

Sepsis Biomarkers Beyond Procalcitonin: Presepsin, MR-proADM and the Decision They Are Meant to Change

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Abstract

Procalcitonin remains the most widely adopted sepsis biomarker, but two further candidates -- presepsin and mid-regional pro-adrenomedullin (MR-proADM) -- are increasingly proposed for roles procalcitonin does not fill well: earlier detection at first presentation and prognostic risk stratification, respectively. We systematically reviewed 41 studies comparing presepsin, MR-proADM or both against procalcitonin for sepsis diagnosis, severity stratification or mortality prediction, and organised the evidence by the specific clinical decision each biomarker is proposed to change rather than by diagnostic accuracy alone. Presepsin showed a modest but consistent advantage over procalcitonin for very early sepsis detection within the first three hours of presentation, while MR-proADM outperformed both for 28-day mortality prediction but added little to the initial diagnostic decision. Neither biomarker's evidence base currently supports replacing procalcitonin outright; the more defensible role for each is additive, targeted at the specific decision point where procalcitonin itself performs least well.

Keywords: Sepsis; Presepsin; MR-proADM; Procalcitonin; Biomarker; Systematic review

Introduction

Procalcitonin's adoption as a sepsis biomarker over the past two decades has not resolved two specific decision points where its performance is acknowledged to be weakest: distinguishing early sepsis from a non-infective inflammatory state within the first few hours of presentation, when procalcitonin has not yet had time to rise, and stratifying mortality risk among patients already diagnosed with sepsis, where procalcitonin's kinetics correlate only loosely with outcome.^[1] Presepsin, a soluble CD14 subtype released earlier in the innate immune response, and mid-regional pro-adrenomedullin (MR-proADM), a stable surrogate for a vasoactive peptide implicated in endothelial and microvascular dysfunction, have both been proposed to address one of these two gaps specifically, rather than to replace procalcitonin generally.^[2]

We conducted a systematic review organised around this decision-specific framing -- early detection against risk stratification -- rather than around aggregate diagnostic accuracy

figures alone, on the premise that a biomarker's evidence should be read against the specific clinical question it is proposed to answer.

Procalcitonin itself took roughly two decades to move from biomarker candidate to a widely adopted, guideline-referenced clinical tool, and that adoption trajectory offers a useful frame for assessing presepsin and MR-proADM: both are now well past the initial discovery stage and have accumulated a substantial body of comparative evidence against procalcitonin, but neither has yet achieved the same breadth of guideline endorsement or routine clinical availability that procalcitonin now enjoys in most health systems.^[1]

The distinction between a diagnostic and a prognostic biomarker role, central to this review's organising framework, matters because the two roles place different demands on a biomarker's performance characteristics: a diagnostic biomarker needs to discriminate sepsis from its mimics at the point of first presentation, often under considerable time pressure, while a

prognostic biomarker needs to stratify risk among patients already known to have sepsis, a fundamentally different statistical and clinical task that a biomarker excelling at one role need not excel at the other.^{[9][10]}

This review's central methodological contribution is organising the available comparative evidence explicitly by this decision-point distinction, rather than reporting pooled diagnostic accuracy figures that blend studies addressing fundamentally different clinical questions into a single summary statistic that answers neither question well.

Methods

We searched three databases for studies published to December 2023 comparing presepsin, MR-proADM or both against procalcitonin in adult patients with suspected or confirmed sepsis, for either early diagnostic discrimination (within six hours of presentation) or 28-day mortality prediction. Forty-one studies met inclusion criteria: 24 addressing early diagnosis, 19 addressing mortality prediction, with some studies contributing to both. Risk of bias was assessed using QUADAS-2 for diagnostic studies and a prognostic-study-specific adaptation for mortality studies.^{[3][4]}

Database searches covered MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials, supplemented by manual reference-list screening of included studies and relevant prior systematic reviews to identify any eligible study the database search strategy might have missed. Search terms combined controlled vocabulary and free-text terms for sepsis, presepsin, MR-proADM, and procalcitonin, without language restriction, though all 41 included studies were ultimately published in English.

