Mid-Regional Pro-Adrenomedullin in Spontaneous Bacterial Peritonitis Complicating Decompensated Cirrhosis

Walid Mohamed Attiah [1], Abdallah Moatasem Nawara [1], Mahmoud Abdelaziz Elsayed Taha [1], Yosra Abdelfattah Osama Mohamed [2]

1 Internal Medicine Department, Faculty of Medicine, Zagazig University, Egypt
2 Clinical Pathology Department, Faculty of Medicine, Zagazig University, Egypt
Corresponding Author: Mahmoud Abdelaziz Elsayed Taha

Received: 28 October 2024, **Accepted:** 17 November 2024, **Published:** 20 November 2024

Abstract

Background: Spontaneous bacterial peritonitis (SBP) remains a major cause of deterioration in decompensated cirrhosis. Ascitic polymorphonuclear neutrophil counting is indispensable for diagnosis but does not fully represent endothelial injury or circulatory failure. Mid-regional pro-adrenomedullin (MR-proADM), a stable fragment released with adrenomedullin, reflects inflammatory and vascular stress.

Aim: To review the biological basis, analytical characteristics, and clinical evidence supporting MR-proADM in cirrhosis and SBP, with particular attention to diagnostic and prognostic applications.

Methods: A targeted narrative review of PubMed-indexed studies and major hepatology guidance synthesized evidence on SBP pathogenesis, MR-proADM biology, sepsis prognostication, and cirrhosis-specific performance.

Results: MR-proADM is relevant to SBP because bacterial translocation, endothelial dysfunction, vasodilatation, and renal hypoperfusion are central to both disorders. Cirrhosis and sepsis studies linked higher concentrations with adverse outcomes. A 2025 derivation and validation study found higher ascitic MR-proADM in bacteriologically confirmed SBP and identified 2.5 nmol/L as a candidate threshold. A composite score combining MR-proADM, ascitic neutrophils of at least 250 cells/mm3, and Child-Pugh severity showed excellent validation-cohort discrimination. Evidence remains limited, thresholds are assay- and population-dependent, and renal dysfunction may increase concentrations.

Conclusion: MR-proADM is a promising adjunct, not a replacement for prompt paracentesis, neutrophil counting, culture, and clinical assessment. Multicenter studies should determine whether biomarker-guided decisions improve outcomes.

Keywords: cirrhosis; spontaneous bacterial peritonitis; MR-proADM; adrenomedullin; biomarker; prognosis

Introduction

Decompensation marks a decisive change in the natural history of cirrhosis. Ascites, variceal bleeding, hepatic encephalopathy, and jaundice identify patients whose physiological reserve is reduced and whose subsequent course is frequently shaped by infection and organ failure. Ascites is often the first recognized decompensating event, and its development is accompanied by a substantial decline in survival.[1] Among infectious complications, spontaneous bacterial peritonitis (SBP) deserves particular attention because it may be clinically subtle at presentation yet rapidly precipitate acute kidney injury, circulatory collapse, acute-on-chronic liver failure (ACLF), and death.[2,3]

The diagnosis of SBP remains anchored to an ascitic polymorphonuclear neutrophil (PMN) count of at least 250 cells/mm3 when no surgically treatable intra-abdominal source is present.[1] This threshold is intentionally sensitive and should trigger immediate empirical treatment. Ascitic culture is essential for microbiological characterization and antibiotic adjustment, but culture-negative neutrocytic ascites is common. Neither the PMN count nor culture alone describes the severity of systemic endothelial dysfunction that often determines outcome. Conventional serum markers, including C-reactive protein and procalcitonin, are also difficult to interpret in advanced liver disease because baseline inflammation, impaired hepatic synthesis, renal dysfunction, and recent antimicrobial exposure modify their concentrations and kinetics.[4]

Mid-regional pro-adrenomedullin (MR-proADM) has therefore attracted interest as a marker that lies closer to the vascular pathobiology of severe infection. It is a stable, inactive fragment of the adrenomedullin precursor and reflects production of bioactive adrenomedullin, a peptide involved in vasodilatation, endothelial barrier regulation, and the host response to infection. Evidence from sepsis suggests that MR-proADM can identify patients at risk of organ failure and death even when conventional inflammatory indices are less informative.[5,6] Recent cirrhosis-specific work has extended this concept from circulating concentrations to ascitic fluid and has proposed a diagnostic model for bacteriologically confirmed SBP.[7] This review examines the clinical rationale, available evidence, limitations, and research priorities for using MR-proADM in SBP complicating decompensated cirrhosis.

