

# Prognostic Utility and Clinical Impact of Soluble Urokinase Plasminogen Activator Receptor in Adult Emergency and Acute-Care Patients: A Systematic Review and Narrative Synthesis

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## Abstract

Soluble urokinase plasminogen activator receptor (suPAR) reflects systemic immune activation and biological vulnerability and has been proposed as a cross-diagnostic prognostic biomarker in emergency care. We systematically reviewed full-text English-language reports published from 1 January 2015 through 20 July 2026 in PubMed/MEDLINE and Scopus. Eligible studies measured plasma or serum suPAR at emergency-department presentation, first acute medical contact, or a directly linked prehospital encounter and reported mortality, deterioration, disposition, length of stay, readmission, incremental prediction, or clinical-impact outcomes. The searches identified 130 records (PubMed/MEDLINE, 66; Scopus, 64). After removal of 39 duplicates, 91 unique records were screened, 54 reports were assessed as full texts, and 43 reports representing 34 coded cohort families were included. Because assay platforms, exposure scales and cut-offs, populations, outcome horizons, effect measures, adjustment sets, and overlapping cohorts were not sufficiently commensurate for a clinically interpretable pooled estimate, the evidence was synthesized narratively using a structured SWiM approach. Higher suPAR was generally associated with short- and longer-term mortality across heterogeneous populations, although residual confounding, assay differences, data-derived cut-offs, and limited external validation reduced certainty. Reported cut-offs were study-specific: <4 ng/mL was evaluated for low-risk enrichment in acute medical and short-stay cohorts, 6 ng/mL in suspected-infection and other acute-care cohorts, 8 ng/mL in one prehospital mortality study, and 12 ng/mL with qSOFA = 1 in the SUPERIOR pathway. Because assay platforms, populations, outcomes, and threshold derivation/validation strategies differed, no universal decision threshold was supported. suPAR improved discrimination or reclassification beyond NEWS, qSOFA, or other clinical models in some studies, but prediction-model risk of bias was frequently high. A large cluster-randomized trial found no mortality benefit from routine biomarker availability, and evidence for discharge, length of stay, readmission, or protocolized treatment remained context-dependent. Certainty was very low for short-term prognostic association, incremental prediction, and most clinical-impact outcomes, whereas the available evidence was insufficient to support a universal suPAR decision threshold; certainty was moderate for the absence of a mortality benefit from routine biomarker availability. suPAR may complement structured acute-care assessment but should not be used as a standalone admission, discharge, intensive care, or treatment rule.



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**Keywords:** soluble urokinase plasminogen activator receptor; suPAR; emergency department; acute care; prognosis; mortality; disposition; clinical impact; systematic review

## 1. Introduction

Rapid prognostic assessment is central to emergency department (ED) and acute medical practice. Clinicians must identify patients at risk of deterioration or death while avoiding unnecessary admission among patients who can be managed safely in ambulatory or short-stay pathways. Clinical examination, vital signs, validated early-warning scores, and routine biomarkers remain the foundation of decision-making, but their performance varies across heterogeneous acute-care populations.

Soluble urokinase plasminogen activator receptor (suPAR) is the circulating form of the membrane-bound urokinase receptor (uPAR/CD87). Plasma concentrations rise with immune activation, endothelial dysfunction, chronic inflammation, comorbidity burden, renal dysfunction, and adverse long-term outcomes [1–3]. Because suPAR captures both acute inflammatory activity and pre-existing biological vulnerability, it may provide cross-diagnostic prognostic information but may also be strongly confounded by age, renal function, smoking, frailty, and chronic disease.

Acute-care investigations have evaluated suPAR in unselected admissions, infection and sepsis, cardiovascular presentations, respiratory disease, trauma, COVID-19, and prehospital cohorts [4–46]. A previous systematic review and meta-analysis reported associations with mortality, readmission, length of stay, and early discharge [47]. Important uncertainties remain regarding cohort overlap, transportability of proposed thresholds, incremental value beyond validated scores, prediction-model bias, and whether suPAR-supported management improves patient-important outcomes.

The present review extends the evidence base through 20 July 2026 and adds methodological elements beyond the 2023 meta-analysis. It separates prognostic-factor association from incremental prediction and clinical impact; applies PROBAST to prediction-model analyses; maps reports to cohort families to avoid double counting; incorporates null and weak findings; evaluates the transportability of reported study-specific thresholds; and grades certainty separately for each outcome. The review is clinically oriented rather than methodological: its purpose is to determine which suPAR findings are sufficiently robust to inform acute-care risk stratification, which proposed thresholds or models remain context-specific, and which questions require prospective validation before bedside implementation.

The objective of this review was to synthesize contemporary evidence from 2015 through 20 July 2026 on suPAR measured at ED presentation or at the first acute-care contact in adults. We separated (i) prognostic-factor association, (ii) incremental prediction, and (iii) clinical impact of biomarker availability or a prespecified suPAR-supported pathway. Prespecified outcomes were mortality, deterioration or intensive care requirement, admission or early discharge, length of stay, readmission, prediction-model performance, and clinical-impact outcomes.

## 2. Materials and Methods

### 2.1. Protocol, Reporting, and Review Scope

This review was conducted and reported with reference to PRISMA 2020, PRISMA-S, and the Synthesis Without Meta-analysis (SWiM) guideline [48–50]. The protocol was not prospectively registered. The analytical framework, eligibility criteria, outcomes, risk-of-bias tools, and synthesis groups are reported transparently in the manuscript and

Supplementary Materials. PRISMA 2020 and PRISMA-S reporting items are mapped in Supplementary Table S11. The publication period was restricted to 1 January 2015 through 20 July 2026 to focus on contemporary acute-care pathways and assays. A concise overview of the methodological frameworks and appraisal tools used in the review, together with their specific role, is provided in Supplementary Table S13.

## 2.2. Eligibility Criteria and Review Questions

Eligibility was defined using a PICOTS framework. Prognostic-factor studies evaluated the association of admission suPAR with an eligible outcome. Incremental-prediction studies evaluated whether suPAR improved a clinical score or a multivariable model. Clinical-impact studies compared suPAR availability or a prespecified suPAR-supported pathway with usual care. Conference abstracts, protocols, reviews, diagnostic-only studies, and reports without an eligible acute-care outcome were excluded. The PICOTS-based eligibility criteria are summarized in Table 1.

