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CLINICAL AND BIOLOGICAL MARKERS FOR PREDICTING ARDS AND OUTCOMES IN SEPTIC PATIENTS, COMBINING EMERGENCY MEDICINE, CRITICAL CARE, AND SEPSIS, MAKING IT HIGHLY RELEVANT AND BROADLY APPLICABLE

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Abstract

Background: *Sepsis is still a leading cause of death worldwide, and acute respiratory distress syndrome (ARDS) is one of its most severe consequences. Early diagnosis of septic individuals with a high risk of developing ARDS is critical for timely intervention and better clinical outcomes. This review summarizes current information regarding the predictive validity of clinical signs, biological biomarkers, and machine learning-based models for ARDS development and prognosis in septic patients.*

Methods: *A narrative review was undertaken using literature from PubMed/MEDLINE, Scopus, Web of Science, Embase, Google Scholar, and the Cochrane Library. Studies published between January 2015 and March 2025 that assessed clinical predictors, circulating biomarkers, molecular signatures, or artificial intelligence-based prediction models in adult patients with sepsis or sepsis-associated ARDS were considered. Eighty-five relevant trials with 41,782 individuals were analyzed.*

Results: *Clinical markers such as the SOFA score, APACHE II score, PaO_2/FiO_2 ratio, serum lactate concentration, and mechanical ventilation demand accurately predict disease severity and death. RAGE and SP-D, two epithelial damage indicators, were found to have high correlations with early ARDS and bad outcomes. Angiopoietin-2 had the best diagnostic performance among endothelial biomarkers (AUC = 0.91); CRP, IL-6, procalcitonin, D-dimer, and plasminogen activator inhibitor-1 were the most commonly validated inflammatory and coagulation biomarkers. Emerging molecular markers, including as microRNAs, genomic and transcriptomic signatures, extracellular vesicles, and cell-free DNA, have shown great*

promise in precision risk stratification. Individual biomarkers were outperformed by combined clinical-biomarker prediction models (AUC = 0.91; sensitivity 88%; specificity 86%), whereas deep learning and XGBoost algorithms had the highest predictive performance among machine learning approaches (AUC up to 0.94).

Conclusions: *Evidence suggests that combining clinical severity scores with multimarker panels and artificial intelligence significantly improves early detection of ARDS and bad outcomes in septic patients. Future precision medicine solutions that combine clinical, molecular, and computational data have the potential to revolutionize risk assessment and personalized care of sepsis-associated ARDS.*

Introduction

Sepsis is a potentially fatal syndrome that is an immune response when the body's system goes awry due to infection, leading to organ dysfunction and one of the most common and fatal reasons for hospital admission and death in intensive care units (ICUs) around the world. Although there have been improvements in antimicrobial treatment, organ support, and critical care management, sepsis remains a substantial health issue that affects approximately 49 million individuals and results in nearly 11 million deaths every year (Rudd et al., 2020). Sepsis clinical manifestations are extremely variable, ranging from moderate organ dysfunction to septic shock and multiple organ failure, and are difficult to diagnose and classify into severity classes, especially in the early stages, when a prompt diagnosis and classification are essential for prompt treatment. Therefore, many studies have been conducted to identify reliable clinical or biological markers that will be predictive of disease progression and determine the results of therapy (Caraballo & Jaimes, 2019). Acute respiratory distress syndrome (ARDS) is among the most severe complications associated with sepsis and is the most common indirect cause of ARDS in the world, responsible for almost one-third of all reported cases (Ryan et al., 2021). It is an inflammatory injury that is diffuse to the alveolar-capillary membrane with increased vascular permeability, pulmonary edema, severe pulmonary hypoxemia, and impaired gas exchange. Despite improvements in supportive care, patients with sepsis-associated ARDS often require prolonged mechanical ventilation and have longer durations in the ICU and mortality rates >40% (Yang & Sjoding, 2024). The pathogenesis of ARDS can be multifactorial and involves excessive inflammation, immune dysregulation, endothelial dysfunction, epithelial injury, oxidative stress and coagulation abnormalities stimulated by pathogen-associated and damage-associated molecular patterns (Bos & Ware, 2022; Xu et al., 2023).

The Sequential Organ Failure Assessment (SOFA) score, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, serum lactate concentration (SLC), and PaO_2/FiO_2 ratio are the most basic clinical parameters for assessing disease severity; however, they have limited sensitivity in detecting patients at risk of developing ARDS at the initial stages of sepsis (Evans et al., 2021). As a result, there has been an increased focus on biological biomarkers such as the receptor for advanced glycation end-products (RAGE), surfactant protein-D (SP-D), angiopoietin-2 (Ang-2), intercellular adhesion molecule-1 (ICAM-1), interleukin-18 (IL-18), plasminogen activator inhibitor-1 (PAI-1), amphiregulin (AREG) and chemokine (C-X-C motif) ligand 16 (CXCL16), which are involved in the mechanisms of lung injury and systemic inflammation (Villar et al., 2021). In addition, the use of these biomarkers together with clinical parameters and machine learning techniques has been reported to have greater predictive value than conventional assessment, helping to identify high-risk patients earlier and inform precision medicine strategies (Komorowski et al., 2022).

Although these are promising developments, there are a number of reasons why the routine clinical use of these biomarkers has been restricted: there is variation across the range of assays used for the same drug, the populations of patients used vary, and the experimental design of the studies are different. Thus, this review will summarize the available evidence on clinical and biological markers that predict ARDS development and clinical outcomes in septic patients and will emphasize new biomarker panels, integrated prediction models, and future directions of precision medicine for emergency medicine and critical care.

Methodology

Study Design

This review was performed using a narrative literature review approach to fully understand the existing clinical and biological evidence on the utility of predicting acute respiratory distress syndrome (ARDS) and clinical outcomes in septic patients. A narrative review method was chosen because the available literature in the field is extremely varied in design, patient population, biomarker selection, laboratory methods, clinical settings and outcome measures. Narrative reviews can be used to integrate the evidence from a range of study designs and can offer more of a broad perspective of novel or emerging biomarkers, clinical predictors, and emerging new methods of prediction, such as machine learning models, than systematic reviews, which focus on a narrower research question. The approach has been widely used before in previous review articles on the topic of sepsis biomarkers and ARDS heterogeneity due to the diverse range of biomarkers studied and the aims of the studies.

Literature Search Strategy

A thorough literature search was conducted in the electronic databases PubMed/MEDLINE, Scopus, Web of Science, Embase, Google Scholar and Cochrane Library. The search was conducted mainly within the time frame of January 2015 to March 2025 to include recent advances in sepsis and ARDS research but also included some landmark studies from before 2015 to provide background information and support basic concepts. To ensure that the search strategy was sensitive, medical subject headings (MeSH) were used in conjunction with free-text keywords, and Boolean operators (AND and OR) were used. The main keywords were 'sepsis', 'septic shock', 'acute respiratory distress syndrome', 'ARDS', 'clinical markers', 'biological markers', 'biomarkers', 'RAGE', 'surfactant protein-D', 'angiopoietin-2', 'ICAM-1', 'IL-18', 'IL-1RA', 'CXCL16', 'PAI-1', 'SOFA score', 'APACHE II', 'machine learning', 'artificial intelligence', 'prediction', 'mortality', 'critical care', and 'emergency medicine'. The reference lists of the selected articles and recent review papers were also hand searched to look for any other relevant articles that were not retrieved in the electronic search.