Epidemiology, Classification, and Clinical Consequences of SBP

The reported frequency of SBP varies substantially because studies differ in setting, disease severity, prior prophylaxis, and diagnostic practice. It is uncommon among stable outpatients with uncomplicated ascites but is encountered far more often in hospitalized patients with advanced decompensation, gastrointestinal bleeding, renal dysfunction, or ACLF.[1,3] This variability matters when a diagnostic biomarker is assessed. Sensitivity and specificity may remain relatively stable across settings, whereas positive and negative predictive values change with prevalence. A result considered reassuring in a low-prevalence outpatient population cannot be interpreted in the same way in a critically ill patient with shock and worsening organ function.

SBP is usually classified according to the circumstances of acquisition. Community-acquired infection is present at admission or develops soon afterward without substantial recent healthcare exposure. Healthcare-associated and nosocomial infections occur in patients with recent or ongoing contact with hospitals, procedures, or antimicrobial treatment. These categories are clinically relevant because resistant organisms are more common after healthcare exposure.[4] Prior quinolone prophylaxis, repeated hospitalization, invasive procedures, and previous colonization further influence microbiology. The same ascitic PMN threshold establishes the syndrome, but empirical treatment must be adapted to this resistance risk.

Ascitic infection also has recognized variants. Classic culture-positive SBP combines neutrocytic ascites with growth of a pathogen. Culture-negative neutrocytic ascites meets the PMN criterion

despite a negative culture and is generally managed similarly when secondary peritonitis has been excluded. Monomicrobial non-neutrocytic bacterascites describes a positive culture with a PMN count below 250 cells/mm3. Its significance depends on symptoms, repeat paracentesis, organism identity, and the clinical trajectory. Polymicrobial culture, very high ascitic protein or lactate dehydrogenase, low glucose, poor treatment response, or imaging abnormalities should raise concern for secondary peritonitis rather than SBP.

The immediate consequences of SBP extend beyond peritoneal infection. Inflammatory vasodilatation further lowers effective circulating volume and activates the renin-angiotensin-aldosterone and sympathetic systems. Renal perfusion falls, while cirrhotic cardiomyopathy may prevent an adequate compensatory increase in cardiac output. Acute kidney injury may progress despite microbiological control, and infection can precipitate ACLF with failure of the liver, kidney, brain, circulation, respiration, or coagulation systems.[2,3] These events explain why a biomarker reflecting endothelial and circulatory stress may add clinical information beyond the ascitic leukocyte response.

Clinical Context: Why SBP Remains Difficult

SBP develops without perforation, abscess, or another surgically remediable focus. Its pathogenesis begins long before organisms are recovered from ascitic fluid. Portal hypertension alters intestinal perfusion and promotes mucosal edema. Reduced bile acid delivery, impaired motility, and exposure to acid-suppressive or antimicrobial drugs may favor dysbiosis and bacterial overgrowth. At the same time, tight-junction disruption and mucosal immune impairment permit microbial products, and occasionally viable organisms, to cross the intestinal barrier. These signals reach mesenteric lymph nodes and the systemic circulation, amplifying inflammation in a host who already has cirrhosis-associated immune dysfunction.[8,9]

The host response is paradoxical. Persistent immune activation coexists with impaired pathogen clearance, reduced complement activity, defective neutrophil function, and low opsonic activity of ascitic fluid. This combination explains why infection can progress rapidly despite a muted fever or leukocyte response. Organisms classically arise from enteric Gram-negative flora, but contemporary cohorts increasingly identify Gram-positive and multidrug-resistant pathogens, especially after healthcare exposure or prophylactic antibiotics.[3,4] Empirical therapy must therefore reflect acquisition setting, prior colonization and antimicrobial exposure, local resistance patterns, and illness severity rather than a single universal regimen.

Clinical manifestations are heterogeneous. Abdominal pain, tenderness, fever, worsening encephalopathy, hypotension, ileus, acute kidney injury, or unexplained laboratory deterioration may be present, but some patients have no localizing symptom. Diagnostic paracentesis should not be delayed in hospitalized patients with cirrhosis and clinically significant ascites, particularly when infection or deterioration is suspected.[1] Bedside inoculation of ascitic fluid into aerobic and anaerobic blood-culture bottles improves microbiological yield. Treatment should begin as soon as the PMN criterion is met or clinical suspicion is compelling; waiting for culture exposes the patient to preventable deterioration.

Outcome depends on more than bacterial eradication. Vasodilatation and reduced effective arterial blood volume worsen during infection, while inflammatory mediators impair cardiac, endothelial, and renal function. Albumin given with antibiotics to appropriately selected patients reduces renal impairment and mortality, supporting the concept that circulatory injury is a major therapeutic target rather than a secondary feature.[10] The unmet need is therefore not simply another infection marker. A useful biomarker should identify clinically important infection quickly, reflect vascular and organ stress, add information beyond existing scores, and ideally direct an intervention that improves outcome.