**Table 1.** PICOTS-based eligibility criteria.

| Domain                 | Inclusion Criteria                                                                                                                                            | Exclusion Criteria                                                                                          |
|------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|
| Population             | Adults aged 18 years or older presenting to an ED, acute medical unit, short-stay unit, or prehospital service directly linked to acute care.                 | Pediatric populations; exclusively outpatient, elective, rehabilitation, ICU-only, or chronic-care cohorts. |
| Index factor           | Plasma or serum suPAR measured at ED presentation or first acute-care contact.                                                                                | suPAR measured only after treatment initiation or during later follow-up.                                   |
| Prognostic outcomes    | In-hospital or 28-, 30-, or 90-day mortality; longer-term mortality; deterioration; ICU requirement; admission; early discharge; length of stay; readmission. | Diagnostic accuracy alone or outcomes unrelated to prognosis/disposition at the index encounter.            |
| Incremental prediction | Addition of suPAR to a validated score, routine predictors, or a multivariable model.                                                                         | Single-marker association without a comparative prediction question.                                        |
| Clinical impact        | Comparison of suPAR availability or a prespecified suPAR-supported pathway with usual care.                                                                   | Association or discrimination without a management comparison.                                              |
| Design                 | Prospective or retrospective cohort; registry; randomized trial; non-randomized implementation study.                                                         | Case report, small case series, protocol, editorial, narrative/systematic review, or abstract-only report.  |
| Publication            | Full-text peer-reviewed report in English, 1 January 2015–20 July 2026.                                                                                       | Non-English report, abstract only, or outside the prespecified period.                                      |

Abbreviations: ED, emergency department; ICU, intensive care unit; suPAR, soluble urokinase plasminogen activator receptor.

## 2.3. Information Sources and Search Strategy

PubMed/MEDLINE and Scopus were searched from 1 January 2015 through 20 July 2026. Search strings combined suPAR synonyms with terms related to emergency, acute medical, short-stay, triage, ambulance, and prehospital settings. No mandatory outcome block or article-type filter was used. No backward or forward citation searching was performed. The review was limited to peer-reviewed full-text reports; trial registries and grey-literature sources were not searched. The PubMed/MEDLINE search returned 66 records and the Scopus search returned 64 records (Figure 1). Complete database-specific strategies, execution dates, and yields are provided in Supplementary Table S1.

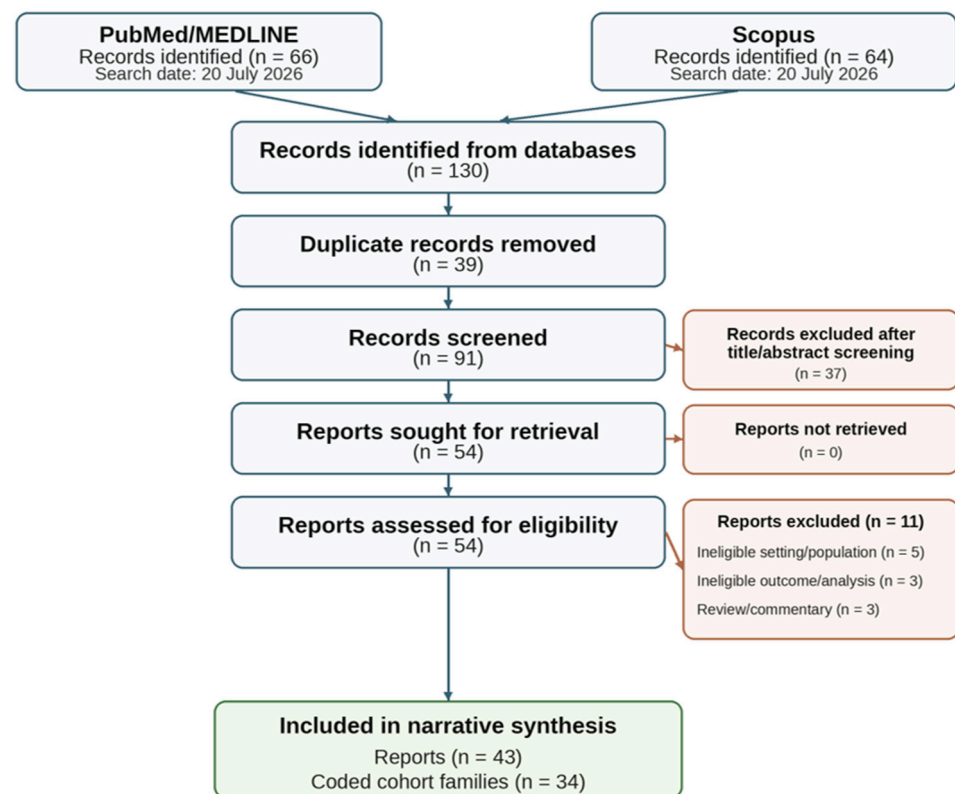


**Figure 1.** PRISMA 2020 flow diagram for study identification, screening, eligibility assessment, and inclusion. Forty-three reports representing 34 coded cohort families were included in the narrative synthesis.

#### 2.4. Study Selection, Deduplication, and Cohort Overlap

Records were deduplicated by DOI and then by normalized title, with manual comparison of first author, year, setting, recruitment period, and cohort characteristics when identifiers were absent or discordant. Thirty-nine duplicate records were removed, leaving 91 unique records. A.K. completed the initial title/abstract and full-text screening in a structured record-level log. O.S.K. reviewed the final inclusion and exclusion decisions, and uncertainties were resolved by discussion, with consultation of F.M. and I.P. when required. Reports from the same or partially overlapping cohort were retained only when they addressed distinct outcomes or analytical questions and were assigned a cohort-family code. Overlapping reports were not treated as independent replication and were never summed across the same synthesis domain.