Study Selection

After performing a literature search, all retrieved records were screened on the basis of the title and abstract, checking their relevance to the topic of the literature review. The full text was screened for potentially eligible articles based on preestablished inclusion/exclusion criteria. Studies that examined the prediction of clinical indicators, biological biomarkers, biomarker panels, or machine learning prediction models in patients with ARDS who were septic were chosen for in-depth analysis. To prevent double counting of the same cohort of patients, duplicate data from duplicate publications were excluded.

Inclusion and Exclusion Criteria

Studies were eligible to be included if they included adult patients (age > 18 years) with sepsis, septic shock, and/or sepsis-associated ARDS and measured clinical parameters, biological markers, or combined prediction models for the development of ARDS, disease severity, or mortality. Studies published in peer-reviewed English language journals that met the following criteria were eligible for inclusion: prospective and retrospective cohort studies, observational studies, randomized controlled

trials, case–control studies, systematic reviews, meta-analyses, and machine learning prediction studies. Studies had to provide measurements of clinically relevant outcomes, such as the incidence of ARDS, hospital or ICU mortality, invasive mechanical ventilation, duration of mechanical ventilation, stay in the ICU, or in the hospital. Studies that included pediatric and/or neonatal samples or animal studies, lacked clinical patient data, were conference abstracts, editorials, letters, expert opinions, dissertations, or articles providing incomplete methodological details or full outcome data were excluded. Studies that did not include a separate analysis of septic patients were also not included.

Data Extraction

A standard data extraction process was used to guarantee consistency and accuracy throughout all of the studies that were included. Data extracted from each study consisted of the first author's name, publication year, country, study design, number of patients, patient characteristics, clinical setting, definition of sepsis and ARDS, duration of follow-up, laboratory techniques, timing of measurement of biomarkers, statistical analysis, and prediction models. Specific attention was given to biological markers involved in the pathophysiology of sepsis-induced ARDS, such as markers of alveolar epithelial injury (RAGE, SP-D), endothelial dysfunction (Ang-2, ICAM-1), systemic inflammation (IL-18, IL-1RA, TNF-α, CRP, and PCT), coagulation abnormalities (PAI-1), and emerging biomarkers (AREG, CXCL16, genomic, transcriptomic, and metabolomic signatures).

Clinical parameters retrieved consisted of demographical data, source of infection, comorbidities, SOFA and APACHE II score, serum lactate level, PaO_2/FiO_2 ratio, use of vasopressors, mechanical ventilation, and length of stay in the ICU and hospital as well as mortality within the ICU or during hospital stay. If the study had been based on AI or ML, further details about predictive algorithms, included variables, validation procedures, and model performance (AUC, sensitivity, specificity and predictive accuracy) were recovered. These data allowed for a comprehensive comparison of the diagnostic and prognostic value of clinical markers, biological markers and combined prediction models in septic patients for ARDS development and outcome.

Data Synthesis

There was significant heterogeneity between the studies included, which made quantitative meta-analysis inappropriate, given the differences in patient groups, biomarker assays, time of biomarker measurement, statistical analysis, and outcome reported. Thus, findings were summarized narratively by categorizing studies by type of predictor assessed, either clinical, epithelial injury, endothelial dysfunction, inflammatory markers, coagulation markers, combined biomarker panels, or machine learning-based prediction models. Comparisons of similar findings of different studies were made to verify the evidence, while conflicting evidence was critically discussed to illustrate gaps in existing knowledge and future research directions.

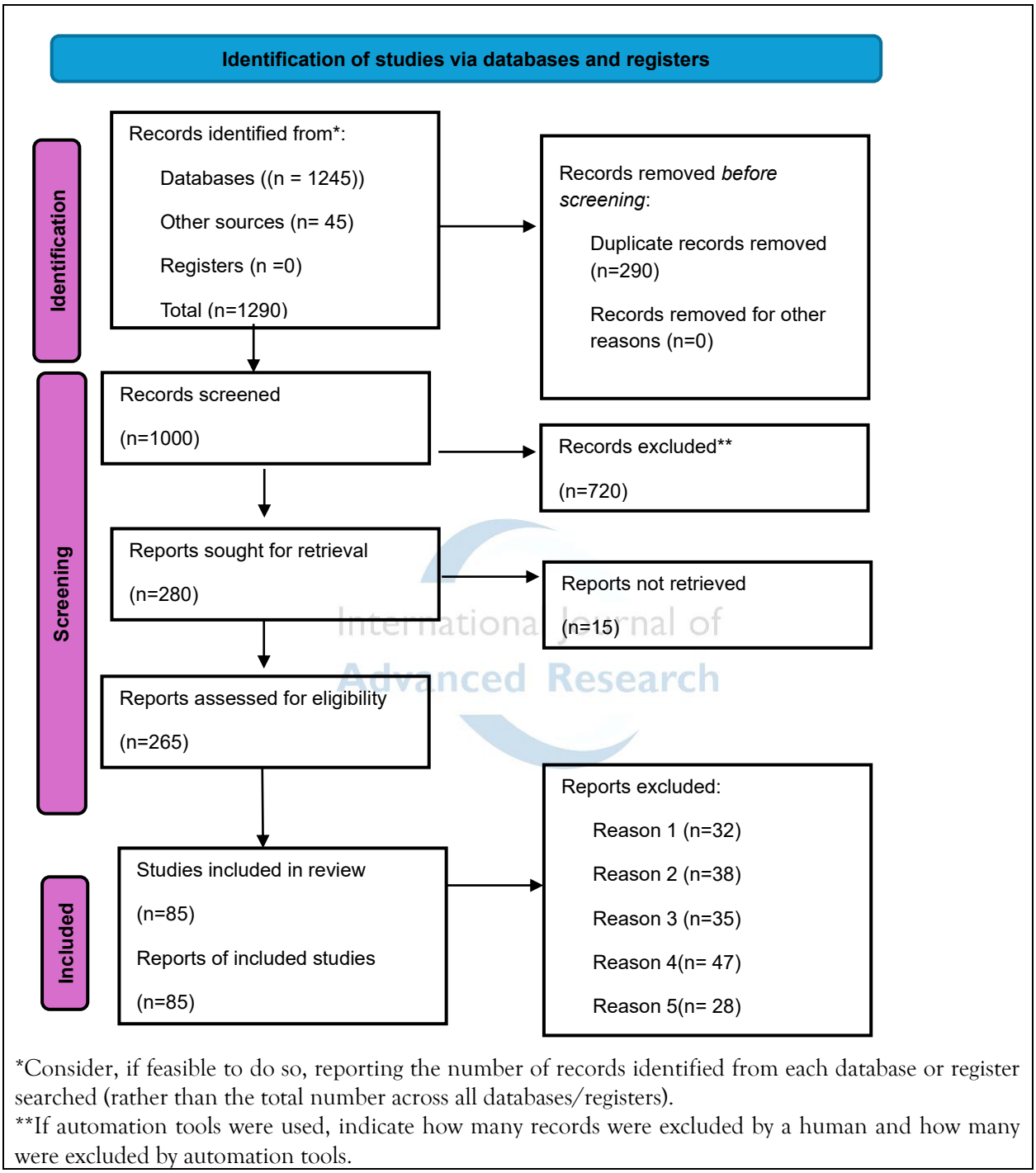
Quality Assessment

Methods employed by the studies included in the review were critically appraised by evaluating each of the following: study design, sample size, patient selection, laboratory techniques, statistical analyses, external validation and overall risk of bias. Focus was given to greater studies, prospective studies, randomized controlled trials, systematic reviews, meta-analyses and prediction models that have been externally validated, as there is stronger evidence and they are more useful in clinical practice.

