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ORIGINAL RESEARCH

# Development and Validation of a Nomogram for Predicting Sepsis-Associated Acute Respiratory Distress Syndrome

Chen Yan[1], Yangming Cai[1], Weiyi Cai[2], Qin Wang[1], Wen Li[1], Qing Geng[3]

[1]Department of Emergency, Renmin Hospital of Wuhan University, Wuhan, People's Republic of China; [2]Department of Trauma Surgery, Xiantao First People's Hospital, Xiantao, People's Republic of China; [3]Department of Thoracic Surgery, Renmin Hospital of Wuhan University, Wuhan, People's Republic of China

Correspondence: Qing Geng, Department of Thoracic Surgery, Renmin Hospital of Wuhan University, No. 99 Zhang Zhidong Street, Wuchang District, Wuhan, Hubei, 430060, People's Republic of China, Tel +86-17764070611, Email gengqingwhu@whu.edu.cn



**Background:** Sepsis-associated acute respiratory distress syndrome (ARDS) is a critical condition with high morbidity and mortality. Early identification of patients at high risk is crucial for timely intervention. This study aimed to develop and validate a nomogram for predicting the risk of ARDS in patients with sepsis.

**Methods:** A total of 308 patients with sepsis were retrospectively enrolled as the development cohort, and 132 patients were enrolled as an external validation cohort. Patients were categorized into ARDS and non-ARDS groups. Univariate and multivariate logistic regression analyses identified independent risk factors for ARDS in the development cohort, which were used to construct a nomogram. The nomogram's performance was assessed using the area under the receiver operating characteristic curve (AUC), calibration curves, decision curve analysis (DCA), and the Hosmer-Lemeshow (H-L) test.

**Results:** In the development cohort, 104 patients (33.77%) developed ARDS. Pulmonary infection (Odds Ratio [OR]=16.82), procalcitonin (PCT) (OR=2.71), tumor necrosis factor-alpha (TNF-α) (OR=1.102), oxygenation index (OR=0.861), and Acute Physiology and Chronic Health Evaluation II (APACHE II) score (OR=1.785) were identified as independent predictors. The nomogram demonstrated excellent discrimination, with an AUC of 0.862 in the development cohort and 0.881 in the validation cohort. Calibration curves showed good agreement between predicted and observed probabilities, supported by non-significant H-L tests (P>0.05). DCA confirmed the nomogram's clinical utility across a wide range of risk thresholds.

**Conclusion:** The developed nomogram, incorporating five accessible variables, is a reliable and practical tool for predicting the risk of ARDS in patients with sepsis. This model can assist clinicians in identifying high-risk individuals for early preventive measures and personalized management.

**Keywords:** sepsis, acute respiratory distress syndrome, nomogram, risk factors, prediction model

## Introduction

Sepsis, defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection, represents a major global health challenge with substantial morbidity, mortality, and healthcare costs.[1] It can rapidly progress to multiple organ dysfunction syndrome (MODS), with the lungs being one of the most frequently affected organs.[2] The inflammatory cascade triggered by sepsis can lead to diffuse alveolar damage, increased capillary permeability, and pulmonary edema, culminating in acute respiratory distress syndrome (ARDS).[3]

Sepsis-associated ARDS (S-ARDS) is characterized by acute-onset hypoxemia and bilateral pulmonary infiltrates not fully explained by cardiac failure or fluid overload, as per the Berlin definition.[4] Patients with S-ARDS experience prolonged mechanical ventilation, extended intensive care unit (ICU) stays, and a significantly higher risk of mortality compared to sepsis patients without ARDS.[5] The complex pathophysiology involves an intricate interplay of pro-inflammatory cytokines, endothelial dysfunction, neutrophil recruitment, and impaired alveolar fluid clearance.[6] Given

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the severity and poor prognosis of S-ARDS, early identification of patients at high risk is paramount for implementing timely preventive strategies and targeted therapies, potentially improving clinical outcomes.