#### 2.5. Data Extraction

A.K. performed the initial extraction using a structured form, and O.S.K. checked the final inclusion set, principal effect estimates, outcome definitions, and methodological fields against the full-text source reports before synthesis. Discrepancies were resolved by discussion. Extracted items included country, setting, design, sample size, cohort family, sample matrix, assay and manufacturer, sampling time, outcome definition and follow-up, event counts, adjusted and unadjusted effect estimates with 95% confidence intervals, adjustment variables, prediction-model discrimination, calibration and validation, threshold derivation, and cohort overlap. All included reports met the eligibility requirement for full-text peer-reviewed publication, and full-text reports—not abstract-level data—were used for the final extraction and synthesis. For Tables 2 and 3, estimate selection followed a reproducible hierarchy. First, the authors' prespecified primary eligible outcome was selected when clearly identified; if no primary eligible outcome was declared, mortality or

clinical deterioration was prioritized for prognostic-factor studies, followed by disposition, length of stay, or readmission according to the review question. Second, an adjusted estimate from the authors' main or most fully adjusted model was preferred to an unadjusted estimate when both were available. Third, when several short-term mortality horizons were reported, 30-day mortality or the nearest reported short-term horizon was prioritized unless another horizon was prespecified as primary. For prediction-model studies, performance from an external or internal validation set was preferred to development-set performance; for clinical-impact studies, the randomized between-group primary-endpoint effect was preferred, followed by the main comparative effect in non-randomized studies. When several estimates remained equivalent under these rules, the estimate with the clearest 95% confidence interval and most complete adjustment reporting was selected. When a 95% confidence interval or an unambiguous adjusted estimate was not reported or extractable, the table identifies the available estimate as crude, model-based, descriptive, or not extractable rather than inferring a value. For consistency, suPAR concentrations reported in  $\mu\text{g/L}$  were expressed as  $\text{ng/mL}$  because the units are numerically equivalent ( $1 \mu\text{g/L} = 1 \text{ ng/mL}$ ); no numerical conversion was required. When an article did not provide a value, did not present a single aggregate event count, or did not permit an unambiguous secondary extraction, the item was explicitly labeled as not reported or not extractable and was not inferred or imputed. The completed report-level extraction matrix is provided in Supplementary Table S2.

**Table 2.** Principal findings from general acute-care, triage, disposition, and implementation studies.

| Risk of Bias         | Selected Principal Finding                                                                                           | Outcome                       | n      | Setting/Population                             | Study                      |
|----------------------|----------------------------------------------------------------------------------------------------------------------|-------------------------------|--------|------------------------------------------------|----------------------------|
| QUIPS: Moderate      | Highest vs. lowest suPAR tertile: crude HR 6.66 (95% CI 2.30–19.10); association attenuated after CRP adjustment     | 30-day mortality; readmission | 1036   | Prospective acute medical cohort, Denmark      | Nayak et al., 2015 [4]     |
| QUIPS: Low           | Highest vs. lowest quartile: mortality adjusted HR 4.11 (95% CI 2.46–6.85); readmission adjusted HR 2.11 (1.70–2.62) | 30-day mortality; readmission | 4343   | Acute medical registry, Denmark                | Rasmussen et al., 2016 [5] |
| PROBAST: Moderate    | AUC increased from 0.86 (95% CI 0.85–0.87) to 0.90 (0.89–0.91) after adding suPAR to NEWS + age + sex                | 30-day mortality prediction   | 17,312 | Acute-admission registry, Denmark              | Rasmussen et al., 2018 [6] |
| RoB 2: Some concerns | Routine suPAR availability did not reduce short- or long-term all-cause mortality                                    | Mortality; clinical impact    | 16,801 | TRIAGE III cluster-randomized trial, Denmark   | Schultz et al., 2018 [7]   |
| PROBAST: Moderate    | Prognostic models discriminated less well in older than middle-aged patients                                         | 7-day mortality prediction    | 42,542 | Age-stratified acute-admission cohort, Denmark | Schultz et al., 2019 [8]   |
| PROBAST: High        | AUC 0.85 (0.80–0.89); 5.9 $\text{ng/mL}$ reclassification threshold was data derived                                 | 7-day mortality               | 4420   | TRIAGE III secondary analysis                  | Schultz et al., 2019 [9]   |

Table 2. Cont.

| Risk of Bias       | Selected Principal Finding                                                                                                   | Outcome                           | n      | Setting/Population                               | Study                            |
|--------------------|------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|--------|--------------------------------------------------|----------------------------------|
| ROBINS-I: Moderate | Early discharge 50.2% vs. 48.6% (difference 1.6%, 95% CI 0.08–3.12); LOS 4.3 vs. 4.6 days; 30-day readmission 10.6% vs. 8.8% | Early discharge; LOS; readmission | 16,801 | TRIAGE III post hoc substudy                     | Schultz et al., 2019 [10]        |
| QUIPS: Moderate    | Adjusted OR 1.96 per doubling of suPAR (95% CI 1.42–2.70); <4 ng/mL: mortality 1.0%, NPV 99.0%                               | 90-day mortality                  | 1747   | Prospective acute medical ED cohort, Finland     | Seppälä et al., 2021 [11]        |
| QUIPS: High        | OR 1.04 (95% CI 0.97–1.13); AUROC 0.58 (0.47–0.69): no reliable disposition discrimination                                   | Admission vs. discharge           | 109    | Prospective prehospital cohort, Finland          | Jousi et al., 2021 [12]          |
| QUIPS: Moderate    | suPAR $\geq$ 8 ng/mL: adjusted OR 25.4 (95% CI 3.2–199.8) with infection; OR 16.1 (2.0–128.6) in sepsis                      | In-hospital mortality             | 871    | Prospective prehospital cohort, Sweden           | Wallgren et al., 2022 [13]       |
| QUIPS: Moderate    | Higher suPAR identified greater baseline risk; medication burden modified associations across suPAR strata                   | 90-day mortality/readmission      | 26,291 | Acute medical registry, Denmark                  | Bengaard et al., 2022 [14]       |
| ROBINS-I: Moderate | Low suPAR was associated with discharge; non-randomized design precluded causal inference                                    | Disposition; short-term safety    | 330    | Non-randomized ED decision study, Finland        | Holstein et al., 2022 [15]       |
| QUIPS: High        | Deaths clustered in older patients with multimorbidity, polypharmacy, and abnormal routine tests despite low suPAR           | 90-day post-discharge mortality   | 15,209 | Discharged low-suPAR registry subgroup, Denmark  | Christensen et al., 2024 [16]    |
| PROBAST: High      | Internal-test AUCs $\approx$ 0.85–0.93; suPAR contributed more to longer- than very-short-term prediction                    | Mortality prediction              | 48,841 | Acute-admission machine learning cohort, Denmark | Jawad et al., 2024 [17]          |
| QUIPS: Moderate    | suPAR > 6 ng/mL: adjusted HR 4.61 (95% CI 1.68–12.67); revisit adjusted HR 1.59 (1.13–2.10)                                  | 90-day mortality                  | 990    | Prospective ED cohort, Spain                     | Herrero-Puente et al., 2024 [18] |
| QUIPS: High        | suPAR AUC 0.705; exploratory multivariable model was not robust                                                              | In-hospital mortality             | 61     | Priority-1 critical ED cohort, Poland            | Wozniak et al., 2025 [19]        |
| QUIPS: High        | suPAR < 4 ng/mL: OR 5.68 (95% CI 2.60–12.40); AUC 0.75 (0.67–0.83)                                                           | 24 h home discharge               | 202    | ED-to-short-stay cohort, France                  | Brailova et al., 2026 [20]       |