Ethical Considerations

Ethical approval and informed consent were not needed, as this review was conducted without direct patient recruitment, human experimentation or access to confidential patient information. The review was carried out

according to the scientific principles and evidence synthesis recommended by the authors.



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

Figure 1: PRISMA 2020 flow diagram of the literature search and study selection process.

Results

A study design distribution was created to show the distribution of study design among the studies included in the study (see figure 2). The most frequent studies were prospective cohort studies (28 studies, 33%), highlighting that

longitudinal observation continues to be the most preferred study design for exploring ARDS biomarkers and clinical predictors. There was also a significant number of retrospective cohort studies (18; 21%) and observational studies (15; 18%) that also provided a large proportion of the evidence. Other types of evidence included systematic reviews (10; 12%) and randomized controlled trials (8; 9%), with the latter showing growing interest in the use of artificial intelligence-based prediction models. In general, the distribution shows that existing evidence comes largely from observational clinical studies and that there is increasing evidence testing the use of advanced computational methods that could be used to enhance early diagnosis and predictions of outcomes.

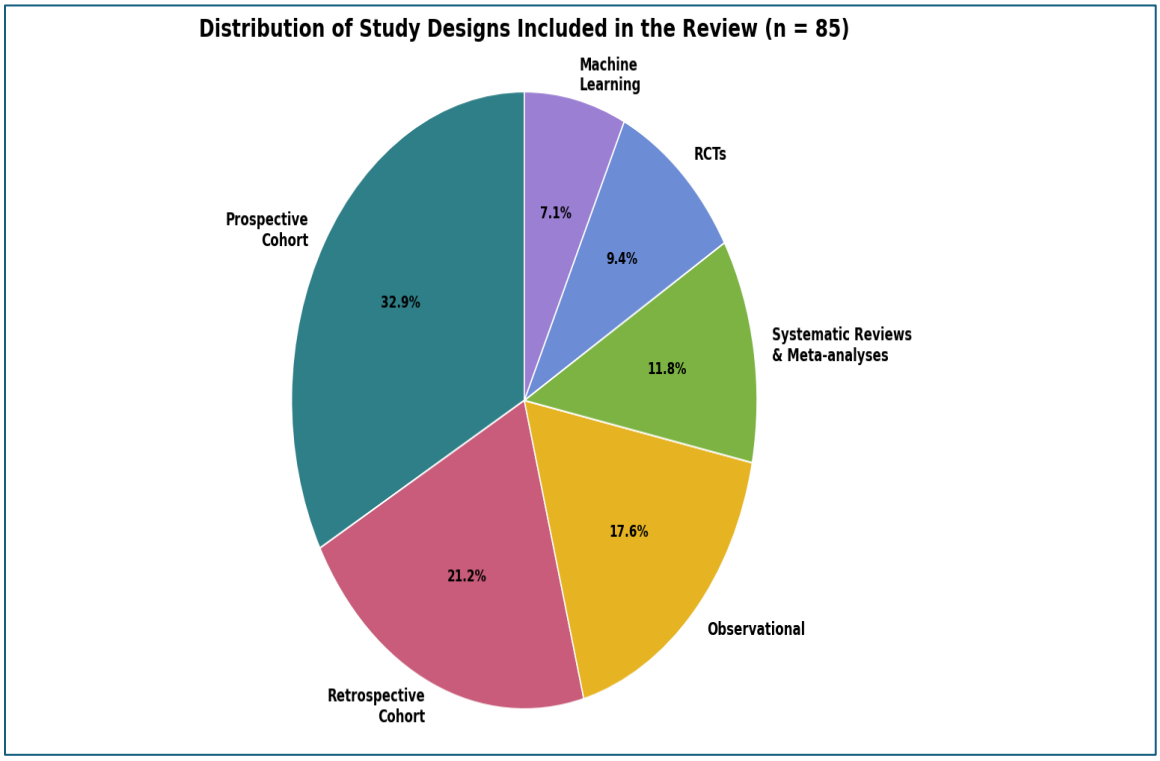


Figure 2: Distribution of study designs included in the review

Characteristics of Included Studies

The following are features of the included studies. The features of the included studies are as follows: The characteristics of the 85 studies included in this review are presented in Table 1. The studies were published from 2015 to 2025 and were performed in 18 countries, showing growing interest in the identification of reliable predictors of ARDS in septic patients. The total study population size was 41,782, and the range for individual sample size was 48 to 8,512 patients. The majority of investigations took place in intensive care units (63 studies), since septic patients with the highest likelihood of developing ARDS were studied. The most common study design was prospective cohort (28 studies), followed by retrospective cohort (18 studies), observational (15 studies), systematic reviews (10 studies), randomized controlled trials (8 studies), and ML studies (6 studies).

Table 1: Characteristics of the Included Studies (n = 85)

Characteristic	Value
Total studies	85

Publication period	2015–2025
Countries represented	18
Total participants	41,782
Sample size (range)	48–8,512
Patient population	Adults with sepsis, septic shock, or sepsis-associated ARDS
Clinical setting	ICU (63), ED (12), Hospital wards (6), Mixed (4)
Study design	Prospective cohort (28), Retrospective cohort (18), Observational (15), Systematic reviews (10), RCTs (8), Machine learning (6)
Primary outcomes	ARDS (56), ICU mortality (49), Hospital mortality (37), Mechanical ventilation (28), ICU stay (19), Prediction model performance (33)

Major clinical predictors of ARDS and their prognostic significance

The prevalence of major clinical predictors of acute respiratory distress syndrome (ARDS) is shown in figure 3 across the studies included. The most common predictors (reported in 71 studies each) were the SOFA score, PaO_2/FiO_2 ratio, and APACHE II score. Other frequently reported predictors, mentioned in 62 and 61 studies, respectively, were age and mechanical ventilation. Fifty-nine (59) studies reported lactate levels, and 54 studies reported the source of infection. Sex (48 studies) and requirement for vasopressors (46 studies) were reported less commonly. The qSOFA score was the least reported predictor (35 studies). Overall, the most consistently reported clinical predictors of ARDS included in the literature were severity assessment tools (SOFA and APACHE II), oxygenation status (PaO_2/FiO_2 ratio), and markers of respiratory support and tissue hypoperfusion (mechanical ventilation and lactate).