Study selection followed a two-stage screening process: titles and abstracts were screened independently by two reviewers against the inclusion criteria, followed by full-text review of all studies passing initial screening, with disagreements at either stage resolved by discussion or, where necessary, arbitration by a third reviewer. Data extraction used a standardised form capturing study design, patient population, sepsis definition used, biomarker assay platform, and the specific diagnostic or prognostic outcome reported.

Where a study reported sufficient data to calculate a pooled area under the receiver operating characteristic curve alongside comparable studies, a random-effects meta-analytic pooling was performed; where heterogeneity in sepsis definition, patient population, or outcome timing was judged too substantial for meaningful pooling, findings are reported narratively by study rather than forced into a single pooled estimate that would obscure that heterogeneity.

Results: Early Diagnosis

Across 24 studies addressing diagnosis within six hours of presentation, presepsin showed a pooled area under the curve modestly but consistently higher than procalcitonin at the earliest sampling point studied (typically one to three hours), narrowing to little difference between the two markers by six hours as procalcitonin's own kinetics caught up.^[5] The advantage was most pronounced in studies specifically enrolling patients within the first hour of emergency department presentation, where procalcitonin had the least time to rise.

MR-proADM's diagnostic performance for early sepsis detection was similar to procalcitonin's across the studies reviewed, without a clear early-detection advantage comparable to presepsin's; MR-proADM's evidence base for this specific decision point is both smaller and less favourable than its evidence base for mortality prediction, discussed below.^[6]

Results: Mortality Prediction

Across 19 studies addressing 28-day mortality prediction in patients already diagnosed with sepsis, MR-proADM outperformed procalcitonin consistently, with several studies reporting MR-proADM as an independent predictor of mortality after adjustment for standard severity scores including SOFA and APACHE II.^{[7][8]} Presepsin's evidence for mortality prediction was more mixed, with several studies reporting no independent predictive value once severity scores were accounted for, consistent with presepsin's proposed mechanism reflecting immune activation timing rather than the vascular dysfunction MR-proADM is thought to track.^[9]

Biomarker	Early diagnosis (<3h)	Mortality prediction (28d)
Procalcitonin	Reference comparator	Reference comparator
Presepsin	Modest, consistent advantage	Mixed; mostly not independent
MR-proADM	No clear advantage	Consistent, independent advantage

Table 1: Summary of comparative performance by biomarker and decision point across the 41 included studies.

Table 1 condenses this review's central organising finding into a single view: presepsin and MR-proADM show essentially mirror-image performance profiles across the two decision points examined, each showing its clearest advantage over procalcitonin at the decision point the other marker does not address well, which is precisely the pattern that supports this review's recommendation for an additive, decision-specific implementation rather than a routine combined panel.

Among the 24 early-diagnosis studies, fourteen enrolled patients specifically within the first three hours of emergency department presentation, and it was within this earliest-presentation subset that presepsin's advantage over procalcitonin was most pronounced; studies enrolling patients later, at four to six hours post-presentation, showed a

progressively narrower gap between the two markers, consistent with procalcitonin's own kinetics beginning to catch up to presepsin's earlier rise.^[5]

Among the 19 mortality-prediction studies, twelve reported MR-proADM retaining independent predictive value after adjustment for a standard severity score such as SOFA or APACHE II, compared with only four of the studies examining presepsin for the same outcome, reinforcing that MR-proADM's mortality-prediction advantage is not merely a reflection of overall illness severity that a standard severity score already captures.^{[7][8]}

Discussion

Organising this evidence by decision point rather than by aggregate diagnostic accuracy clarifies what each biomarker's literature actually supports: presepsin's advantage is narrow, early, and diagnostic; MR-proADM's advantage is broader, later, and prognostic. Neither pattern supports a laboratory replacing procalcitonin outright with either marker, and the more defensible implementation for a laboratory considering either is additive -- presepsin alongside procalcitonin specifically for patients tested within the first few hours of presentation, MR-proADM specifically once a sepsis diagnosis is established and risk stratification, not diagnosis, is the question.^[10]

A laboratory introducing either marker without this decision-specific framing risks ordering it routinely alongside procalcitonin for every sepsis presentation, adding cost without adding the specific incremental value the evidence actually supports; a targeted order set restricting presepsin to early presentations and MR-proADM to risk-stratification decisions after diagnosis would better match implementation to evidence than an unrestricted panel would.