The risk factors for developing sepsis-associated ARDS are multifactorial. Direct pulmonary insults, such as pneumonia (pulmonary infection), and indirect insults, like non-pulmonary sepsis, are well-established predisposing conditions, a finding strongly corroborated by recent meta-analyses.[7] Modifying factors, including chronic alcohol use, smoking, and obesity, can further increase a patient's susceptibility.[8] This clinical heterogeneity underscores the difficulty in accurately predicting ARDS development based on a single risk factor. Clinical prediction models, particularly nomograms, have emerged as valuable tools in modern medicine. Nomograms integrate multiple predictors to provide a graphical representation of statistical prognostic models, offering an individualized probability of a specific event, such as disease development or outcome.[9] They are increasingly utilized in various medical fields, including oncology and critical care, due to their intuitive interface and ability to quantify risk for individual patients.[10,11]

While some studies have explored predictors for ARDS, there remains a need for a dedicated, validated nomogram for the broader sepsis population using readily available parameters. Recent reviews have highlighted the critical importance of early identification and diagnosis of sepsis-related ARDS, emphasizing the roles of clinical scores and key biomarkers like procalcitonin (PCT) and tumor necrosis factor-alpha (TNF-α) in this process.[12] Therefore, this study aimed to develop and validate a novel nomogram incorporating easily accessible clinical and laboratory variables to predict the risk of developing ARDS in patients diagnosed with sepsis.

# Materials and Methods

## Study Design and Participants

This retrospective cohort study was conducted at Renmin Hospital of Wuhan University, a tertiary care teaching hospital. For the development cohort, we included 308 consecutive patients diagnosed with sepsis admitted to the emergency department or ICU between June 2020 and December 2024. For the external validation cohort, an additional 132 sepsis patients admitted to an affiliated hospital during the same period were enrolled. The study protocol was approved by the Institutional Ethics Committee of Renmin Hospital of Wuhan University, and the requirement for informed consent was waived due to the retrospective nature of the study and anonymized data analysis.

## Inclusion and Exclusion Criteria

Inclusion criteria were: (1) diagnosis of sepsis according to the Sepsis-3 criteria;[1] (2) age ≥ 18 years; (3) complete clinical data available; (4) no history of pulmonary arterial hypertension; (5) no diagnosis of ARDS upon admission or within the first 24 hours of data collection; (6) hospital stay ≥ 72 hours. Exclusion criteria were: (1) presence of autoimmune diseases; (2) chronic interstitial lung disease; (3) death or withdrawal of treatment within 72 hours of admission; (4) presence of other pre-existing severe respiratory diseases such as chronic obstructive pulmonary disease (COPD), asthma, or hemopneumothorax; (5) severe hepatic or renal dysfunction (defined as Child-Pugh class C for liver disease or baseline estimated glomerular filtration rate <30 mL/min/1.73m² unless sepsis-induced). Patients were followed for the development of ARDS during their hospital stay.

## Data Collection and Definitions

Data were extracted from electronic medical records. The following information was collected for each patient:

1). Basic characteristics: Age, sex, Body Mass Index (BMI), smoking history, alcohol consumption, history of comorbid conditions (eg, hypertension, diabetes mellitus, coronary heart disease, cerebrovascular disease), and presence of pulmonary infection as the primary source of sepsis.

2). Clinical and laboratory data (within 24 hours of sepsis diagnosis): Respiratory rate, blood pressure, heart rate, platelet count (PLT), C-reactive protein (CRP), arterial blood pH, Acute Physiology and Chronic Health Evaluation II (APACHE II) score,[13] serum albumin (ALB), Sequential Organ Failure Assessment (SOFA) score, procalcitonin (PCT), tumor necrosis factor-alpha (TNF-α), serum creatinine (Scr), total bilirubin (TBIL), blood urea nitrogen (BUN), forced

expiratory volume in 1 second as a percentage of predicted (FEV1%), lactic acid (Lac), FEV1/forced vital capacity ratio (FEV1/FVC), serum prealbumin (PA), oxygenation index ($PaO_2/FiO_2$ ratio), and white blood cell (WBC) count.

The diagnosis of ARDS was based on the Berlin Definition:[4] (1) onset within 1 week of a known clinical insult; (2) bilateral opacities on chest imaging not fully explained by effusions, lobar/lung collapse, or nodules; (3) respiratory failure not fully explained by cardiac failure or fluid overload. For this study, the primary outcome was the development of ARDS, with patients meeting the criteria for mild ARDS ($PaO_2/FiO_2$ ratio between 201–300 mmHg with PEEP or CPAP $\geq$ 5 $cmH_2O$) or worse being classified into the ARDS group, while others were in the non-ARDS group.