Note: The selected result follows the prespecified hierarchy in Section 2.5; adjusted estimates were preferred when available. AUC, area under the receiver operating characteristic curve; CI, confidence interval; ED, emergency department; HR, hazard ratio; LOS, length of stay; NPV, negative predictive value; OR, odds ratio; suPAR, soluble urokinase plasminogen activator receptor.

**Table 3.** Principal findings from disease-specific and selected acute-care populations.

| Risk of Bias                   | Selected Principal Finding                                                                                               | Outcome                             | n    | Setting/Population                               | Study                               |
|--------------------------------|--------------------------------------------------------------------------------------------------------------------------|-------------------------------------|------|--------------------------------------------------|-------------------------------------|
| QUIPS: Moderate                | Day-1 suPAR AUC 0.72 (95% CI 0.59–0.85) for 7-day and 0.77 (0.68–0.86) for 30-day mortality                              | 7-/30-day mortality                 | 130  | Multicenter ED sepsis cohort, Italy              | Casagrande et al., 2015 [21]        |
| QUIPS: High                    | Weak discrimination: AUC 0.60 (95% CI 0.48–0.72)                                                                         | Mortality                           | 69   | Trauma; HEMS/ED, Netherlands                     | Timmermans et al., 2015 [22]        |
| QUIPS: High                    | suPAR differed between severe and non-severe groups ( $p = 0.001$ ); incremental value not established                   | ICU admission/death                 | 121  | Pneumococcal pneumonia, Netherlands              | Loonen et al., 2017 [23]            |
| QUIPS: Moderate                | suPAR underperformed MR-proADM; no universal threshold supported                                                         | 30-day mortality                    | 136  | Older adults with infection; 8 Spanish EDs       | Julian-Jimenez et al., 2019 [24]    |
| QUIPS: Moderate                | Highest vs. lowest quartile: adjusted HR 4.52 (95% CI 1.51–13.48); added discrimination to established assessment        | 1-year mortality                    | 1314 | Suspected myocardial infarction, German ED       | Sorensen et al., 2019 [25]          |
| QUIPS: Moderate; PROBAST: High | suPAR > 3.3 ng/mL independently associated with events; low suPAR + NT-proBNP + HEART score identified low-risk patients | 30-day event                        | 198  | Multicenter chest-pain cohort                    | Chenevier-Gobeaux et al., 2021 [26] |
| QUIPS: Moderate                | Higher suPAR quartiles associated with events; low eosinophils strengthened risk                                         | 365-day readmission/mortality       | 1341 | Acute asthma admissions, Denmark                 | Håkansson et al., 2019 [27]         |
| QUIPS: Moderate                | Q4 vs. Q1: readmission adjusted HR 1.61 (95% CI 1.40–1.85); mortality adjusted HR 3.40 (2.64–4.39)                       | 365-day readmission/mortality       | 4022 | Acute COPD admissions, Denmark                   | Håkansson et al., 2020 [28]         |
| QUIPS: Moderate                | suPAR did not reliably identify serious illness but was associated with 30-day mortality                                 | Serious condition; 30-day mortality | 414  | Prehospital nonspecific complaints, Sweden       | Ivic et al., 2021 [29]              |
| ROBINS-I: Moderate             | Low suPAR supported low-risk enrichment; cohort overlaps with related COVID-19 analyses                                  | Early discharge/adverse outcome     | 386  | COVID-19-symptom ED cohort, Denmark              | Stauning et al., 2021 [30]          |
| QUIPS: High                    | Severe events: AUC 0.78 (95% CI 0.67–0.89); ~4.99 ng/mL cut-off was data-derived                                         | 30-day adverse events               | 201  | Prospective ED cohort, Spain                     | Álvarez-Kailis et al., 2021 [31]    |
| PROBAST: Moderate              | Validation calibration slope 1.01; at 10% threshold: 22 TP, 52 FP, 1 FN, and 25 TN per 100                               | Oxygen requirement                  | 423  | Moderate COVID-19 development/validation cohorts | Chandna et al., 2022 [32]           |

Table 3. Cont.