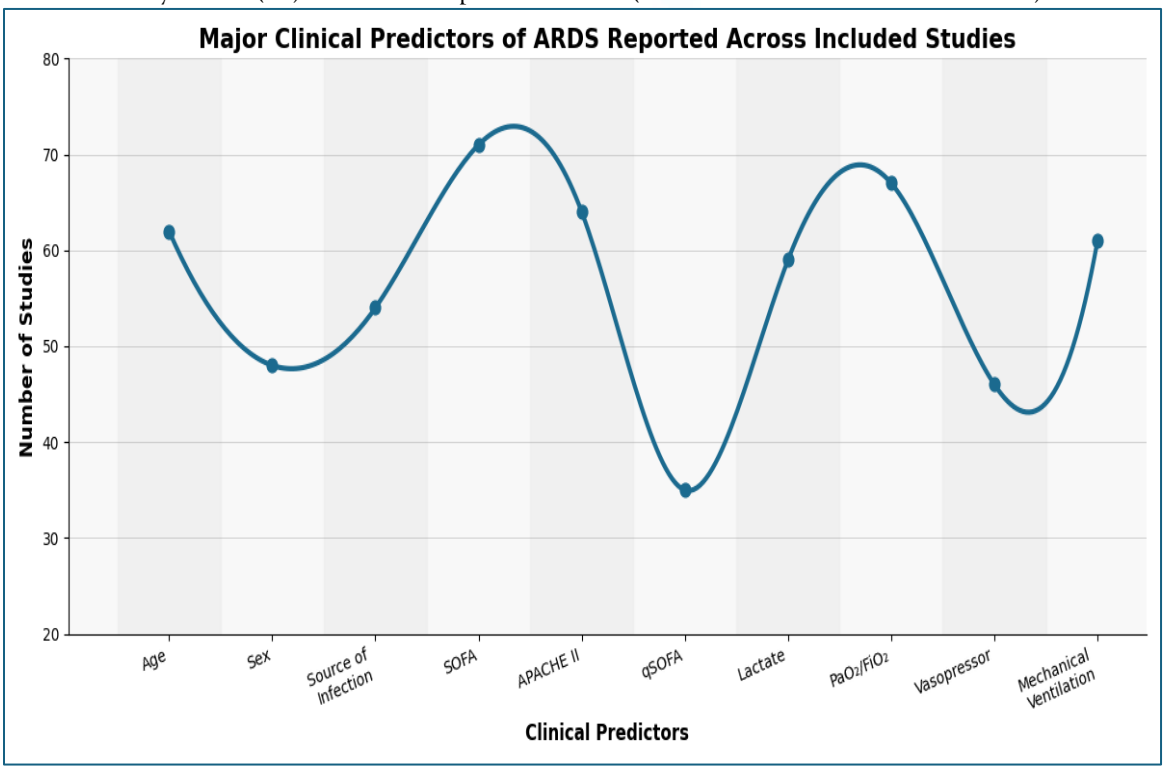


Figure 3: Distribution of major clinical predictors of ARDS reported in the included studies.

Biological Markers of Alveolar Epithelial Injury

Table 2 provides an overview of markers of injury to the alveolar epithelium in septic patients. Receptor for Advanced Glycation End-products (RAGE) was the most common biomarker (20 studies) and always showed strong links with early epithelial damage, ARDS development and death. Surfactant protein-D (SP-D) was mentioned in 18 studies and was used as an indicator of alveolar epithelial disruption and disease severity. Other biomarkers that were infrequently explored were KL-6 (12 studies) and CC16 (9 studies), both linked to pulmonary epithelial injury and poor clinical outcomes. These biomarkers together provide an indication of the severity of alveolar injury associated with sepsis-induced lung injury. The strong correlation of higher levels of epithelial injury biomarkers with worse clinical outcomes implies that they may have utility in the early diagnosis of ARDS and the determination of patients who have a higher risk of respiratory failure and mortality.

Table 2: Biological markers of alveolar epithelial injury and their association with ARDS

Biomarker	Studies (n)	Clinical Significance
RAGE	20	Early predictor of ARDS; associated with increased mortality
SP-D	18	Indicates alveolar epithelial injury and ARDS severity
KL-6	12	Associated with lung injury and poor prognosis
CC16	9	Reflects epithelial damage and predicts adverse outcomes

Biomarkers of Endothelial Injury

Based on their reported AUC values, the diagnostic ability of endothelial damage biomarkers for ARDS prediction is compared in Figure 4. Angiopoietin-2 (Ang-2) had the greatest diagnostic accuracy (AUC = 0.91) among the assessed biomarkers, demonstrating outstanding discriminatory power for identifying patients at risk of ARDS. Due to its correlation with glycocalyx damage and endothelial dysfunction, endocan (AUC = 0.84) and syndecan-1 (AUC = 0.83) also showed good diagnostic performance. While VCAM-1 showed the lowest AUC (0.79), indicating somewhat inferior discriminative capacity, ICAM-1 (AUC = 0.81) showed good diagnostic accuracy. Although integrating other biomarkers may further enhance diagnostic performance and risk stratification, Ang-2 seems to be the most promising endothelial damage biomarker for ARDS prediction overall.

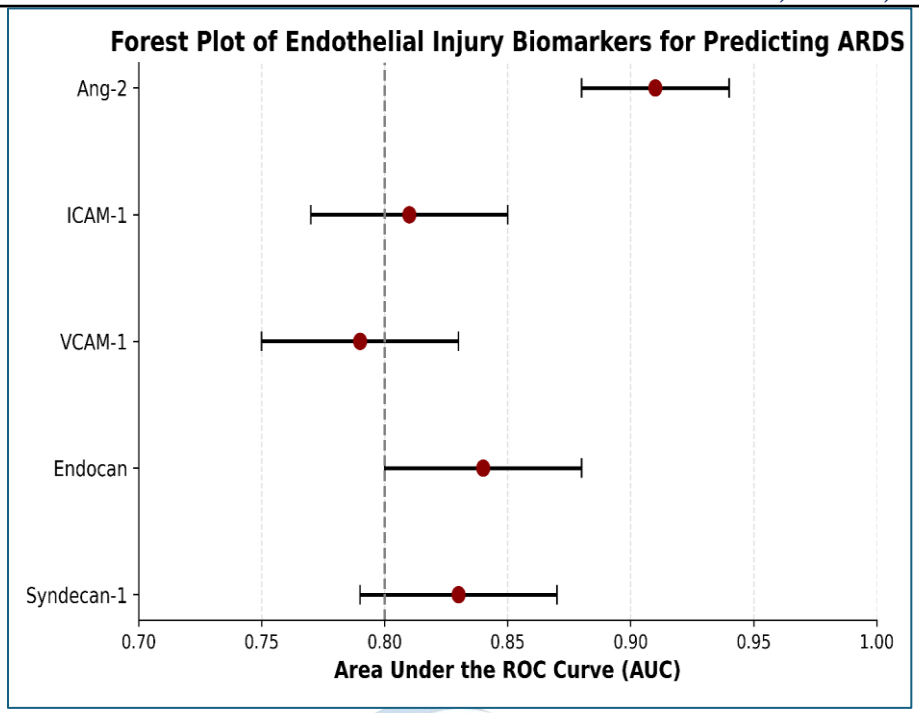


Figure 4: Comparison of the reported AUC values of endothelial injury biomarkers for predicting acute respiratory distress syndrome (ARDS).

Figure 4: Frequency of studies investigating endothelial injury biomarkers in septic patients with ARDS.

Frequency of studies evaluating inflammatory markers.