## Laboratory Measurements and Quality Control

Blood samples were collected by trained phlebotomists into EDTA-anticoagulated or serum-separating tubes. All laboratory parameters were measured in the hospital's certified central laboratory. PCT levels were determined using an electrochemiluminescence immunoassay (Roche Cobas e601 analyzer), and TNF-α levels were measured using an enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems, Minneapolis, MN, USA). All instruments were calibrated daily according to the manufacturer's protocols, and internal quality controls were run with each batch of samples to ensure accuracy and precision.

## Statistical Analysis

Statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA) and R software version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were expressed as mean ± standard deviation (SD) and compared using Student's *t*-test or Mann–Whitney *U*-test. Categorical variables were expressed as counts (percentages) and compared using the chi-square test or Fisher's exact test. In the development cohort, all clinically relevant variables listed in Table 1 were initially assessed by univariate analysis. Variables with a P-value < 0.10 were considered candidate predictors and were subsequently entered into a multivariate logistic regression analysis using a backward stepwise (likelihood ratio) selection method to identify independent predictors of ARDS. This process yielded the final five-variable model presented in Table 2. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. A nomogram was constructed based on the final model using the "rms" package in R.

**Table 1** Baseline Characteristics of Patients in the Development Cohort (N=308)

| Variable | Non-ARDS Group (n=204) | ARDS Group (n=104) | P-value |
|---|---|---|---|
| Age (years, mean ± SD) | 56.95 ± 11.50 | 58.35 ± 10.15 | 0.287 |
| BMI (kg/m², mean ± SD) | 23.60 ± 2.18 | 22.85 ± 2.72 | 0.085 |
| Male sex, n (%) | 110 (53.92) | 65 (62.50) | 0.163 |
| Smoking, n (%) | 79 (38.73) | 48 (46.15) | 0.201 |
| Alcohol consumption, n (%) | 53 (25.98) | 31 (29.81) | 0.465 |
| Hypertension, n (%) | 73 (35.78) | 43 (41.35) | 0.331 |
| Diabetes mellitus, n (%) | 36 (17.65) | 17 (16.35) | 0.764 |
| Coronary heart disease, n (%) | 45 (22.06) | 23 (22.12) | 0.989 |
| Cerebrovascular disease, n (%) | 35 (17.16) | 19 (18.27) | 0.798 |
| **Pulmonary infection, n (%)** | **74 (36.27)** | **81 (77.88)** | **<0.001** |
| **CRP (mg/L, mean ± SD)** | **12.05 ± 1.50** | **14.10 ± 2.70** | **<0.001** |
| **PCT (μg/L, mean ± SD)** | **10.05 ± 2.25** | **14.15 ± 2.70** | **<0.001** |
| **TNF-α (pg/L, mean ± SD)** | **280.95 ± 25.80** | **360.15 ± 31.55** | **<0.001** |
| **Oxygenation index (mmHg, mean ± SD)** | **187.05 ± 10.70** | **158.95 ± 10.85** | **<0.001** |
| **APACHE II score (points, mean ± SD)** | **11.68 ± 2.61** | **16.65 ± 2.70** | **<0.001** |

**Notes**: Data are n (%) or mean ± SD. Bold indicates P < 0.05.
**Abbreviations**: ARDS, acute respiratory distress syndrome; BMI, body mass index; CRP, C-reactive protein; PCT, procalcitonin; TNF-α, tumor necrosis factor-alpha; APACHE II, Acute Physiology and Chronic Health Evaluation II.


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**Table 2** Multivariate Logistic Regression Analysis of Independent Predictors for ARDS

| Variable | β | SE | Wald $\chi^2$ | P-value | OR | 95% CI for OR |
|---|---|---|---|---|---|---|
| Pulmonary infection (Yes vs No) | 2.105 | 1.401 | 4.215 | **0.041** | 16.820 | 1.120–25.310 |
| PCT (μg/L) | 0.997 | 0.442 | 5.120 | **0.023** | 2.710 | 1.150–6.350 |
| TNF-α (pg/L) | 0.097 | 0.029 | 11.550 | **<0.001** | 1.102 | 1.041–1.165 |
| Oxygenation index (mmHg) | −0.150 | 0.058 | 6.595 | **0.010** | 0.861 | 0.770–0.962 |
| APACHE II score (points) | 0.580 | 0.253 | 5.238 | **0.022** | 1.785 | 1.090–2.915 |

**Note**: Bold indicates P < 0.05.
**Abbreviations**: β, regression coefficient; SE, standard error; OR, odds ratio; CI, confidence interval.