| Risk of Bias                          | Selected Principal Finding                                                                                      | Outcome                         | n         | Setting/Population                                     | Study                               |
|---------------------------------------|-----------------------------------------------------------------------------------------------------------------|---------------------------------|-----------|--------------------------------------------------------|-------------------------------------|
| PROBAST: High                         | AUC: suPAR 0.646 (95% CI 0.553–0.740), qSOFA 0.832, combined model 0.864 (0.802–0.928)                          | 28-day mortality                | 175       | ED sepsis/septic shock, China                          | Wang et al., 2022 [33]              |
| QUIPS: Moderate                       | suPAR $\geq 6$ ng/mL identified higher risk within both qSOFA strata                                            | 30-day mortality                | 958       | Suspected-infection ED cohort, Netherlands             | Tong-Minh et al., 2023 [34]         |
| QUIPS: High                           | suPAR alone was not significant; suPAR + IL-6 AUC 0.74 and did not clearly outperform IL-6                      | 28-day mortality                | 67        | ED sepsis, Romania                                     | Luka et al., 2024, Medicina [35]    |
| QUIPS: High                           | 24 h suPAR AUC 0.813; no external validation/calibration                                                        | 28-day mortality                | 47        | ED sepsis/septic shock, Romania                        | Luka et al., 2024, J Clin Med [36]  |
| QUIPS: Moderate; RoB 2: Some concerns | qSOFA = 1 + suPAR $\geq 12$ ng/mL: mortality HR 2.98 (95% CI 2.11–3.96); SUPERIOR deterioration 40.4% vs. 15.9% | Mortality; early deterioration  | 1787 + 91 | Suspected infection; cohort + SUPERIOR RCT             | Adami et al., 2024 [37]             |
| PROBAST: High                         | Higher suPAR associated with worsening in multivariable analysis; transportability not established              | 7-day clinical worsening        | 511       | Multicenter COVDeF cohort, France                      | Cancella de Abreu et al., 2024 [38] |
| PROBAST: High                         | Biomarker combinations identified high-/low-risk groups; no events in a low-marker subgroup                     | 12-month composite outcome      | 360       | ED chest pain, Italy                                   | Piccioni et al., 2024 [39]          |
| PROBAST: Moderate                     | suPAR independently associated with outcome; discrimination improved in both cohorts                            | 1-year HF hospitalization/death | 612 + 483 | Acute breathlessness; New Zealand/Singapore ED cohorts | Chew-Harris et al., 2024 [40]       |
| QUIPS: High                           | Higher early suPAR remained associated with severe progression after adjustment                                 | Severe progression              | 255       | Acute COVID-19 cohort, France                          | Negre et al., 2025 [41]             |
| PROBAST: High                         | suPAR AUC 0.65 (95% CI 0.60–0.70); clinical + sVEGFR2 + suPAR AUC 0.74 (0.69–0.78)                              | 72 h deterioration              | 724       | SEPSIGN suspected-infection cohort                     | Lafon et al., 2025 [42]             |
| QUIPS: Moderate                       | Adjusted HR 1.12 (95% CI 1.05–1.20) per 1 ng/mL increase                                                        | 1-year mortality                | 339       | Acute atrial fibrillation ED cohort, Denmark           | Wisborg et al., 2025 [43]           |
| QUIPS: High                           | Exploratory thresholds: 10.2 ng/mL for mortality; 5.96 ng/mL for severity/longer stay                           | 28-day mortality/severity/LOS   | 125       | Febrile infection/sepsis ED cohort, Italy              | Leggeri et al., 2026 [44]           |
| QUIPS: High                           | Study-derived 11.15 ng/mL cut-off; values above cut-off associated with 8.29-fold higher mortality risk         | 28-day mortality                | 125       | Potentially infected ED patients, Italy                | Baldetti et al., 2026 [45]          |

Table 3. Cont.

| Risk of Bias    | Selected Principal Finding                               | Outcome          | n   | Setting/Population           | Study                     |
|-----------------|----------------------------------------------------------|------------------|-----|------------------------------|---------------------------|
| QUIPS: Moderate | Adjusted HR 1.06 (95% CI 1.03–1.10) per 1 ng/mL increase | 1-year mortality | 386 | Acute heart failure, Denmark | Kandiah et al., 2026 [46] |

Note: The selected result follows the prespecified hierarchy in Section 2.5; adjusted estimates were preferred where available. AUC, area under the receiver operating characteristic curve; CI, confidence interval; ED, emergency department; HEMS, helicopter emergency medical service; HR, hazard ratio; ICU, intensive care unit; LOS, length of stay; RCT, randomized controlled trial; suPAR, soluble urokinase plasminogen activator receptor.

## 2.6. Risk of Bias

Observational prognostic-factor studies were assessed with QUIPS [51]. Model-development, validation, extension, and incremental-prediction analyses were assessed with PROBAST [52]. The TRIAGE III cluster-randomized trial was assessed with the cluster-randomized RoB 2 framework, the individually randomized SUPERIOR substudy with standard RoB 2 [53], and non-randomized implementation analyses with ROBINS-I [54]. A.K. prepared the initial domain-level judgments and O.S.K. reviewed the completed assessments; disagreements were resolved by discussion. Overall QUIPS judgments were harmonized with the rule reported beneath Supplementary Table S4; in particular, a high-risk key-domain judgment was not retained as an overall moderate rating. Overall rules and report-level judgments are provided in Supplementary Tables S4–S7.

## 2.7. Certainty of Evidence

Certainty was assessed by outcome using GRADE guidance adapted for prognostic-factor evidence [55–57]. Prognostic association, incremental prediction, routine biomarker availability, protocolized treatment, and flow/disposition outcomes were rated separately. Reporting bias was assessed qualitatively because formal small-study analyses were not meaningful for heterogeneous, often overlapping outcome groups.

## 2.8. Synthesis Methods and Pooling Feasibility

Studies were grouped first by review question and then by outcome. Meta-analysis was not undertaken because exposure scales, thresholds, assay platforms, populations, outcome horizons, effect measures, adjustment sets, and overlapping cohorts were not sufficiently commensurate to support a clinically interpretable pooled effect without combining non-equivalent estimates or double-counting related populations. A structured narrative synthesis was therefore used as the more defensible approach, preserving outcome-specific and cohort-specific distinctions and avoiding a single summary estimate with questionable clinical meaning. Consistent with SWiM, synthesis considered effect direction, magnitude, precision, risk of bias, and cohort independence rather than statistical-significance vote counting. Reported thresholds were interpreted as cohort-specific risk-enrichment bands, not universal clinical decision thresholds. Outcome-specific pooling decisions are documented in Supplementary Table S9.

# 3. Results

## 3.1. Study Selection

The searches identified 130 records: 66 from PubMed/MEDLINE and 64 from Scopus. After removal of 39 duplicates, 91 unique records were screened. Thirty-seven records were excluded during title/abstract screening. Fifty-four reports were sought and retrieved for full-text assessment. Eleven reports were excluded after full-text assessment: five because

the setting or population did not meet eligibility criteria, three because the outcome was ineligible or suPAR was not evaluated as an independent prognostic factor, and three because they were reviews or commentaries without eligible primary data. Forty-three reports were included, representing 34 coded distinct or partially overlapping cohort families. The complete record-level screening log and reasons for full-text exclusion are provided in Supplementary Tables S10 and S12.