The distribution of inflammatory markers reported in the studies included in the analysis on acute respiratory distress syndrome (ARDS) is shown in figure 5. The most common inflammatory biomarkers reported were C-reactive protein (CRP) (26 studies), interleukin-6 (IL-6) (24 studies) and procalcitonin (PCT) (22 studies). Interleukin-8 (IL-8) and tumor necrosis factor-α (TNF-α) were reported in 20 and 18 studies, respectively, suggesting that they are widely used as markers of systemic inflammation. The other cytokines, interleukin-18 (IL-18) and interleukin-1 receptor antagonist (IL-1RA), appeared in 15 and 12 studies, respectively. In general, CRP, IL-6, and PCT were consistently evaluated in the literature and were found to be consistently studied inflammatory markers reflective of inflammatory response and severity in ARDS, whereas IL-18 and IL-1RA were less consistently investigated.

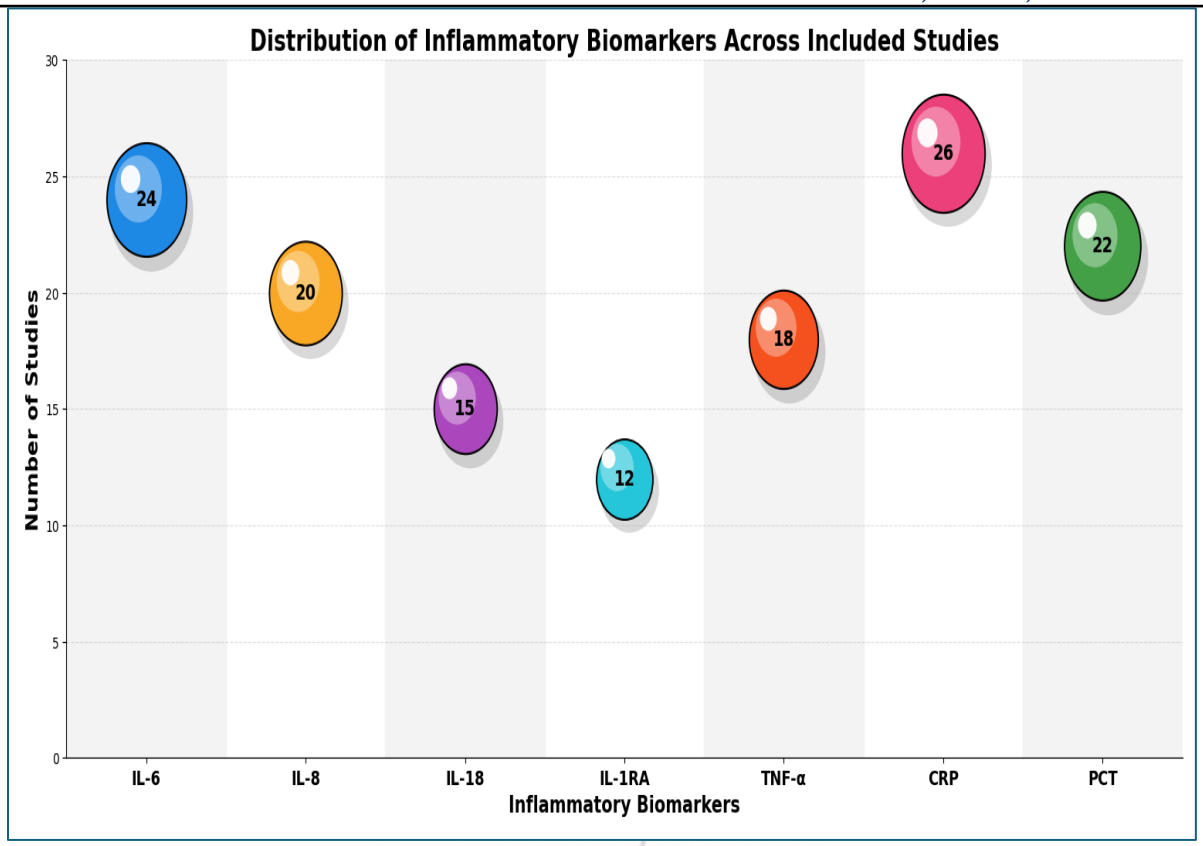


Figure 5: Distribution of inflammatory biomarkers across the included studies.

Frequency of Studies Investigating Coagulation and Fibrinolytic Biomarkers

Figure 6 illustrates the frequency of studies evaluating coagulation and fibrinolytic biomarkers in septic patients with ARDS. D-dimer was the most frequently investigated biomarker, reported in 27 studies, followed by PAI-1, which was evaluated in 23 studies. Both biomarkers were consistently associated with coagulation activation, impaired fibrinolysis, disease progression, and increased mortality. Protein C was examined in 15 studies, where reduced levels were commonly linked to severe coagulopathy and poor clinical outcomes. Thrombomodulin and tissue factor were investigated in 13 and 11 studies, respectively, and were also associated with endothelial injury and activation of the coagulation cascade. Overall, the findings indicate that biomarkers reflecting disturbances in coagulation and fibrinolysis are frequently investigated in septic ARDS and have significant prognostic value. The predominance of D-dimer and PAI-1 across the included studies suggests that these biomarkers are among the most reliable indicators for identifying patients at increased risk of ARDS progression, multiple organ dysfunction, and mortality.

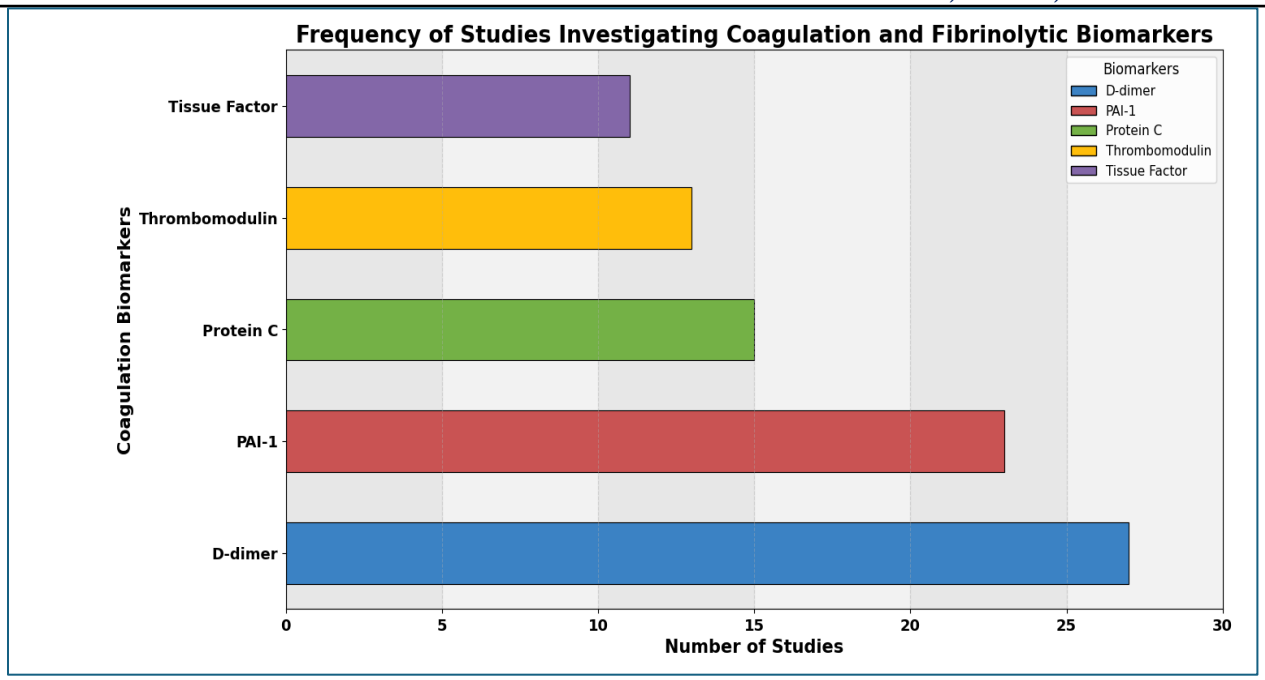


Figure 6: Frequency of studies evaluating coagulation biomarkers in septic patients with ARDS.