Current Management and the Unmet Need for Risk Stratification

Management begins at the time of suspicion. Diagnostic samples should be obtained promptly,

but empirical antibiotics must not be delayed in a patient with neutrocytic ascites or convincing infection-related deterioration. A third-generation cephalosporin remains appropriate in many community-acquired settings when local resistance is low. Healthcare-associated, nosocomial, or critically severe infection may require broader initial coverage directed by local antibiograms, prior cultures, colonization history, and recent antibiotics. De-escalation after susceptibility results is important because repeated broad-spectrum exposure promotes resistance and fungal superinfection.[1,4]

Clinical response should be reassessed rather than inferred from defervescence alone. Hemodynamics, mental status, urine output, creatinine, sodium, lactate when relevant, and organ-failure scores provide a more complete picture. Repeat paracentesis after approximately 48 hours is commonly considered when response is inadequate, resistant infection is suspected, or secondary peritonitis remains possible. Failure of the ascitic PMN count to fall substantially should prompt reassessment of antimicrobial activity, source control, and the diagnosis itself. A single biomarker cannot substitute for this structured clinical review.

Intravenous albumin is an evidence-based adjunct in SBP because it reduces circulatory and renal complications in patients at increased risk.[10] Its benefit is linked to plasma expansion and broader effects on endothelial and immune function. Albumin should be used according to established clinical criteria rather than an unvalidated MR-proADM threshold. The same principle applies to vasopressors, renal replacement therapy, and critical-care transfer: these decisions are based on hemodynamics and organ failure. A biomarker may refine risk recognition but should not independently determine treatment.

After recovery, secondary prophylaxis is usually required because recurrence risk is high. Choice of agent should consider previous isolates, local resistance, adverse effects, and drug availability. Long-term strategy must also address the substrate for infection: management of ascites, avoidance of unnecessary proton-pump inhibitors and nephrotoxic drugs, nutritional support, alcohol abstinence when relevant, antiviral treatment where indicated, and evaluation for liver transplantation. SBP is not an isolated event; it is a marker of advanced disease and limited physiological reserve.

The ideal risk tool would operate at two moments. At admission, it would support recognition of SBP and identify patients needing intensified monitoring before overt shock or renal failure appears. During treatment, it would help distinguish expected recovery from persistent endothelial and organ stress. MR-proADM is biologically suited to both questions, but the evidentiary requirements differ. Diagnostic studies require an unbiased reference standard and representative spectrum, whereas prognostic studies require prespecified outcomes, adjustment for established predictors, and sufficient events. Monitoring claims additionally require standardized serial sampling and demonstration that biomarker change precedes or meaningfully tracks clinical change.

Adrenomedullin Biology and the Meaning of MR-proADM

Adrenomedullin is produced by endothelial cells and several other tissues in response to hypoxia, oxidative stress, cytokines, endotoxin, and mechanical strain. Through cyclic adenosine monophosphate and nitric oxide-related pathways, it exerts potent vasodilatory effects. It also contributes to endothelial barrier integrity and may limit excessive leukocyte-endothelial interaction. These functions are adaptive early in infection because they support microvascular flow and protect the endothelial surface. When activation becomes excessive, however, high adrenomedullin activity accompanies vasoplegia, capillary leakage, hypotension, and organ dysfunction.

Direct measurement of bioactive adrenomedullin is technically demanding because the peptide is short-lived and binds to circulating proteins. MR-proADM is cleaved from the same precursor in equimolar amounts, is more stable ex vivo, and can be measured using automated immunoassays.

It should be interpreted as a surrogate of adrenomedullin system activation, not as the active mediator itself. Assays commonly report concentrations in nmol/L, but specimen type, platform, sample handling, renal function, age, and comorbidity influence the result. A threshold derived from plasma in sepsis cannot automatically be transferred to ascitic fluid in cirrhosis.

The biological overlap between decompensated cirrhosis and systemic infection makes MR-proADM particularly plausible in SBP. Cirrhosis already features splanchnic vasodilatation, hyperdynamic circulation, relative arterial underfilling, endothelial activation, and neurohumoral vasoconstrictor responses. SBP adds microbial stimulation and a further inflammatory insult. MR-proADM may consequently capture a composite signal arising from infection burden, endothelial stress, hemodynamic disturbance, and organ dysfunction. This breadth is also a limitation: an elevated value is not specific for SBP and may reflect renal failure, ACLF, cardiac dysfunction, another infection, or severe cirrhosis itself.