### 3.2. Study Characteristics and Cohort Structure

The evidence base included prospective and retrospective cohorts, registry studies, one cluster-randomized trial, one small individually randomized substudy, post hoc analyses, and non-randomized implementation studies. Most reports originated from European acute-care systems. Seven reports arose from the Danish Hvidovre acute-admission registry family, three from TRIAGE III, and two Romanian sepsis reports were considered potentially overlapping. These clusters were retained for distinct questions but were not treated as independent replications. Tables 2 and 3 summarize the report-level evidence; Supplementary Table S3 provides the overlap map.

### 3.3. Prognostic Association with Mortality and Deterioration

#### 3.3.1. Unselected and Mixed Acute-Care Cohorts

Across unselected and mixed acute-care cohorts, higher admission suPAR was associated with in-hospital, 30-day, 90-day, or longer-term mortality [4,5,11,13,17–19]. Associations frequently persisted after adjustment for age, comorbidity, C-reactive protein, renal function, medication burden, or routine clinical variables, although adjustment sets were inconsistent. The large machine learning cohort confirmed useful prognostic information but also illustrated that suPAR contributed more to longer-term than to very-short-term prediction [17].

#### 3.3.2. Disease-Specific and Selected Populations

Disease-specific reports extended the association to sepsis and suspected infection, pneumonia, trauma, chest pain, suspected myocardial infarction, asthma, COPD, acute breathlessness, atrial fibrillation, and acute heart failure [21–29,33–46]. Findings were not uniformly positive: admission suPAR had weak discrimination in the small trauma cohort (AUC 0.60, 95% CI 0.48–0.72) [22]; suPAR was not a significant standalone predictor in one Romanian sepsis report, and adding it to IL-6 did not clearly outperform IL-6 alone [35]; a second Romanian sepsis/septic-shock report showed stronger discrimination for 24 h suPAR (AUC 0.813) [36]; and SEPSIGN showed only modest standalone discrimination (AUC 0.65, 95% CI 0.60–0.70) [42]. These null and mixed findings temper the overall interpretation and reduce concern that the synthesis reflects positive-result selection alone.

Reported cut-off points were study-specific rather than nested universal concentration bands. Seppälä et al. evaluated <4, 4–6, and >6 ng/mL in a Finnish acute medical ED cohort [11]; Wallgren et al. used  $\geq 8$  ng/mL in a Swedish prehospital mortality analysis [13]; Herrero-Puente et al. evaluated <4, 4–6, and >6 ng/mL in a Spanish ED cohort [18]; Tong-Minh et al. applied a prespecified  $\geq 6$  ng/mL cut-off in suspected infection [34]; and Adami et al. evaluated  $\geq 12$  ng/mL only in patients with suspected infection and qSOFA = 1 [37]. Brailova et al., Baldetti et al., and Kandiah et al. reported additional population-specific thresholds [20,45,46]. Assay context, population, outcome, selected effect estimate, and validation status are summarized in Table 4. These thresholds are not interchangeable and should not be interpreted as a single ordinal clinical scale.

**Table 4.** Study-specific suPAR thresholds and their clinical context and validation status.

| Threshold Status                                                                      | Key Result                                                                          | Clinical Context            | Threshold             | Assay/Platform                                         | Study/Population                                                             |
|---------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------|-----------------------|--------------------------------------------------------|------------------------------------------------------------------------------|
| Previously proposed thresholds prospectively tested; independent replication needed   | OR 1.96 per doubling (95% CI 1.42–2.70); <4 ng/mL: 1.0% mortality, NPV 99.0%        | 90-day mortality            | <4, 4–6, >6 ng/mL     | suPARnostic TurbiLatex; Cobas c501                     | Seppälä et al., 2021 [11]; acute medical ED, Finland; n = 1747               |
| Derived from prior sepsis-identification work; not externally validated for mortality | OR 25.4 (95% CI 3.2–199.8) with infection; OR 16.1 (2.0–128.6) in sepsis            | In-hospital mortality       | ≥8 ng/mL              | ViroGates suPAR assay                                  | Wallgren et al., 2022 [13]; prehospital, Sweden; n = 871                     |
| Clinical decision points; no external validation                                      | >6 ng/mL: adjusted HR 4.61 (95% CI 1.68–12.67); <4 ng/mL: mortality 1.0%            | 90-day mortality            | <4, 4–6, >6 ng/mL     | Assay details insufficiently reported                  | Herrero-Puente et al., 2024 [18]; ED, Spain; n = 990                         |
| Single-center disposition study; no external validation                               | <4 ng/mL: OR 5.68 (95% CI 2.60–12.40); AUC 0.75 (0.67–0.83)                         | 24 h discharge              | <4 vs. ≥4 ng/mL       | Assay details insufficiently reported                  | Brailova et al., 2026 [20]; ED-to-short-stay, France; n = 202                |
| Prespecified threshold; multicenter validation needed                                 | qSOFA = 0: 5.5% vs. 0.9%; qSOFA ≥ 1: 10.7% vs. 2.1%                                 | 30-day mortality            | ≥6 ng/mL              | ViroGates turbidimetric assay; COBAS                   | Tong-Minh et al., 2023 [34]; suspected infection, Netherlands; n = 958       |
| Derived in registry, then tested in selected RCT; trial prematurely stopped           | Cohort mortality HR 2.98 (95% CI 2.11–3.96); SUPERIOR deterioration 40.4% vs. 15.9% | Mortality/treatment pathway | ≥12 ng/mL + qSOFA = 1 | suPARnostic ELISA/Quick Triage                         | Adami et al., 2024 [37]; qSOFA = 1 suspected infection                       |
| Study-derived; external validation required                                           | Above threshold: 8.29-fold higher mortality risk                                    | 28-day mortality            | 11.15 ng/mL           | Plasma assay; exact platform not sufficiently reported | Baldetti et al., 2026 [45]; potentially infected ED patients, Italy; n = 125 |
| Disease-specific stratification; not externally validated as a decision rule          | Continuous model: adjusted HR 1.06 (95% CI 1.03–1.10) per 1 ng/mL increase          | 1-year mortality            | ≥6 ng/mL              | suPARnostic AUTO Flex ELISA                            | Kandiah et al., 2026 [46]; acute heart failure, Denmark; n = 386             |

Note: Thresholds are study-specific and should not be interpreted as a common ordinal clinical scale. Concentrations are reported in ng/mL (1 ng/mL = 1 µg/L). Assay/platform details are reported only when explicitly available from the source publication.

