by culture [42]; these results cannot be extrapolated directly to the population with decompensated cirrhosis.

In 29 patients with cirrhosis, melting temperature (T_m) mapping detected bacteria more frequently than culture [43]. These techniques may facilitate etiological identification and the guidance of targeted therapy, but none has been evaluated as a substitute for PMN counting. Although study [42] reported changes in inflammatory markers under sequencing-guided therapy, there is insufficient evidence of a benefit on mortality or on other major clinical outcomes.

Heterogeneity and limitations of the evidence

Direct comparison of these markers is hampered by several sources of heterogeneity.

The populations and the units of analysis differ between studies. The proportion of samples meeting the criterion for SBP was 5.5% in the multicenter study [8] and 10.1% in the lactoferrin study [16], whereas the proportion of patients with SBP was 62–65.8% in studies [10, 38]. Predictive values depend on prevalence and on test performance, so that they cannot be transferred automatically between populations. Differences in recruitment and in clinical spectrum must be assessed separately; a high prevalence does not, by itself, demonstrate selection bias.

The reference standard is not uniform: some studies use the clinical diagnosis, others exclusively $PMN > 250/\mu L$ as the target condition [11]; in the latter case the adjudicated clinical diagnosis does not constitute the standard of the main analysis, the index test being evaluated through its capacity to identify this threshold, which changes the clinical meaning of the estimates.

The assay methods and the thresholds are heterogeneous: for calprotectin, ELISA techniques and rapid platforms, with thresholds in different units (445 ng/mL, 0.63 $\mu g/mL$, 0.51 $\mu g/mL$, 1.51 $\mu g/mL$, 1.57 $\mu g/mL$, 21 $\mu g/mL$) and kits from different manufacturers; for lactoferrin, 46.1–300 ng/mL [13, 29]. Preanalytical conditions also contribute: in 20 samples, the type of tube and the centrifugation conditions significantly altered the measured calprotectin concentration ($P < 0.001$) [44]. The study is preanalytical, but it shows that

thresholds are not transferable between processing protocols.

The meta-analysis by Patel et al. quantifies this dispersion: for calprotectin, moderate heterogeneity for sensitivity ($I^2 = 43.04\%$) and considerable heterogeneity for specificity ($I^2 = 89.70\%$); for lactoferrin, 65.51% and 91.04% [13]. The summary estimates therefore do not describe uniform behavior across populations and laboratories, and a pooled negative predictive value is not reported.

The Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) assessment in the same meta-analysis rated the risk of bias as low for the index test, the reference standard and patient flow, but identified a high risk of bias in patient selection in several studies [13]. Numerous primary studies derive and test the threshold in the same dataset, some include multiple samples from the same patient without adjustment, and confidence intervals are lacking in most [12, 13].

The discordance between the studies reporting a high accuracy of ascitic calprotectin and a recent prospective study that did not find its discriminative capacity [15] remains unexplained; the conclusions should therefore be regarded as qualitative guidance rather than as a quantitative estimate.

Clinical implications

In the patient with decompensated cirrhosis and ascites, the clinically applicable evidence concerns the diagnostic procedure rather than any single marker. Diagnostic paracentesis with PMN counting and bedside inoculation into blood culture bottles before antibiotic therapy remains the reference procedure, and its early performance has been associated with lower mortality, albeit in observational studies [4, 5]. Automated cell counters can replace time-consuming manual counting only after local validation, because their performance varies between instruments [21–23].

Interpretation must respect the separation of the functional categories: SAAG for the mechanism of ascites, low ascitic protein as a risk factor, the Runyon biochemical criteria and the features recognized by current guidelines for the suspicion of secondary peritonitis (Table 3), and the PMN count as the diagnostic criterion. Neither SAAG nor ascitic protein confirms or excludes infection, and features suggesting a secondary source call for prompt imaging, because no isolated biochemical parameter establishes the diagnosis [1, 2, 6].

Leukocyte esterase reagent strips were highly specific in some cohorts [8, 9], but their sensitivity is insufficient or manufacturer-dependent [8, 9, 24], so that a negative strip cannot exclude SBP, and the guidelines do not recommend them [1]. Ascitic calprotectin and lactoferrin remain investigational biomarkers: they are not recommended by the guidelines for triage or for routine treatment decisions and must not replace or delay PMN counting, culture inoculation and empirical treatment [1, 2, 6]. The evidence on rapid testing is more developed for calprotectin [11, 27, 28], although the point-of-care platform was evaluated on processed samples in a central laboratory, not at the bedside [11]; for lactoferrin, no comparable device validation was identified. No investigational biomarker, on its own, supports

the initiation or the discontinuation of antibiotic therapy.

Thresholds and methods further limit the transfer of these results to practice. Published thresholds range from 445 ng/mL to 21 µg/mL for calprotectin [10, 11, 14, 27, 28] and from 46.1 to 300 ng/mL for lactoferrin [13], and preanalytical processing alters the measured calprotectin concentration [44]. Predictive values obtained at one prevalence of SBP cannot be transferred to another, and the lack of discrimination in a recent prospective cohort [15] shows that a high pooled accuracy does not guarantee comparable performance in an individual center. Outside research protocols, these markers should therefore not guide clinical decisions.

Before these biomarkers can enter diagnostic algorithms, they require prospective multicenter validation in consecutive patients, with prespecified, platform-specific thresholds; a reference definition combining PMN counting, microbiological assessment and exclusion of secondary peritonitis; adjustment for repeated samples; bedside evaluation of point-of-care devices; and studies of clinical impact. The other markers are at an earlier stage: MR-proADM has only a temporal validation in the same center [37], and molecular methods increase pathogen identification without a demonstrated benefit on mortality [40-43].

Conclusions

The current diagnostic criterion for spontaneous bacterial peritonitis remains an ascitic polymorphonuclear cell count

≥250 cells/µL, irrespective of culture, provided that a secondary intra-abdominal source is excluded; none of the other ascitic fluid markers reviewed can currently replace it.

The other routine parameters have distinct roles: the serum-ascites albumin gradient characterizes the mechanism of ascites, low ascitic protein identifies patients at increased risk, and the biochemical criteria raise the suspicion of secondary peritonitis; none of them diagnoses infection. Leukocyte esterase reagent strips are not sufficiently sensitive to exclude spontaneous bacterial peritonitis.

Among the investigational markers, ascitic calprotectin and lactoferrin have the most extensive evidence base; this evidence remains heterogeneous and partly discordant, however, and no externally validated threshold is available. The other markers — endocan, interleukin-6, TNF-α, mid-regional pro-adrenomedullin, NGAL, microRNA-155 and amyloid A — remain investigational, without harmonized thresholds and without sufficient clinical validation for routine use.

Emerging microbiological technologies complement but do not replace the cellular criterion.

Future studies must use a prespecified reference definition — PMN ≥250 cells/µL, microbiological assessment and exclusion of secondary peritonitis — and must ensure assay standardization, externally validated platform-specific thresholds, prospective multicenter validation and assessment of clinical impact.

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Information about authors: Sergiu Pisarenco - <https://orcid.org/0009-0003-6516-1630>; Tatiana Zugrav - <https://orcid.org/0009-0003-1063-2802>; Gheorghe Anghelici - <https://orcid.org/0009-0003-1063-2802>; Ana Otgon - <https://orcid.org/0009-0009-1172-2627>

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