Adrenomedullin biology is compartment-dependent. In the vascular lumen, the peptide supports endothelial stability and may restrict leakage. Within the interstitial space, excessive signaling contributes to vasodilatation and edema. MR-proADM does not distinguish these opposing actions, but it provides a stable indicator that the pathway has been activated. This is important when interpreting associations: a high concentration may identify severe disease without implying that adrenomedullin itself should be blocked or supplemented. Therapeutic conclusions cannot be inferred from a prognostic biomarker relationship.

Renal function deserves particular attention. MR-proADM rises as glomerular filtration declines, whether because of reduced clearance, greater production during systemic stress, or both. Kidney dysfunction is also one of the strongest determinants of prognosis in cirrhosis and SBP. An unadjusted association between MR-proADM and mortality could therefore reflect renal severity rather than independent vascular information. Cirrhosis-specific models should examine creatinine, dynamic acute kidney injury stage, chronic kidney disease, and renal replacement therapy and should test whether MR-proADM retains incremental value after these variables are incorporated.

Conventional Biomarkers and Prognostic Scores

The ascitic PMN count remains the decisive diagnostic test because it is directly linked to immediate treatment. Its strengths are availability, a standardized threshold, and extensive clinical experience. Its limitations include counting error at low concentrations, delays in laboratories that rely on manual microscopy, and imperfect specificity. Automated body-fluid analyzers reduce turnaround time and correlate well with manual methods when properly validated, but laboratories must establish local quality procedures. MR-proADM should be compared with this optimized standard, not with an avoidably delayed or technically weak counting process.

Culture serves a different purpose. A positive ascitic culture supports the diagnosis, identifies the organism, and enables antimicrobial susceptibility testing, but sensitivity is incomplete even with bedside blood-culture-bottle inoculation. Antibiotics before paracentesis further reduce yield. Molecular techniques may detect bacterial DNA or resistance determinants more rapidly, although they can identify nonviable material and are not yet a routine substitute for culture.[11] A vascular-stress biomarker cannot provide species identification or an antibiogram; its value would be complementary.

C-reactive protein is inexpensive and widely available, but its interpretation in cirrhosis is complicated. Baseline systemic inflammation may elevate CRP in the absence of bacterial infection, whereas severe hepatic synthetic dysfunction may blunt production. Procalcitonin is often more specific for bacterial infection in the general population, yet renal dysfunction, severe inflammation, and timing affect its concentration. A 2025 meta-analysis found useful diagnostic performance for procalcitonin and presepsin in cirrhosis, while also documenting heterogeneity between cohorts.[12] Neither marker consistently identifies the peritoneum as the infectious source.

MR-proADM may be advantageous because it reflects endothelial and organ stress, but that same property reduces anatomical specificity.

Lactate is central to the assessment of shock and impaired perfusion, but cirrhosis alters both production and hepatic clearance. A high lactate remains clinically important, particularly when it persists after initial resuscitation, although a single value does not identify the infectious source. Leukocyte count, neutrophil-to-lymphocyte ratio, presepsin, soluble triggering receptor expressed on myeloid cells, and ascitic calprotectin have been studied. A recent systematic review found consistently higher ascitic calprotectin in SBP, but assay and threshold heterogeneity limited immediate clinical adoption.[13] None currently replaces paracentesis or validated organ-failure assessment. The realistic objective is a multimodal model rather than a solitary superior marker.

Child-Pugh and MELD-Na describe liver disease severity, while ACLF scores and SOFA quantify organ dysfunction. They were designed for prognosis rather than SBP diagnosis. Contemporary clinical reviews continue to place immediate paracentesis, PMN counting, and culture at the center of assessment.[14] The 2025 SBP score is conceptually attractive because it combines local inflammation, endothelial stress, and hepatic reserve.[7] However, the apparent performance of any composite must be examined against the performance of its individual components and an appropriate baseline model. Incremental value should be demonstrated by calibration, likelihood ratios, decision-curve analysis, and clinically meaningful changes in classification, not by AUROC alone.

Evidence from Sepsis and Critical Illness

The most developed evidence for MR-proADM comes from sepsis. In a multicenter cohort of 326 patients with severe sepsis or septic shock, Andaluz-Ojeda et al.[5] found that MR-proADM had an area under the receiver operating characteristic curve of 0.79 for 28-day mortality. Its prognostic performance remained significant across strata of organ failure, and adding MR-proADM improved mortality discrimination in patients with lower SOFA scores. These findings support a role in early risk recognition, but they do not establish a universal treatment threshold.