### 3.4. Disposition, Length of Stay, and Readmission

Lower suPAR was generally associated with discharge and shorter hospitalization, whereas higher values were associated with admission or prolonged stay [10,12,15,20,30]. The prehospital Jousi cohort was an important counterexample: suPAR did not reliably distinguish discharge from admission (AUROC 0.58, 95% CI 0.47–0.69) [12]. These outcomes

were highly sensitive to clinician judgment, local bed capacity, follow-up arrangements, and patient frailty.

Readmission findings were less consistent than mortality findings. Associations were reported in acute medical, asthma, COPD, and medication-burden cohorts [4,5,10,14,27,28]. In TRIAGE III, biomarker availability was associated with more discharges within 24 h and shorter stays, but also with more overall 30-day readmissions [10]. Residual confounding by multimorbidity, prior utilization, social circumstances, and healthcare-system organization remained substantial.

### 3.5. Incremental Prediction

suPAR improved prediction beyond conventional scores or clinical variables in several analyses. It added information to NEWS in a large registry cohort, improved triage reclassification in a TRIAGE III secondary analysis, and contributed to selected infection, COVID-19, chest pain, acute breathlessness, and machine learning models [6,8,9,17,32–34,38–40,42]. The Wang sepsis cohort reported AUC 0.646 (95% CI 0.553–0.740) for suPAR, 0.832 for qSOFA, and 0.864 (95% CI 0.802–0.928) for the combined model [33]; SEPSIGN reported AUC 0.65 (95% CI 0.60–0.70) for suPAR and 0.74 (95% CI 0.69–0.78) for a clinical plus sVEGFR2 plus suPAR model [42].

However, model development frequently used data-derived thresholds, incompletely handled missing data, had limited event counts, relied on internal validation only, or lacked independent external validation. Calibration, decision-curve analysis, model updating, and net benefit were inconsistently reported. Improved AUC or reclassification does not by itself establish clinical utility.

### 3.6. Clinical Impact of suPAR-Supported Care

The clinical-impact evidence was substantially weaker than the prognostic-association evidence. TRIAGE III found no reduction in short- or long-term all-cause mortality when suPAR became routinely available in participating EDs [7]. The trial tested biomarker availability rather than a mandatory response algorithm. Post hoc and non-randomized studies suggested changes in risk perception, early discharge, or length of stay, but these analyses were vulnerable to confounding and selective analyses [10,15,30].

The SUPERIOR double-blind randomized substudy enrolled a narrowly selected qSOFA = 1 and suPAR  $\geq 12$  ng/mL suspected-infection phenotype and reported less early deterioration with early antibiotics [37]. Its small sample, premature termination, and selected population do not establish a general mortality or treatment benefit for suPAR-guided care in unselected ED patients.

### 3.7. Risk of Bias and Certainty of Evidence

Frequent QUIPS concerns were incomplete control of renal function, frailty, multimorbidity, smoking, medication burden, and prior healthcare use; data-derived cut-offs; small event counts; and incomplete reporting of calibration or clinical utility. Prediction-model analyses frequently had high PROBAST risk because of limited events, data-driven predictor handling, internal validation only, and absent external validation. TRIAGE III had some concerns because of the small number of randomized clusters and the lack of a mandated management response. Non-randomized implementation analyses were at moderate risk of bias.

Certainty was very low for short-term prognostic association, longer-term mortality, admission/discharge, length of stay, readmission, incremental prediction, and protocolized-treatment claims. The evidence regarding heterogeneous thresholds was insufficient to support a universal suPAR decision threshold. Observational prognostic and prediction evidence started at low certainty and was downgraded for serious risk of bias and imprecise

cision; consistency of effect direction alone was not considered sufficient for upgrading. Certainty was moderate for the finding that routine biomarker availability did not reduce mortality, based primarily on the large cluster-randomized trial. Detailed judgments are provided in Supplementary Table S8.

## 4. Discussion

### 4.1. Principal Clinical Findings

This systematic review and narrative synthesis included 43 reports representing 34 coded distinct or partially overlapping cohort families. The primary purpose of the review was clinical rather than methodological: the reporting, bias-assessment, cohort-mapping, and certainty frameworks were used to organize heterogeneous evidence and make its limitations transparent, not to propose a new methodology for systematic reviews. The central question is how far current evidence supports suPAR as an adjunct to emergency and acute-care risk assessment and whether any reported threshold, prediction model, or suPAR-supported pathway is sufficiently validated for practice. Higher suPAR at first acute-care contact was generally associated with adverse outcomes across heterogeneous adult populations, with the most reproducible signal concerning mortality. The inclusion of null or weak findings from trauma, prehospital disposition, and selected sepsis analyses tempers the overall interpretation and supports a graded rather than binary view of prognostic value. Despite the broadly consistent direction of association, certainty for short-term mortality/deterioration and incremental prediction was very low because residual confounding, small event counts, model-development limitations, and incomplete external validation remained substantial.

The key distinctions are between prognostic association, incremental prediction, and clinical effectiveness. suPAR may identify biological vulnerability and improve risk discrimination in selected models, but neither association nor improved AUC proves that acting on the biomarker improves outcomes. Routine suPAR availability did not reduce mortality in TRIAGE III, and available threshold-based pathways remain insufficiently validated for universal use.

### 4.2. Clinical Interpretation

The most plausible role for suPAR is as an adjunct to structured assessment. In a patient with reassuring examination, stable physiology, limited comorbidity, preserved renal function, and appropriate follow-up, a low concentration may increase confidence in a low-risk pathway. Conversely, an unexpectedly high concentration may prompt reconsideration of occult organ dysfunction, frailty, multimorbidity, or the need for observation. Neither interpretation should override clinical findings or a validated pathway.

suPAR differs conceptually from C-reactive protein, procalcitonin, lactate, and organ-specific biomarkers. Those markers more directly reflect acute inflammation, bacterial infection, hypoperfusion, or organ injury, whereas suPAR integrates chronic inflammatory burden and biological vulnerability [1–3]. This broader signal may explain its cross-diagnostic prognostic value but also limits its specificity for reversible acute deterioration.