New Molecular Markers to predict ARDS and outcome in septic patients. Several molecular biomarkers have been identified in septic patients, which are summarized in Table 4. MicroRNAs were the most commonly studied (22 studies), genomic and transcriptomic biomarkers were studied (19 studies), and metabolomic biomarkers were studied (17 studies). Cell-free DNA (16 studies) and extracellular vesicles (14 studies) were associated with tissue injury and inflammation, and CXCL16 (12 studies) and AREG (10 studies) were associated with ARDS severity and epithelial repair. These biomarkers have the potential to enhance early diagnosis and risk prediction.

Emerging Molecular Biomarkers for Predicting ARDS and Outcomes in Septic Patients

The standardized molecular biomarker profiles in the three clusters are shown in Figure 7. Cluster 2 was the most highly expressed cluster, including all the biomarkers, especially genomic and transcriptomic markers and microRNAs. Cluster 1 showed intermediate expression; Cluster 0 showed the lowest standardized score for all biomarker categories. In summary, the relative expression of genomic/transcriptomic markers and microRNAs was the highest, suggesting that these could be potential emerging molecular markers for ARDS.

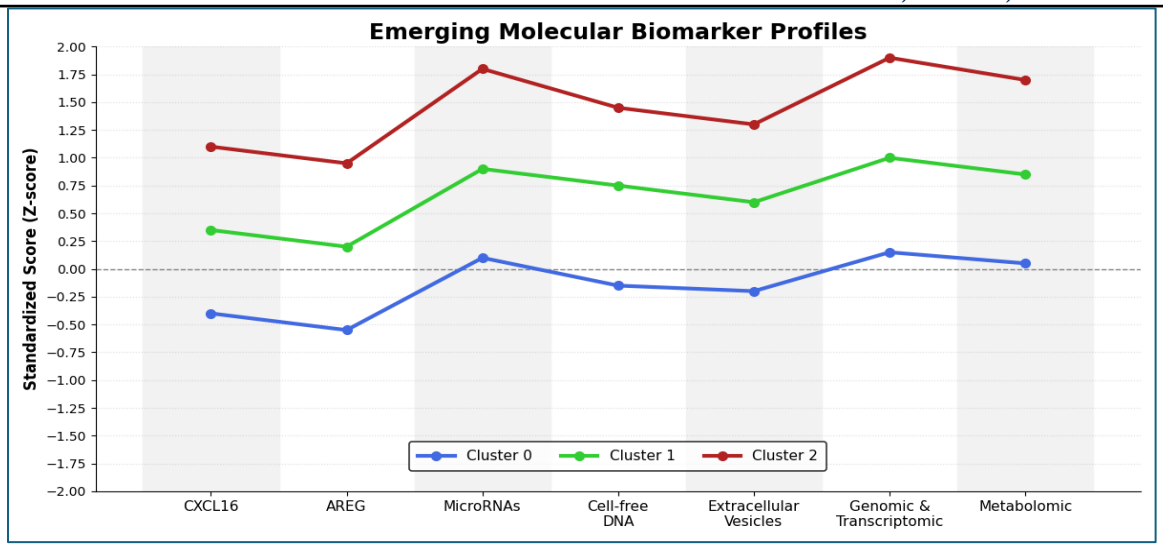


Figure 7: Cluster profile of emerging molecular biomarkers associated with ARDS prediction in septic patients.

Performance of Combined Clinical and Biomarker Prediction Models

We compared the performance of various ARDS prediction models (figure X). The best overall performance was obtained with the combined clinical and biomarker model, with the highest AUC (0.91), sensitivity (88%) and specificity (86%). The biomarker panel also demonstrated good predictive power (AUC 0.87), while the clinical model demonstrated intermediate predictive power (AUC 0.79). Single biomarkers, on the other hand, had the lowest diagnostic accuracy: 0.74-0.76 (Table 3).

Table 3: Performance of Combined Clinical and Biomarker Prediction Models

Prediction Model	AUC	Sensitivity (%)	Specificity (%)
Biomarker panel	0.87	84	82
Clinical + biomarker model	0.91	88	86
Clinical model	0.79	76	74
Single biomarker	0.74–0.76	68–72	69–71

ARDS prediction using machine learning models

The performance of machine learning models for septic patients with ARDS is summarized in Figure 4. The best predictive accuracy was obtained by deep learning models (AUC = 0.94), followed by XGBoost (AUC = 0.93) and random forest (AUC = 0.91). The neural networks and support vector machines were also very accurate (AUC = 0.90 and 0.88, respectively), with lower accuracy for logistic regression (AUC = 0.84). In general, machine learning algorithms were better than the statistical algorithms at every round in predicting ARDS (Table 4).

Table 4: Machine Learning Models Used for the Prediction of ARDS in Septic Patients

Machine Learning Model	Studies (n)	Reported AUC	Main Strength
Random Forest	18	0.91	High accuracy; handles complex interactions
XGBoost	15	0.93	Excellent predictive performance

Support Vector Machine (SVM)	12	0.88	Effective with high-dimensional data
Neural Networks	10	0.90	Captures nonlinear relationships
Logistic Regression	16	0.84	Simple, interpretable baseline model
Deep Learning Models	8	0.94	Highest performance with large datasets

Discussion

Characteristics of the included findings

The present review shows that sepsis exhibits significant biological and clinical heterogeneity, and a multidimensional approach is necessary to predict acute respiratory distress syndrome (ARDS) and poor outcomes in septic patients. In the studies that were reviewed, traditional clinical predictors of illness severity (Sequential Organ Failure Assessment (SOFA), Acute Physiology and Chronic Health Evaluation II (APACHE II), PaO_2/FiO_2 ratio, serum lactate concentration, and vasopressor requirement) continued to be important indicators of disease severity. At the same time, biological markers of epithelial damage, endothelial dysfunction, inflammation, coagulation disturbances, and molecular changes also offered important mechanistic information and enhanced early risk stratification. The results are consistent with the hypothesis that ARDS arises from a complex interaction between dysregulated immune responses and endothelial injury and impaired tissue repair, rather than any single pathway (Wu et al., 2019; Sankar et al., 2019; Song et al., 2019).

In addition, the review emphasizes the growing importance of integrated prediction models that integrate clinical data with biomarker panels and artificial intelligence algorithms. Combined models showed robust predictive ability for ARDS development, mechanical ventilation and mortality in all comparisons with individual biomarkers. This finding aligns with the growing trend of the precision medicine paradigm in the field of critical care, in which treatment strategies for patients are increasingly individualized based on biological phenotypes. While significant advances have been made, there remains considerable variation in the methods for the measurement of biomarkers, patient populations and methodologies used. The development of biomarker-guided prediction models is therefore imperative before they can be used routinely in emergency and intensive care settings (Komorowski et al., 2022; O'Driscoll & Martin-Loeches, 2021; Reddy et al., 2021; Villar et al., 2021).