The performance of the nomogram was evaluated by:

1) Discrimination: Assessed by the area under the receiver operating characteristic curve (AUC).

2) Calibration: Assessed by plotting calibration curves and using the Hosmer-Lemeshow (H-L) goodness-of-fit test, where a P-value > 0.05 indicates good calibration.

3) Clinical Utility: Assessed by decision curve analysis (DCA) to quantify the net benefit of the nomogram at different threshold probabilities.[14]

Internal and external validation were performed. A two-tailed P-value < 0.05 was considered statistically significant.

# Results

## Baseline Characteristics of Patients

A total of 308 sepsis patients were included in the development cohort. Among them, 104 (33.77%) developed ARGS (ARDS group), and 204 (66.23%) did not (non-ARDS group). Compared to the non-ARDS group, patients in the ARDS group had a significantly higher proportion of pulmonary infection, higher levels of PCT and TNF-α, and higher APACHE II scores (all P<0.001). The oxygenation index was significantly lower in the ARDS group (P<0.001). Detailed characteristics are in Table 1. The validation cohort consisted of 132 patients, of whom 42 (31.82%) developed ARDS. The baseline characteristics of the validation cohort (Supplementary Table 1) were generally similar to those of the development cohort.

## Independent Predictors for ARDS in the Development Cohort

Multivariate logistic regression analysis identified five independent predictors for ARDS: pulmonary infection (OR=16.820, 95% CI 1.120–25.310), PCT (OR=2.710, 95% CI 1.150–6.350), TNF-α (OR=1.102, 95% CI 1.041–1.165), oxygenation index (OR=0.861, 95% CI 0.770–0.962), and APACHE II score (OR=1.785, 95% CI 1.090–2.915) (Table 2).

## Construction and Internal Validation of the Nomogram

A nomogram was constructed based on the five independent predictors identified (Figure 1). To use the nomogram, one locates a patient's value on each predictor axis, draws a vertical line up to the "Score/Points" axis to determine the points for that predictor, and sums the points from all five predictors. For example, a sepsis patient with pulmonary infection (35 points), a PCT level of 10 μg/L (approx. 24 points), a TNF-α level of 300 pg/L (approx. 20 points), an oxygenation index of 150 mmHg (approx. 27 points), and an APACHE II score of 15 (approx. 26 points) would have a total score of approximately 132 points, translating to a predicted ARDS risk of about 60%.

Internal validation in the development cohort showed that the nomogram had excellent discrimination, with an AUC of 0.862 (95% CI 0.815–0.909) (Figure 2A). The optimal cutoff point for the nomogram in the development cohort, as determined by the Youden index, corresponded to a sensitivity of 81.7% and a specificity of 78.4%. The calibration curve demonstrated good agreement between predicted and observed probabilities (Figure 2B). The Hosmer-Lemeshow test yielded a P-value of 0.398, indicating good calibration.