This non-specificity also has practical implications for implementation. A high suPAR concentration should not, by itself, trigger additional investigations, hospital admission, or escalation of care. In older or multimorbid patients, an elevated value may predominantly reflect chronic biological vulnerability rather than a reversible acute process. Uncritical use could therefore increase diagnostic testing, observation or hospitalization, resource use, and patient anxiety without proven clinical benefit. Future implementation studies should evaluate these potential downstream harms alongside prognostic performance, discharge safety, and cost-effectiveness.

#### 4.3. Prognostic Performance Is Not Clinical Effectiveness

Improved discrimination does not necessarily improve patient outcomes. Future impact trials should compare explicit, prespecified suPAR-supported algorithms with usual care and measure mortality, deterioration, discharge safety, unintended escalation, equity, resource utilization, cost-effectiveness, and clinician adherence. Studies should also report whether the biomarker changed management and whether the change mediated the observed outcome.

The TRIAGE III and SUPERIOR findings address different clinical questions and should not be interpreted as contradictory. TRIAGE III tested routine availability of suPAR across a broad acute medical population without a mandated management response and found no mortality benefit. SUPERIOR, in contrast, evaluated a specific biomarker-gated treatment strategy in a narrowly selected suspected-infection phenotype with qSOFA = 1 and suPAR  $\geq 12$  ng/mL, and reported less early deterioration with early antibiotic treatment. The latter signal is therefore pathway- and phenotype-specific, rather than evidence that routine suPAR testing improves outcomes in unselected patients. Given the small sample, premature termination, and restricted eligibility of SUPERIOR, it does not offset the broader TRIAGE III result. Together, these trials suggest that clinical impact depends on the actionable pathway linked to the biomarker, not on biomarker availability alone.

#### 4.4. Methodological Strengths and Limitations

This review has several methodological strengths. A structured, reproducible database search was conducted in PubMed/MEDLINE and Scopus without restrictive outcome or publication-type filters, and the database yields, deduplication process, and record-level screening decisions were reported transparently. The review questions were explicitly separated into prognostic association, incremental prediction, and clinical impact, thereby avoiding the inappropriate assumption that prognostic performance necessarily translates into improved patient outcomes. Data extraction incorporated study design, assay characteristics, sampling time, event counts, effect estimates, model performance, and cohort overlap when reported. Risk of bias was assessed using design-appropriate tools, including QUIPS, PROBAST, RoB 2, and ROBINS-I, while certainty was evaluated at the outcome level using a conservative GRADE approach. In addition, report-to-cohort mapping was used to identify overlapping populations and to prevent related publications from being interpreted as independent replication. The synthesis also incorporated null and weak findings and followed a structured narrative approach consistent with SWiM principles.

Several limitations should be considered. At the review level, the protocol was not prospectively registered. The search was restricted to PubMed/MEDLINE and Scopus, English-language full-text publications, and studies published from 2015 onward; no backward or forward citation searching was performed. The review was intentionally focused on peer-reviewed full-text evidence, and trial registries and grey-literature sources were not searched. Accordingly, ongoing or unpublished studies, including negative results, were outside the review scope, and the completeness of the evidence base cannot be guaranteed. This restriction may also increase susceptibility to publication and availability bias. This consideration is particularly relevant to the smaller clinical-impact evidence base. Study selection, data extraction, and risk-of-bias assessment followed a structured two-stage process with initial assessment and within-team verification, with discrepancies resolved by discussion. To maximize transparency and reproducibility, the complete search strategies, record-level screening log, reasons for full-text exclusion, extraction matrix, cohort-overlap map, and domain-level appraisal tables are provided in the Supplementary Materials. At the evidence-base level, several reports had small sample sizes, limited

event counts, data-derived cut-offs, incomplete adjustment for important confounders, and insufficient reporting of assay characteristics, calibration, validation, or clinical utility. Most studies were conducted in European healthcare systems, which may limit generalizability to other settings. Furthermore, several reports originated from overlapping institutional cohorts, reducing the amount of truly independent replication. Substantial heterogeneity in populations, assays, exposure scales, thresholds, outcome definitions, follow-up periods, effect measures, and adjustment strategies precluded a methodologically defensible meta-analysis. These limitations primarily constrain evidence completeness, threshold transportability, and claims regarding clinical effectiveness; they do not negate the recurrent prognostic association observed across multiple acute-care populations. Consistency in the direction of association was not used to upgrade certainty because robust evidence of large effects, dose–response relationships, or residual confounding that would strengthen the observed associations was not demonstrated across sufficiently independent and adequately adjusted cohorts.

#### 4.5. Research Priorities

Future studies should use prospective multicenter designs, harmonized assays and units, prespecified thresholds, age- and renal-function-aware calibration, transparent handling of missing data, and external validation. Prediction studies should report discrimination, calibration, net benefit, and decision curves. Pragmatic trials should compare explicit suPAR-supported pathways with usual care and assess patient-important outcomes, discharge safety, resource use, cost-effectiveness, and equity. Individual-participant-data meta-analyses could clarify non-linearity, effect modification, and threshold transportability while accounting for cohort overlap.

## 5. Conclusions

suPAR is a promising adjunctive prognostic biomarker in adult emergency and acute-care populations. Higher concentrations are generally associated with mortality and biological vulnerability, while lower concentrations enrich for lower-risk groups. Evidence is strongest for prognostic association, weaker for incremental prediction, and insufficient for universal cut-offs or standalone management rules. suPAR should be interpreted alongside clinical assessment, comorbidity, renal function, routine biomarkers, and validated scores. Clinical impact should be evaluated at the level of the complete suPAR-supported pathway, because routine biomarker availability and a targeted biomarker-gated intervention address different causal questions. Broad clinical implementation requires externally validated pathways and prospective clinical-impact and cost-effectiveness studies.

**Supplementary Materials:** The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/sci8100296/s1>, Table S1, Database-specific search strategies and execution log; Table S2, Detailed study-level extraction matrix; Table S3, Cohort-overlap map; Tables S4–S7, Risk-of-bias assessments; Table S8, Outcome-level GRADE profile; Table S9, Meta-analysis feasibility assessment; Table S10, Complete PubMed/Scopus screening log; Table S11, PRISMA 2020 and PRISMA-S reporting checklist; Table S12, Reports excluded after full-text assessment and reasons [58–68]; and Table S13, Methodological frameworks and appraisal tools used in the review.

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