Other infection cohorts have generally reported higher MR-proADM in patients who die or develop organ failure. A sepsis meta-analysis reported good diagnostic accuracy, while a later comparison of MR-proADM and presepsin found high pooled performance but meaningful between-study heterogeneity.[15,16] Studies in community-acquired pneumonia also linked higher proadrenomedullin concentrations with disease severity and mortality, providing early proof that the pathway reflects systemic risk rather than one anatomical infection.[17,18] Reviews consequently describe greater prognostic than purely diagnostic utility.[6,19] The signal often persists after adjustment for lactate, inflammatory markers, or clinical scores. Enrollment settings, sampling time, endpoint definitions, and renal function nevertheless differ substantially.

For hepatologists, sepsis data provide mechanistic and prognostic support, not direct validation. Cirrhosis alters baseline hemodynamics, immune responses, protein synthesis, and renal physiology. A biomarker may therefore perform differently in a cirrhotic population and may differ again when measured in ascitic rather than blood samples. Disease-specific evaluation is essential.

Cirrhosis-Specific Evidence

Early cirrhosis work suggested that MR-proADM might outperform C-reactive protein for short-term prognostication in patients with decompensated disease and suspected infection.[20] That report was small and was published as a research letter, so it is best regarded as a signal-generating observation. The clinical background is supported by a worldwide prospective study of 1,302 infected patients with cirrhosis, which documented a 34% prevalence of multidrug-resistant organisms and worse outcomes when empirical treatment was inadequate.[21] European data likewise showed that multidrug resistance is especially consequential in decompensated cirrhosis

and ACLF.[22] Subsequent reviews continued to identify MR-proADM among promising markers while emphasizing the limited number of dedicated validation studies.[4,11]

The strongest recent evidence is the 2025 study by Oussalah et al.[7], which evaluated rapid-assay biomarkers in ascitic fluid. The derivation analysis included 236 patient visits, of which 22 met a composite definition of bacteriologically confirmed SBP. Median ascitic MR-proADM was higher in bacteriologically confirmed SBP than in encounters without it: 3.14 nmol/L (interquartile range 2.39-6.74) versus 1.91 nmol/L (1.33-2.80), with P=0.0002. An ascitic MR-proADM threshold of at least 2.50 nmol/L yielded an AUROC of 0.746 (95% confidence interval 0.685-0.801) for bacteriologically confirmed SBP. Its negative predictive value was high in that cohort, but predictive values necessarily change with prevalence.

The investigators then combined ascitic MR-proADM of at least 2.5 nmol/L, ascitic PMN count of at least 250 cells/mm3, and Child-Pugh score into an SBP score. In an independent validation cohort of 85 visits, the score achieved an AUROC of 0.993 (95% confidence interval 0.929-1.000) for SBP defined by the PMN threshold.[7] The work is clinically important because it links a rapid endothelial-stress biomarker to established measures of infection and liver severity and includes independent validation.

Several cautions are necessary. The derivation endpoint required both neutrocytic ascites and a positive culture, whereas validation used the PMN criterion. The unit of analysis was the patient visit, meaning repeated visits could arise from the same individual. Only 22 derivation encounters had bacteriologically confirmed SBP, which limits precision and the stability of multivariable coefficients. The very high validation AUROC may partly reflect inclusion of the PMN threshold within both the diagnostic construct and the composite score. A separate 2025 machine-learning study illustrates growing interest in multivariable SBP diagnosis, but such models also require transparent external validation before bedside use.[23] Most importantly, the MR-proADM study addressed diagnosis; it did not prove that biomarker-guided management reduces renal failure, ACLF, or mortality.

Table 1. Selected evidence relevant to MR-proADM in SBP and severe infection

Study	Population	Key finding	Interpretation
Reuken et al., 2012	Decompensated cirrhosis at risk of infection	MR-proADM associated with short-term survival and appeared more informative than CRP.	Signal-generating cirrhosis-specific prognostic evidence; small research-letter dataset.
Andaluz-Ojeda et al., 2017	326 patients with severe sepsis or septic shock	AUROC 0.79 for 28-day mortality; performance persisted across SOFA strata.	Supports severity assessment, but not specific to cirrhosis or SBP.
Oussalah et al., 2025: derivation	236 cirrhosis patient visits; 22 bacteriologically confirmed SBP	Ascitic MR-proADM 3.14 vs 1.91 nmol/L; threshold >=2.50 nmol/L; AUROC 0.746.	Direct ascitic-fluid diagnostic evidence; limited event count.
Oussalah et al., 2025: validation	85 independent paracentesis visits	Composite SBP score AUROC 0.993.	Promising internal-external validation; needs multicenter external validation and impact testing.

Abbreviations: AUROC, area under the receiver operating characteristic curve; CRP, C-reactive protein; MR-proADM, mid-regional pro-adrenomedullin; SBP, spontaneous bacterial peritonitis; SOFA, Sequential Organ Failure Assessment.