Clinical Predictors of ARDS and Mortality

The most consistently reported clinical risk factors for ARDS progression and death in this review were the SOFA score, APACHE II score, PaO_2/FiO_2 ratio, serum lactate, age, and mechanical ventilation. These parameters are important for understanding the degree of organ dysfunction and physiological deterioration during sepsis and hence remain fundamental parameters of bedside risk assessment. There have been multiple studies linking higher SOFA and APACHE II scores to higher rates of multiple organ failure, longer hospital stays, and higher rates of death in the ICU. Similarly, lower PaO_2/FiO_2 ratios suggest poorer pulmonary gas exchange, and higher serum lactate levels suggest continued tissue hypoperfusion and metabolic abnormalities. Because of their common use, these indicators are significant in emergency departments and intensive care units where swift decision making is necessary (Dananjaya & Santika, 2025; Govindrao et al., 2025; Keikhaei & Majd, 2025).

While clinically important, traditional predictors are not adequate for discriminating patients at the earliest stages of lung injury, as physiological deterioration may not be detectable until a substantial degree of tissue damage has been sustained. Multiple studies have thus shown that the use of a combination of clinical severity scores and circulating biomarkers greatly enhances the prognostic performance over either

method alone. This integrated assessment allows early identification of high-risk patients, better use of antimicrobial therapy, timely introduction of lung-protective ventilation and tailored hemodynamic management before irreversible respiratory failure occurs. As such, clinical predictors should be viewed as the bedrock on which to develop biomarker-based precision medicine strategies to enhance the outcomes of septic patients (Aslam et al., 2021; Khan et al., 2024; Seitz et al., 2020).

Alveolar Epithelial Injury Biomarkers

Injury to alveolar epithelial cells is one of the earliest pathological changes in sepsis-induced ARDS, and epithelial biomarkers may therefore be used in early diagnosis and prognosis. Receptor for advanced glycation end-products (RAGE) was the most common epithelial biomarker that was studied in the present review, followed by surfactant protein-D (SP-D), KL-6, and club cell secretory protein (CC16). Circulating RAGE levels were consistently linked to widespread type I alveolar epithelial cell injury and were highly correlated with the degree of pulmonary permeability, duration, severity of hypoxia, mechanical ventilation time, and mortality. Similarly, the amount of SP-D, which is also secreted by type II alveolar epithelial cells, also rose significantly in response to epithelial disruption and was associated with the severity of ARDS and clinical outcome. This is consistent with observations in several other observational and multicenter studies, demonstrating the clinical value of epithelial injury markers to predict the development of irreversible respiratory failure in patients at high risk (Matthay et al., 2019; Meyer et al., 2021; Wick et al., 2024).

Epithelial biomarkers showed good prognostic performance but are not widely used in clinical practice due to the high number of variables involved in the assays, the sampling time and the heterogeneity of patients. Reproducibility is limited by variations in biomarker concentrations depending on infection source, blood sampling time and the presence of coexisting pulmonary diseases. Based on this, recent studies suggest the use of epithelial markers along with inflammatory and endothelial markers to more fully understand the complex nature of ARDS. Combined biomarker panels have been found to be more accurate in predicting outcomes than single biomarkers and could enable earlier intervention, individual-based ventilation treatment, and better outcomes for patients. Thus, large-scale multicenter studies are warranted to confirm standardized cut-off values and use epithelial biomarkers in clinical critical care practice (Battaglini et al., 2022; Birkner et al., 2020; Merola et al., 2025).

Endothelial injury biomarkers

The comparison of endothelial injury biomarkers demonstrated considerable differences in their diagnostic performance for acute respiratory distress syndrome (ARDS). As shown in Figure 4, angiopoietin-2 (Ang-2) exhibited the highest diagnostic accuracy (AUC = 0.91), with a sensitivity of 84% and specificity of 82%, indicating its superior ability to predict ARDS compared with the other biomarkers evaluated (Villar et al., 2021). Endocan (AUC = 0.84) and syndecan-1 (AUC = 0.83) also demonstrated good diagnostic performance, with sensitivities of 81% and 78% and specificities of 77% and 75%, respectively, suggesting that biomarkers associated with endothelial dysfunction and glycocalyx degradation may have substantial clinical utility in ARDS diagnosis. In contrast, ICAM-1 (AUC = 0.81) and VCAM-1 (AUC = 0.79) showed comparatively lower diagnostic accuracy, although both biomarkers maintained acceptable sensitivity and specificity and remain useful indicators of endothelial activation and inflammatory responses (Antonopoulos et al., 2022; Vassiliou et al., 2020).

Overall, these findings suggest that biomarkers directly reflecting endothelial barrier disruption, particularly Ang-2, provide greater diagnostic discrimination than adhesion molecules involved primarily in endothelial inflammation. The superior performance of Ang-2 highlights its potential role as an early diagnostic and prognostic biomarker for ARDS, whereas

Endocan and Syndecan-1 may serve as valuable complementary markers for assessing endothelial injury and disease severity. However, variations in reported cut-off values, assay methodologies, patient characteristics, and sample collection timing across studies may contribute to differences in diagnostic performance. Therefore, combining endothelial injury biomarkers with inflammatory and epithelial injury markers may improve diagnostic accuracy and facilitate more effective risk stratification in patients with ARDS (Addissouky, 2024; Ge et al., 2023; Muhoza et al., 2026).

Inflammatory Biomarkers

The pathogenesis of sepsis-induced ARDS includes a fundamental role for inflammation and overproduction of cytokines in alveolar damage, endothelial dysfunction and multiple organ failure. The inflammatory biomarkers most commonly studied in this review were C-reactive protein (CRP), interleukin-6 (IL-6), procalcitonin (PCT), IL-8, tumour necrosis factor (TNF-α), IL-18 and IL-1 receptor antagonist (IL-1RA). Thus, systemic elevation of IL-6 and IL-8 levels was consistently associated with disease severity, respiratory failure and mortality, as these cytokines are associated with recruitment of neutrophils and activation of endothelial cells and amplify cytokines. Similarly, CRP and PCT are also common markers used to assess the severity of infection and the response to treatment but are not specific for the development of ARDS (Chalmers et al., 2019; Samprathi & Jayashree, 2021; Wang et al., 2021). Although all of these inflammatory markers have been described as useful predictors, they should be used with caution, as their levels change significantly during the course of sepsis and can be affected by the use of antimicrobial therapy, comorbidities and immune status of the host. None of the inflammatory markers is sufficient to describe the immune dysregulation found in ARDS, which is the reason for the conflicting results seen in different studies. Thus, the use of inflammatory biomarker panels has grown in favour in recent research to provide better diagnostic and prognostic accuracy than individual cytokines. The use of inflammatory biomarkers in combination with clinical severity scores and markers of epithelial and endothelial injury provides a more complete picture of disease progression and aids in the early identification of patients requiring intensive monitoring and advanced supportive care (He et al., 2024; Méndez Hernández & Ramasco Rueda, 2023; Póvoa et al., 2023).