This review is limited by substantial heterogeneity in sepsis definitions across the included studies, several of which predate the Sepsis-3 consensus definition, and by the relatively small number of studies for MR-proADM's early-diagnosis role specifically, which limits confidence in the negative finding reported for that particular comparison.

Biological Basis for the Observed Performance Differences

Understanding why presepsin and MR-proADM show such distinctly different performance profiles across the two decision points examined in this review requires some grounding in each biomarker's underlying biology, which the Discussion above references briefly but is worth developing more fully.

Presepsin is a soluble fragment of CD14, a receptor expressed on monocytes and macrophages that is cleaved and released into circulation rapidly upon phagocytic activation during the innate immune response to infection; this rapid release mechanism explains presepsin's early-rise kinetics relative to procalcitonin, which depends on a somewhat slower induction pathway involving multiple cytokine-mediated

signalling steps before significant procalcitonin release occurs.^[9]

MR-proADM is a stable fragment derived from the precursor of adrenomedullin, a peptide hormone with vasodilatory and endothelial-protective properties that is upregulated during the vascular and microcirculatory dysfunction characteristic of sepsis progression toward septic shock; this mechanistic link to vascular dysfunction, rather than to the initial immune activation presepsin reflects, explains why MR-proADM tracks mortality risk -- which correlates closely with the degree of vascular and organ dysfunction a patient develops -- more closely than it tracks the simple presence or absence of infection at initial presentation.^[10]

This mechanistic distinction is, in our view, the most useful single piece of context for a clinician or laboratory deciding how to implement either biomarker: presepsin's biology predicts it should excel at early detection and predicts it should not necessarily track mortality risk well, while MR-proADM's biology predicts the reverse, and the empirical findings summarised in Table 1 are consistent with exactly these biologically motivated predictions rather than representing an unexplained empirical curiosity.

Proposed Implementation Model: Targeted Order Sets

Translating this review's decision-specific findings into a practical laboratory implementation requires more than a general recommendation against routine combined ordering; we propose a concrete targeted order-set model below.

For patients presenting within the first three hours of a suspected sepsis episode, a targeted early-presentation order set would include presepsin alongside procalcitonin, restricted specifically to this time window given the narrowing advantage shown in the studies reviewed as time since presentation increases; ordering presepsin routinely for patients presenting later than three to four hours post-onset would, on this evidence, add cost without the diagnostic advantage the earliest-presentation evidence supports.^[5]

For patients with an already-established sepsis diagnosis, a separate risk-stratification order set would include MR-proADM specifically at the point severity assessment and disposition planning occurs, rather than at initial presentation, reflecting the evidence base's clear concentration of MR-proADM's advantage in the mortality-prediction rather than diagnostic role.^[7]

This two-order-set model requires the ordering clinician or electronic order-entry system to distinguish between these two clinical moments -- initial presentation versus post-diagnosis risk stratification -- which is a workflow distinction most sepsis care pathways already make implicitly through their staged structure, making this targeted model a relatively modest addition to existing sepsis pathway infrastructure rather than a wholesale redesign.

A laboratory implementing this model should expect presepsin ordering volume to concentrate in the emergency department and MR-proADM ordering volume to concentrate in

the intensive care unit or step-down ward settings where risk stratification decisions are typically made, and should structure its analytical capacity and turnaround-time expectations for each marker accordingly.

Assay Platform Considerations

A further practical consideration for a laboratory implementing either biomarker, distinct from the clinical decision-point framing discussed elsewhere in this report, concerns the analytical platforms on which presepsin and MR-proADM are measured and how these compare to the widely deployed procalcitonin assay infrastructure most laboratories already operate.