Potential Clinical Roles

A first potential role is diagnostic support when the ascitic PMN count is near the treatment threshold, automated counting is unavailable, or prior antibiotics reduce culture yield. Ascitic MR-proADM may provide independent evidence of local infection-related stress. It must not be used to postpone antibiotics when PMN count and clinical findings already support SBP. Conversely, a low value should not overrule strong clinical suspicion, especially in immunologically blunted patients or after antimicrobial exposure.

A second role is severity assessment. Plasma MR-proADM may complement MELD-Na, Child-Pugh, ACLF grade, lactate, renal indices, and hemodynamic evaluation by indicating endothelial and microcirculatory stress. The biologically most attractive use is identifying a patient who appears only moderately ill but is entering a trajectory toward renal dysfunction or circulatory failure. This remains a hypothesis for SBP until prospective studies demonstrate incremental prognostic performance and define a clinically usable risk category.

A third role is serial monitoring. Declining concentrations might reflect recovery of endothelial function, whereas persistent elevation could indicate uncontrolled infection, resistant organisms, a second infectious focus, or evolving organ failure. Yet the kinetics of MR-proADM in SBP are insufficiently characterized, and no validated percentage change or repeat-testing interval exists. Daily or 48-hour measurement should therefore be considered investigational rather than routine.

A pragmatic future pathway would preserve current care: immediate paracentesis, PMN count, culture, blood cultures when indicated, antibiotics selected by acquisition setting and resistance risk, albumin according to established criteria, and active surveillance for kidney and organ failure. Current cirrhosis reviews and international ascites guidelines reinforce this sequence.[24,25,26] MR-proADM could then be layered onto the pathway as an adjunctive result. Any escalation triggered by the biomarker should be predefined and tested, for example closer monitoring, earlier critical-care review, broader microbiological assessment, or accelerated reassessment of antimicrobial adequacy. Biomarker-guided albumin or vasopressor therapy cannot currently be recommended because interventional evidence is absent.

Clinical usefulness also depends on turnaround time. A result returned after treatment and disposition decisions have been made offers limited diagnostic value, although it may still aid prognostication. Institutions considering MR-proADM should map the interval from paracentesis to centrifugation, analysis, verification, and clinical review. The rapid analytical time reported for automated platforms does not necessarily equal a rapid bedside decision. Round-the-clock availability, specimen transport, and integration into the electronic record are practical determinants of impact.

Cost effectiveness cannot be assumed. Added laboratory expenditure may be justified if testing prevents delayed recognition, unnecessary broad-spectrum antibiotics, avoidable intensive-care transfer, or organ failure. It may instead increase cost without changing care if results merely repeat information already available from PMN count, renal function, and clinical scores. Economic evaluation should therefore be embedded in prospective impact studies and should measure both patient outcomes and antimicrobial use.

Interpretive Pitfalls

MR-proADM should be interpreted in context. Renal dysfunction can elevate concentrations through impaired clearance and greater systemic stress. Advanced age, heart failure, systemic infection outside the peritoneum, and ACLF may also raise values. A high plasma concentration may therefore be prognostically meaningful without being anatomically specific. Ascitic measurement could improve local relevance, but concentration may still depend on vascular permeability, ascitic protein content, dilution, and the timing of paracentesis. Contemporary SBP cohorts also show that multidrug-resistant organisms and complications change over time and across centers, further limiting simple transport of a fixed threshold.[27,28,29,30]

Analytical standardization is equally important. Plasma, serum, and ascitic fluid are not interchangeable matrices. Laboratories must validate sample handling, storage, precision, reportable range, and quality control for the intended specimen. Published cutoffs should be reported with the assay platform, sampling time, case definition, and clinical setting. Applying 2.5 nmol/L outside the assay and population studied by Oussalah et al.[7] would be premature.

The intended use must also be explicit. Diagnostic discrimination, mortality prediction, and monitoring response are different claims and require different study designs. A marker can have

a statistically impressive AUROC yet add little to a readily available clinical model. Decision-curve analysis, calibration, net reclassification, cost, turnaround time, and the consequence of false-negative and false-positive results are as important as discrimination.

Research Priorities

Future studies should enroll consecutive patients with cirrhosis undergoing clinically indicated paracentesis at multiple centers and should distinguish community-acquired, healthcare-associated, and nosocomial infection. Case definitions must separate classic SBP, culture-negative neutrocytic ascites, bacterascites, and secondary peritonitis. The reference assessment should include standardized PMN counting, bedside culture inoculation, adjudication of alternative intra-abdominal sources, and documentation of antibiotics received before sampling.

Paired plasma and ascitic measurements would clarify whether the local compartment adds information beyond systemic MR-proADM. Sampling at baseline and predefined intervals could establish kinetics and determine whether change predicts treatment response. Models should adjust for renal function, ACLF, hemodynamics, liver severity, and other infection sites. Repeated admissions from the same patient require statistical methods that account for within-person correlation.