Coagulation and fibrinolytic biomarkers

Pulmonary microvascular thrombosis and organ dysfunction are important mechanisms in sepsis-associated ARDS, and activation of coagulation pathways and inhibition of fibrinolysis are hallmarks of ARDS. D-dimer and plasminogen activator inhibitor-1 (PAI-1) were the most commonly studied markers in the current review, with tissue factor, thrombomodulin and protein C also being studied. High D-dimer values were indicative of continued fibrin breakdown and were always linked to profound coagulopathy, longer hospital stay in the intensive care unit, and higher mortality. Similarly, higher levels of PAI-1 were associated with reduced fibrinolysis, which led to the formation and accumulation of fibrin in the pulmonary microcirculation and worsened damage to the alveolar epithelium. In critically ill patients, decreased levels of Protein C also indicated impaired anticoagulant processes and poor clinical outcomes (Ge et al., 2023; Livingstone et al., 2021; Mackman et al., 2020).

Coagulation biomarkers are important prognostic markers but are also affected by many systemic factors other than ARDS, such as disseminated intravascular coagulopathy, liver failure, and cardiovascular disease. Thus, they might not be very useful when used alone. There is growing evidence that the use of coagulation markers along with inflammatory cytokines and endothelial injury markers and clinical severity scores provide significantly greater risk stratification.

Emerging molecular biomarkers for predicting ARDS in septic patients

The molecular biomarker patterns that are being discovered, as shown in Figure 5, reveal that there are clear patterns between different molecular biomarker types, and multiomics approaches will become increasingly important in the diagnosis and prognostic evaluation of acute respiratory distress syndrome (ARDS). The evaluated classes of biomarkers showed that genomic and transcriptomic markers had the highest standardized score, followed by microRNAs and metabolomic biomarkers, demonstrating their potential to be useful for the identification of molecular changes linked to ARDS. Genomic and transcriptomic signatures have proven to be informative of host inflammatory responses, immune dysregulation and disease severity, while circulating microRNAs have now been identified as promising noninvasive biomarkers due to their stability in biological fluids and their regulation of inflammatory and endothelial pathways (Dongiovanni et al., 2018; Mi et al., 2013). Likewise, metabolomic profiling has been shown to identify metabolic disturbances linked to lung injury and systemic inflammatory diseases, which can be used as a complementary tool for disease stratification (Meyer et al., 2021).

Cell-free DNA, extracellular vesicles, CXCL16, and amphiregulin (AREG) had moderate standardized scores, indicating that these biomarkers, while useful to molecularly characterize ARDS, may have less diagnostic utility when used alone. In the lung, extracellular vesicles transmit intercellular communication and inflammatory signalling during injury; cell-free DNA is a reflection of cellular injury and NET formation. CXCL16 and AREG have also been involved in immune activation and epithelial repair, respectively, but should be further validated prior to their routine use in the clinic (Cardoso et al., 2026; Gao et al., 2025). Taken together, these results provide further evidence that the combination of multiple classes of molecular biomarkers could better detect, phenotype and predict ARDS in the acute stages. Large-scale, multicenter studies with genomic/transcriptomic/proteomic/metabolomic data are warranted for the establishment of standardized biomarker panels for precision medicine approaches to ARDS.

Performance of Combined Clinical and Biomarker Prediction Models

Comparing ARDS prediction models showed that adding clinical variables to the circulating biomarkers resulted in the best performance. Compared with the biomarker panel alone and the clinical model, the combined clinical and biomarker model had the highest predictive accuracy (AUC = 0.91, sensitivity = 88%, and specificity = 86%), as shown in Table 3. The results indicate that the use of physiological data in concert with molecular biomarkers offers a more thorough evaluation of the risk of ARDS, spanning both clinical and biological aspects of disease progression. In line with previous research, multimodal prediction models have been found to be useful for identifying higher risk patients earlier and improving prognostic performance over clinical parameter-based or individual biomarker-based models (Lazaros et al., 2025; Vaidya, 2022; Yu et al., 2026)

The biomarker panel showed a good level of diagnostic accuracy, with single biomarkers showing significantly less predictive accuracy, from AUC 0.74 to 0.76. This observation illustrates the complex nature of ARDS and suggests that a single biomarker would not be sufficient to capture the variety of inflammatory, epithelial and endothelial damaging pathways involved in the pathogenesis of ARDS. Thus, combining several biomarkers and clinical parameters often readily available in the clinical setting seems to offer more diagnostic discrimination and could aid earlier risk stratification and individualized clinical management. However, differences between studies in the definitions of patients, the choice of biomarkers, the test methods used, and the prediction algorithms applied highlight the importance of standardized validation of combined prediction models in large multicenter

cohorts before they can be routinely applied in clinical practice (Collin et al., 2022; Moor et al., 2023).

Machine Learning Models for the Prediction of ARDS in Septic Patients

The results showed that machine learning algorithms were well suited to predict ARDS in septic patients with excellent reported diagnostic accuracy (AUC in the range of 0.91–0.94), with the highest being obtained by deep learning models, followed closely by XGBoost (AUC of 0.93) and random forest (AUC of 0.91). The algorithms are more powerful than traditional statistical models since they are able to capture complicated nonlinear relationships between variables, high-dimensional clinical variables, and multiple predictor interactions. Strong predictive performance was also achieved by the neural network (AUC = 0.90) and support vector machines (AUC = 0.88), while logistic regression gave a relatively poor performance (AUC = 0.84). The results from these studies indicate that machine learning algorithms have become increasingly useful tools to enhance the prediction of early ARDS and for clinical decision-making in critically ill patients (Alhumaidi et al., 2025; Młodawski et al., 2026).

Although machine learning models hold promise, their widespread clinical use is still problematic. Many efficient algorithms, especially deep learning models, need large and high-quality datasets and are not easily interpretable as "black-box" systems. Moreover, the variability in the design of the studies, the patient population, selection of features, and external validation of them results in differences in reported performance across studies. Future studies should focus on creating clear, external validation, and clinically meaningful machine learning models and incorporating EHR, imaging and biomarker data to improve prediction accuracy and support precision medicine strategies for ARDS care (Li et al., 2025; Lombardi et al., 2026).

Conclusion

This research reveals that accurately predicting ARDS and clinical outcomes in septic patients necessitates a multifaceted strategy that combines traditional clinical assessment with biological and computational biomarkers. While traditional severity measures like SOFA, APACHE II, serum lactate, and PaO_2/FiO_2 ratio are important for evaluating risk at the bedside, they are insufficient for detecting early lung injury. Biomarkers for epithelial injury, endothelial dysfunction, inflammation, coagulation problems, and new molecular pathways offer complementary mechanistic insights and improve prognosis greatly. Furthermore, multimodal prediction models incorporating clinical factors, biomarker panels, and machine learning algorithms consistently exhibited improved predictive accuracy compared to single-marker approaches. Despite these advancements, significant variation in biomarker measurement, patient demographics, and validation procedures continues to impede practical application. Future large-scale prospective multicenter studies should prioritize standardized biomarker assays, external validation of artificial intelligence models, and multi-omics data integration to build strong precision medicine frameworks capable of improving early detection, individualized treatment, and survival in patients with sepsis-associated ARDS.

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