Procalcitonin is now available on a wide range of automated immunoassay platforms from multiple manufacturers, reflecting its mature, high-volume adoption across the laboratory medicine field; most laboratories already offering procalcitonin testing can therefore expect rapid turnaround and routine-level analytical support for that specific marker.^[1]

Presepsin and MR-proADM, by contrast, remain available on a comparatively narrower range of platforms, with presepsin more commonly available on point-of-care or rapid turnaround platforms suited to its proposed early-diagnosis role, and MR-proADM more commonly measured on platforms optimised for batch rather than rapid single-sample processing, consistent with its proposed prognostic rather than time-critical diagnostic role.^[6]

A laboratory considering the targeted implementation model proposed above should confirm that its chosen presepsin platform genuinely supports the rapid, near-patient turnaround the early-diagnosis use case demands, since a presepsin result returned with the same turnaround time as a batch-processed MR-proADM result would undermine the specific time-sensitive clinical value this review's early-diagnosis evidence supports.

Laboratories without existing experience with either biomarker platform should budget implementation time not only for reagent procurement and analyser validation, but for staff training on assay-specific preanalytical requirements, since both presepsin and MR-proADM, like many less widely established immunoassays, carry specific sample handling and stability requirements that may differ from the procalcitonin workflow staff are already familiar with.

Comparison with Previously Published Meta-Analyses

This systematic review sits alongside several prior, more narrowly scoped meta-analyses of presepsin or MR-proADM individually, and comparing its findings against that prior literature helps confirm the robustness of this review's decision-specific framing.

Zhang and colleagues' earlier systematic review and meta-analysis of presepsin for sepsis diagnosis reported a pooled diagnostic accuracy broadly consistent with the early-diagnosis advantage identified in this review, though their analysis did not

stratify findings by time since presentation in the detailed way this review does, potentially understating how concentrated presepsin's advantage actually is within the earliest presentation window.^[5]

Kondo and colleagues' comparative meta-analysis of procalcitonin and presepsin similarly found presepsin broadly comparable to, rather than dramatically superior to, procalcitonin when pooled across all time points, a finding consistent with this review's observation that presepsin's advantage narrows considerably beyond the earliest presentation window and is easily diluted in an analysis that does not stratify by time since presentation.^[2]

Andaluz-Ojeda and colleagues', and separately Elke and colleagues', work on MR-proADM for mortality prediction both reported findings consistent with this review's identification of MR-proADM's mortality-prediction advantage as independent of standard severity scores, reinforcing that this is a well-replicated finding across multiple independent study groups rather than an artefact of any single study or research group's methodology.^{[7][8]}

This review's distinct contribution relative to these single-biomarker prior analyses is the explicit, side-by-side decision-point comparison presented in Table 1, directly contrasting both biomarkers' performance at both decision points within a single analytic framework, which none of the single-biomarker prior reviews cited above were designed to provide.

Economic Considerations for Biomarker Adoption

Adopting either presepsin or MR-proADM as a targeted addition to procalcitonin carries a direct reagent and analyser cost that should be weighed against the decision-specific clinical value this review's evidence supports.

Both presepsin and MR-proADM typically carry a materially higher per-test reagent cost than procalcitonin, reflecting their comparatively lower testing volume and, in some cases, requirement for a dedicated or less widely available analyser platform; a laboratory considering adoption should budget for this higher per-test cost explicitly rather than assuming cost parity with procalcitonin.^[6]

The targeted order-set model proposed above is specifically designed to limit this added cost to the patient population where the evidence supports genuine incremental clinical value -- early presenters for presepsin, already-diagnosed patients needing risk stratification for MR-proADM -- rather than extending the added cost across every sepsis presentation regardless of timing or clinical question, which a routine combined panel approach would do.

Against this added reagent cost, MR-proADM's mortality-prediction value, if acted upon through earlier escalation of care for high-risk patients identified by the marker, could plausibly offset its cost through improved outcomes or reduced length of stay for the subset of patients it correctly identifies as higher-risk than standard severity scores along

would suggest, though this review's scope did not extend to directly costing this downstream economic argument.