External validation should precede clinical adoption of the SBP score. Studies must report calibration and performance within clinically relevant subgroups, not only overall AUROC. Prophylaxis exposure also requires explicit documentation because contemporary national-cohort data suggest that recurrence and resistance patterns may differ from historical assumptions.[31] The final step should be an impact trial in which an explicit MR-proADM-guided pathway is compared with guideline-based care. Patient-centered outcomes should include time to effective treatment, acute kidney injury, ACLF, intensive-care transfer, length of stay, antimicrobial exposure, 28- or 90-day mortality, and cost effectiveness. Prospective sepsis evidence linking MR-proADM with organ damage and mortality can inform study design, but cirrhosis-specific thresholds and outcomes must be derived independently.[32]

Strengths and Limitations of the Evidence

The MR-proADM concept has a coherent biological basis and is supported by consistent prognostic associations across severe infection cohorts. Automated measurement is relatively rapid, and the recent ascitic-fluid study included both derivation and validation phases. These features justify further investigation in SBP.

Current evidence remains insufficient for routine decision-making. Cirrhosis-specific studies are few, sample sizes and event numbers are modest, and diagnostic definitions differ. Much of the prognostic rationale is extrapolated from heterogeneous sepsis populations. Optimal specimen, timing, threshold, and repeat-testing strategy have not been established. No trial has shown that acting on MR-proADM improves outcomes. The available data therefore support cautious adjunctive use in research settings rather than replacement of established diagnostic or therapeutic steps.

Conclusion

MR-proADM connects two central features of SBP in decompensated cirrhosis: infection-driven inflammation and endothelial-circulatory dysfunction. Ascitic MR-proADM has shown promising diagnostic performance, particularly when integrated with the PMN count and Child-Pugh severity, while systemic sepsis evidence supports its potential prognostic value. The biomarker should presently be regarded as complementary. Prompt paracentesis, ascitic PMN counting, culture, early appropriate antibiotics, albumin when indicated, and surveillance for organ failure remain the standards of care. Multicenter validation and biomarker-guided impact trials are required before MR-proADM can be assigned a routine role in SBP management.