Patient Population Heterogeneity Across Included Studies

Beyond the sepsis-definition heterogeneity already noted in the Discussion, the 41 included studies also varied considerably in patient population, a further source of heterogeneity worth detailing given its relevance to how broadly this review's findings should be expected to generalise.

Several included studies enrolled exclusively intensive care unit patients already meeting severe sepsis or septic shock criteria at enrolment, a population with a necessarily higher baseline mortality and illness severity than the broader emergency department population other included studies enrolled from the point of initial presentation, before a definitive sepsis diagnosis was established.^[4]

This population difference bears directly on how each biomarker's findings should be interpreted: MR-proADM's mortality-prediction advantage was demonstrated predominantly in intensive-care-enrolled populations already known to have sepsis, which is exactly the population the risk-stratification role proposed in this report's implementation model targets, while presepsin's early-diagnosis advantage was demonstrated predominantly in emergency-department populations at the point of undifferentiated presentation, again matching the specific role proposed for it.

A smaller number of included studies enrolled paediatric or immunocompromised populations specifically, and this review's pooled findings and proposed implementation model should be understood as most directly applicable to the general adult sepsis population that dominates the included evidence base, with paediatric or immunocompromised-specific adoption decisions requiring separate consideration of the smaller, population-specific evidence available for each biomarker in those populations.

Study Limitations

Beyond the heterogeneity and small-sample limitations already noted in the Discussion, this review carries several further limitations worth stating explicitly.

This review restricted inclusion to studies published in English, and while the search strategy did not impose a language restriction at the search stage, no non-English study ultimately met full inclusion criteria, raising the possibility that relevant non-English-language evidence exists but was not captured by this review's search and screening process.

The decision-specific organising framework used in this review, while we believe clarifies the evidence considerably relative to a single pooled accuracy figure, necessarily involves a classification judgement about which decision point each included study primarily addresses, and a study addressing both decision points, or addressing a decision point not cleanly

captured by either category, required a classification choice that another reviewer might have made differently.

This review did not perform a formal cost-effectiveness analysis of the targeted implementation model proposed above, and the economic considerations discussed in this report should be read as a qualitative framing of the relevant cost and value considerations rather than as a quantified cost-effectiveness conclusion.

Risk of Bias Assessment Findings

The Methods notes that risk of bias was assessed using QUADAS-2 for diagnostic studies and a prognostic-study-specific adaptation for mortality studies; the results of this assessment, not detailed elsewhere in this report, are worth summarising given their bearing on how confidently this review's findings should be interpreted.

Among the 24 early-diagnosis studies, risk of bias on the QUADAS-2 patient selection domain was judged low in the majority but unclear or high in a meaningful minority, most often because the study did not clearly report whether patients were enrolled consecutively or through some less systematic selection process that could introduce selection bias into the reported diagnostic accuracy estimates.^[3]

The reference standard domain, assessing whether the sepsis diagnosis used as the comparison standard was itself applied without knowledge of the biomarker result under study, showed generally better performance, with most studies reporting blinded or at least independently adjudicated reference-standard diagnosis, reducing concern that the reported diagnostic accuracy estimates were inflated by circularity between the biomarker result and the diagnosis it was being compared against.

Among the 19 mortality-prediction studies, the most common risk of bias concern, assessed using the Hayden and colleagues' prognostic-study framework, was incomplete reporting of how missing outcome data were handled, which, where present, could bias the reported association between biomarker level and mortality in either direction depending on whether missingness was related to the biomarker result itself.^[4]

Overall, this review judged the included evidence base, while not without methodological limitations typical of this clinical research area, sufficiently consistent in direction and magnitude across studies with differing individual risk-of-bias profiles to support the pattern reported in Table 1 and discussed throughout this report, rather than concluding the evidence base was too compromised by bias to draw any conclusion.

Heterogeneity and the Decision to Pool or Report Narratively

The Methods section notes that a pooling-versus-narrative decision rule was applied separately to each biomarker and each clinical decision point rather than adopted uniformly across the whole review; the reasoning behind that decision, and its practical consequences for how Table 1 should be read, are worth making explicit.

Statistical heterogeneity across the included presepsin early-diagnosis studies, assessed using I-squared, was high enough in several candidate pooled analyses that a single summary sensitivity and specificity estimate risked implying a precision the underlying studies did not actually support, particularly once studies using different presepsin assay platforms and different reference-standard sepsis definitions were combined.^[3]

Where heterogeneity was judged too high for a clinically meaningful pooled point estimate, this review instead reported the range and central tendency of individual study results narratively, as reflected in the qualitative categories used in Table 1, a choice that sacrifices the apparent precision of a single pooled number in exchange for not overstating the certainty of the underlying evidence base.

For MR-proADM mortality-prediction studies, heterogeneity was generally lower, in part because outcome definitions, death at a fixed 28-day horizon, were more consistent across studies than the diagnostic reference standards used in the early-diagnosis literature, allowing somewhat more confidence in the qualitative mortality-prediction pattern reported here than in the early-diagnosis pattern.

Readers using Table 1 to inform local implementation decisions should therefore weight the mortality-prediction column somewhat more heavily than the early-diagnosis column when precision matters to the decision at hand, reflecting the differing statistical confidence underlying each column rather than treating both as equivalently precise summary judgements.

Implications for Antimicrobial Stewardship Programmes

Although this review's primary focus is diagnostic and prognostic performance, the targeted implementation model proposed above has direct implications for antimicrobial stewardship that merit separate comment.

A biomarker panel capable of improving early sepsis detection without increasing false-positive escalations could, in principle, support more confident early empirical antibiotic initiation in genuinely septic patients while also supporting more confident de-escalation or discontinuation in patients whose presentation initially raised concern but whose biomarker trajectory and clinical course do not support ongoing infection, a dual effect that is often lost when a biomarker's stewardship value is framed only in terms of antibiotic reduction.^[10]

Conversely, a mortality-prediction biomarker such as MR-proADM does not, on its own, provide evidence for or against infection, and stewardship programmes should take care not to conflate a high MR-proADM-predicted mortality risk with a stronger case for broad-spectrum empirical therapy; the two questions, how likely is this patient to die, and how likely is this presentation to be infective, are related but distinct, and this review's scope was limited to the first.

Any local protocol built on this review's recommendations should therefore route presepsin results toward antibiotic initiation and de-escalation decisions specifically, and route MR-proADM results toward escalation-of-care and monitoring-intensity decisions specifically, rather than presenting both biomarkers to clinicians as general-purpose sepsis severity indicators interchangeable with one another.

Comparison Across Care Settings: Emergency Department Versus Intensive Care

The included studies were drawn from both emergency department and intensive care unit settings, and this review's findings should not be assumed to transfer uniformly between the two.

Emergency department studies generally enrolled a broader population spanning the full range of illness severity at first presentation, including many patients ultimately found not to have sepsis, a population in which the early-diagnosis question this review addresses is most clinically relevant and most difficult, since the diagnostic uncertainty is greatest at that point in the care pathway.^[3]

Intensive care unit studies, by contrast, generally enrolled patients in whom a sepsis diagnosis was already established or strongly suspected on admission, making the mortality-prediction question this review addresses more directly applicable than the early-diagnosis question, since the diagnostic work in that setting has typically already been substantially completed by the time biomarker results are available.

This setting-dependent alignment between each biomarker's strongest evidence and each setting's most pressing clinical question is, in our view, a further argument for the decision-specific implementation model proposed above: presepsin ordering concentrated in the emergency department at initial presentation, and MR-proADM ordering concentrated in the intensive care unit once a sepsis diagnosis is established, rather than a uniform ordering policy applied identically across both settings.

Interaction with Existing Sepsis Screening and Early-Warning Tools

Most participating sites already operate some form of sepsis screening based on vital-sign early-warning scores or structured triage criteria, and any biomarker-based addition to practice must be considered in relation to, rather than in isolation from, these existing tools.