References

1. Biggins SW, Angeli P, Garcia-Tsao G, et al. Diagnosis, evaluation, and management of ascites, spontaneous bacterial peritonitis and hepatorenal syndrome: 2021 practice guidance by the American Association for the Study of Liver Diseases. Hepatology. 2021;74(2):1014-1048.
2. Jalan R, D'Amico G, Trebicka J, Moreau R, Angeli P, Arroyo V. New clinical and pathophysiological perspectives defining the trajectory of cirrhosis. J Hepatol. 2021;75(suppl 1):S14-S26.
3. Moreau R, Jalan R, Gines P, et al. EASL Clinical Practice Guidelines on acute-on-chronic liver failure. J Hepatol. 2023;79(2):461-491.
4. Ferguson Toll J, Sola E, Perez MA, et al. Infections in decompensated cirrhosis: pathophysiology, management, and research agenda. Hepatol Commun. 2024;8(10):e0539.
5. Andaluz-Ojeda D, Nguyen HB, Meunier-Beillard N, et al. Superior accuracy of mid-regional proadrenomedullin for mortality prediction in sepsis with varying levels of illness severity. Ann Intensive Care. 2017;7(1):15.
6. Valenzuela-Sanchez F, Valenzuela-Mendez B, Rodriguez-Gutierrez JF, Estella-Garcia A, Gonzalez-Garcia MA. New role of biomarkers: mid-regional pro-adrenomedullin, the biomarker of organ failure. Ann Transl Med. 2016;4(17):329.
7. Oussalah A, Haghnejad V, Silva Rodriguez M, et al. Mid-regional pro-adrenomedullin: a rapid sepsis biomarker for diagnosing spontaneous bacterial peritonitis in cirrhosis. Eur J Clin Invest. 2025;55(6):e70021.
8. Tilg H, Adolph TE, Trauner M. Gut-liver axis: pathophysiological concepts and clinical implications. Cell Metab. 2022;34(11):1700-1718.
9. Zhou Z, Lv H, Lv J, et al. Alterations of gut microbiota in cirrhotic patients with spontaneous bacterial peritonitis: a distinctive diagnostic feature. Front Cell Infect Microbiol. 2022;12:999418.
10. Sort P, Navasa M, Arroyo V, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med. 1999;341(6):403-409.
11. Kumar R, Mehta G, Jalan R. Sepsis in liver failure patients: diagnostic challenges and recent advancements. World J Crit Care Med. 2025;14(2):101587.
12. Wejnaruemarn S, Susantitaphong P, Komolmit P, Treeprasertsuk S, Thanapirom K. Procalcitonin and presepsin for detecting bacterial infection and spontaneous bacterial peritonitis in cirrhosis: a systematic review and meta-analysis. World J Gastroenterol. 2025;31(6):99506.
13. Fortuny M, Sarrias MR, Torner M, et al. Systematic review of the role of calprotectin in cirrhosis. Eur J Clin Invest. 2024;54(2):e14111.
14. Khan S, Linganna M. Diagnosis and management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome. Cleve Clin J Med. 2023;90(4):209-213.
15. Li P, Wang C, Pang S. The diagnostic accuracy of mid-regional pro-adrenomedullin for sepsis: a systematic review and meta-analysis. Minerva Anestesiol. 2021;87(10):1117-1127.
16. Liang J, Cai Y, Shao Y. Comparison of presepsin and mid-regional pro-adrenomedullin in the diagnosis of sepsis or septic shock: a systematic review and meta-analysis. BMC Infect Dis. 2023;23(1):288.
17. Liu D, Xie L, Zhao H, Liu X, Cao J. Prognostic value of mid-regional pro-adrenomedullin in patients with community-acquired pneumonia: a systematic review and meta-analysis. BMC Infect Dis. 2016;16:232.
18. Christ-Crain M, Morgenthaler NG, Stolz D, et al. Pro-adrenomedullin to predict severity and outcome in community-acquired pneumonia. Crit Care. 2006;10(3):R96.
19. Spoto S, Basili S, Cangemi R, et al. Mid-regional pro-adrenomedullin can predict organ failure and prognosis in sepsis? Int J Mol Sci. 2023;24(24):17429.
20. Reuken PA, Kiehntopf M, Stallmach A, Bruns T. Mid-regional pro-adrenomedullin (MR-proADM): an even better prognostic biomarker than C-reactive protein to predict short-term survival in patients with decompensated cirrhosis at risk of infection? J Hepatol. 2012;57(5):1156-1158.
21. Piano S, Singh V, Caraceni P, et al. Epidemiology and effects of bacterial infections in patients with cirrhosis worldwide. Gastroenterology. 2019;156(5):1368-1380.e10.
22. Fernandez J, Prado V, Trebicka J, et al. Multidrug-resistant bacterial infections in patients with decompensated cirrhosis and acute-on-chronic liver failure in Europe. J Hepatol. 2019;70(3):398-411.
23. Khorsand B, Rajabnia M, Jahanian A, Fathy M, Taghvaei S, Houri H. Enhancing the accuracy and effectiveness of diagnosis of spontaneous bacterial peritonitis in cirrhotic patients: a machine learning approach utilizing clinical and laboratory data. Adv Med Sci. 2025;70(1):1-7.
24. Tapper EB, Parikh ND. Diagnosis and management of cirrhosis and its complications: a review. JAMA. 2023;329(18):1589-1602.
25. Aithal GP, Palaniyappan N, China L, et al. Guidelines on the management of ascites in cirrhosis. Gut. 2021;70(1):9-29.
26. European Association for the Study of the Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. J Hepatol. 2010;53(3):397-417.
27. Li H, Wieser A, Zhang J, et al. Patients with cirrhosis and SBP: increase in multidrug-resistant organisms and complications. Eur J Clin Invest. 2020;50(2):e13198.
28. Kremer WM, Gairing SJ, Kaps L, et al. Characteristics of bacterial infections and prevalence of multidrug-resistant bacteria in hospitalized patients with liver cirrhosis in Germany. Ann Hepatol. 2022;27(5):100719.
29. Bejar-Serrano S, Del Pozo P, Fernandez-de la Varga M, Benlloch S. Multidrug-resistant bacterial infections in patients with liver cirrhosis in a tertiary referral hospital. Gastroenterol Hepatol. 2019;42(4):228-238.
30. Trad N, Mohamed G, Bizid S, Abdallah HB, Bouali R, Abdelli MN. Clinical impact of multidrug-resistant bacterial infections in patients with cirrhosis. Future Sci OA. 2024;10(1):FSO945.

31. Silvey S, Patel N, Tsai SY, et al. Higher rate of spontaneous bacterial peritonitis recurrence with secondary spontaneous bacterial peritonitis prophylaxis compared with no prophylaxis in two national cirrhosis cohorts. Am J Gastroenterol. 2025;120(5):1066-1075.
32. Bernal-Morell E, Garcia-Villalba E, Vera MDC, et al. Usefulness of midregional pro-adrenomedullin as a marker of organ damage and predictor of mortality in patients with sepsis. J Infect. 2018;76(3):249-257.