Vital-sign-based screening tools are intentionally sensitive and non-specific, designed to flag a broad population for further assessment rather than to confirm a diagnosis, and the early-diagnosis role proposed for presepsin in this review is best understood as a second-tier test applied after a positive screening result, narrowing a broad flagged population toward a smaller group in whom empirical treatment is more confidently indicated, rather than as a replacement for vital-sign screening itself.^[3]

This sequential positioning matters for interpreting this review's reported diagnostic accuracy estimates, most of which were derived in populations already selected by some form of clinical suspicion or screening trigger rather than in wholly unselected populations, meaning the reported performance should be understood as performance within a pre-screened population rather than as performance against an undifferentiated general population.

Similarly, MR-proADM's mortality-prediction role sits naturally alongside, rather than in competition with, existing severity scoring systems such as SOFA or APACHE II, several of the included mortality-prediction studies explicitly evaluated MR-proADM as an addition to an existing severity score rather than as a standalone predictor, with the incremental predictive value of that addition, rather than MR-proADM's standalone performance, being the more clinically relevant finding for sites that already calculate a severity score as standard practice.^[4]

Sites considering adoption of either biomarker should therefore map the proposed new test explicitly onto their existing screening and scoring workflow, identifying the specific point in that workflow at which the new biomarker result would be expected to change a decision that the existing tools alone would not already have prompted, rather than introducing the biomarker as an additional, loosely integrated data point alongside unchanged existing practice.

Reader Guidance for Applying This Review Locally

Given the decision-specific framing adopted throughout this review, we close this section with brief, practical guidance for a laboratory or clinical team deciding whether and how to act on its findings.

A team primarily concerned with shortening time-to-antibiotics in an emergency department population with diagnostic uncertainty in the first few hours after presentation should focus on the early-diagnosis evidence summarised for presepsin, and should not expect a comparable diagnostic benefit from MR-proADM, whose evidence base for this specific question was the weakest of the three decision points examined.^[3]

A team primarily concerned with risk-stratifying already-diagnosed septic patients for escalation of care, intensity of monitoring, or early goals-of-care discussion should focus on the mortality-prediction evidence summarised for MR-proADM, which this review found the most consistent of the patterns

examined, and should not expect presepsin to add comparable prognostic information once a sepsis diagnosis is already established.^[4]

Teams considering both biomarkers together should budget for the assay-platform and governance considerations discussed above before committing to adoption, since the practical burden of introducing either test is similar regardless of which specific clinical question it is being introduced to answer, and that burden should be weighed against the comparatively narrow, decision-specific benefit this review's evidence base actually supports rather than against a broader, less well-supported claim of general sepsis-biomarker value.

Future Directions

Several extensions of this review's evidence synthesis would strengthen the case for, or against, the targeted implementation model proposed in this report.

A prospective implementation study directly testing the two-order-set targeted model proposed above, comparing clinical and economic outcomes against a standard procalcitonin-only pathway, would provide direct evidence for whether the decision-specific implementation this review recommends produces the clinical and economic benefits its underlying evidence base suggests it should.^[10]

Further primary research specifically addressing MR-proADM's performance for early diagnosis, the decision point where this review found its evidence base smallest and least favourable, would help confirm whether this is a genuine absence of diagnostic value or simply an under-studied question relative to MR-proADM's better-established mortality-prediction role.

Finally, as newer candidate sepsis biomarkers continue to emerge, we would recommend any future comparative evidence synthesis adopt a similar decision-specific organising framework from the outset, rather than defaulting to pooled aggregate diagnostic accuracy reporting that this review's findings suggest can obscure more than it reveals when a biomarker's value is concentrated at one specific clinical decision point rather than distributed evenly across the sepsis care pathway.

Conclusion

Presepsin offers a modest, time-limited advantage over procalcitonin for sepsis detection within the first few hours of presentation, while MR-proADM offers a more consistent advantage for 28-day mortality prediction once sepsis is already diagnosed. Evidence for either marker supports a targeted, decision-specific addition to procalcitonin rather than a routine combined panel or an outright replacement.

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