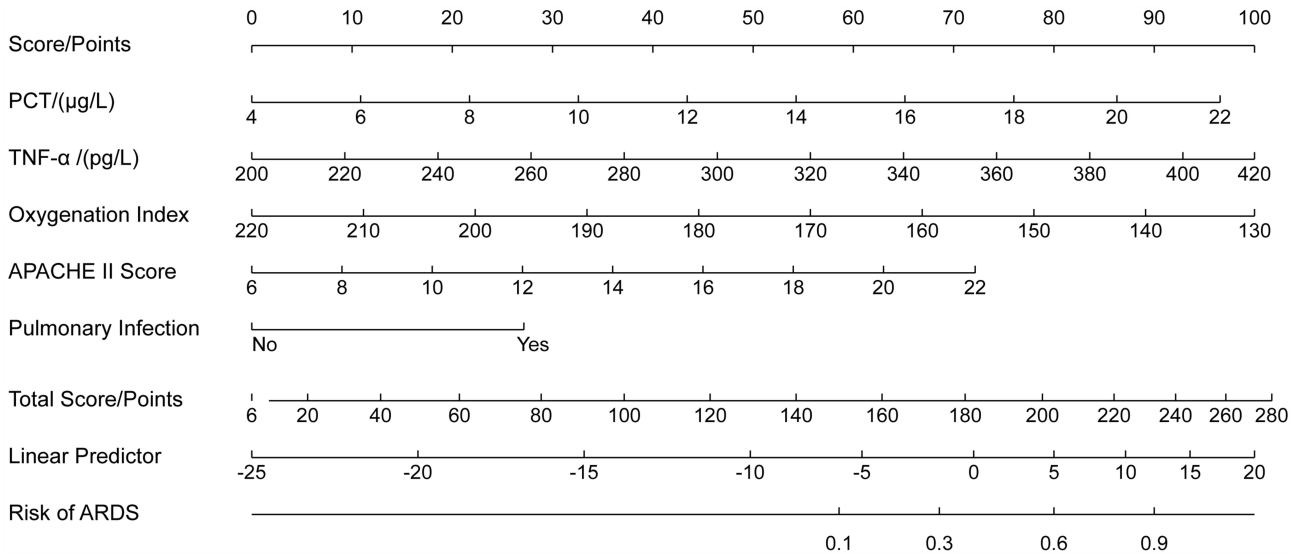


**Figure 1** Nomogram for predicting the risk of sepsis-associated acute respiratory distress syndrome (ARDS). To use the nomogram, locate a patient's value on each variable axis, draw a vertical line to the top "Score/Points" axis to determine the points for that variable, and sum the points. The total score corresponds to the predicted probability of ARDS on the bottom axis.

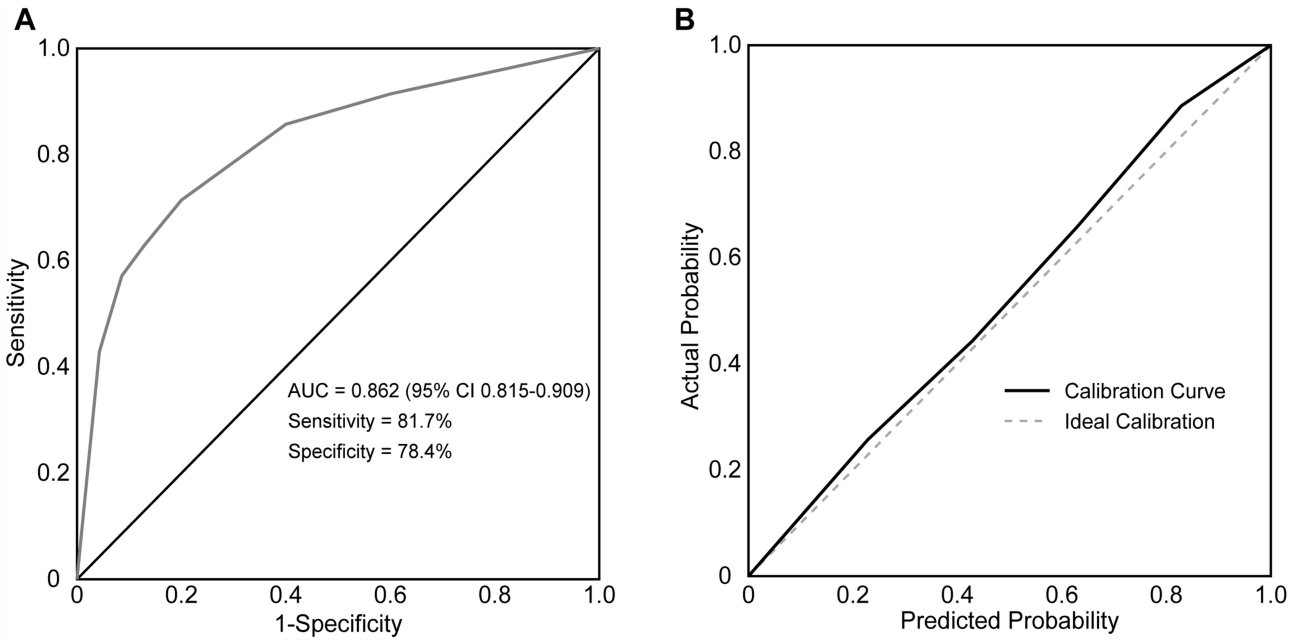


**Figure 2** Performance of the nomogram in the development cohort (N=308). (**A**) Receiver operating characteristic (ROC) curve. (**B**) Calibration curve.

## External Validation of the Nomogram

In the external validation cohort, the nomogram also demonstrated excellent discrimination with an AUC of 0.881 (95% CI 0.825–0.957) (Figure 3A). At the optimal cutoff value, the sensitivity was 83.3% and the specificity was 80.0%. The calibration curve showed good consistency between predicted and observed probabilities (Figure 3B), and the Hosmer-Lemeshow test was not significant (P=0.445), confirming good calibration.


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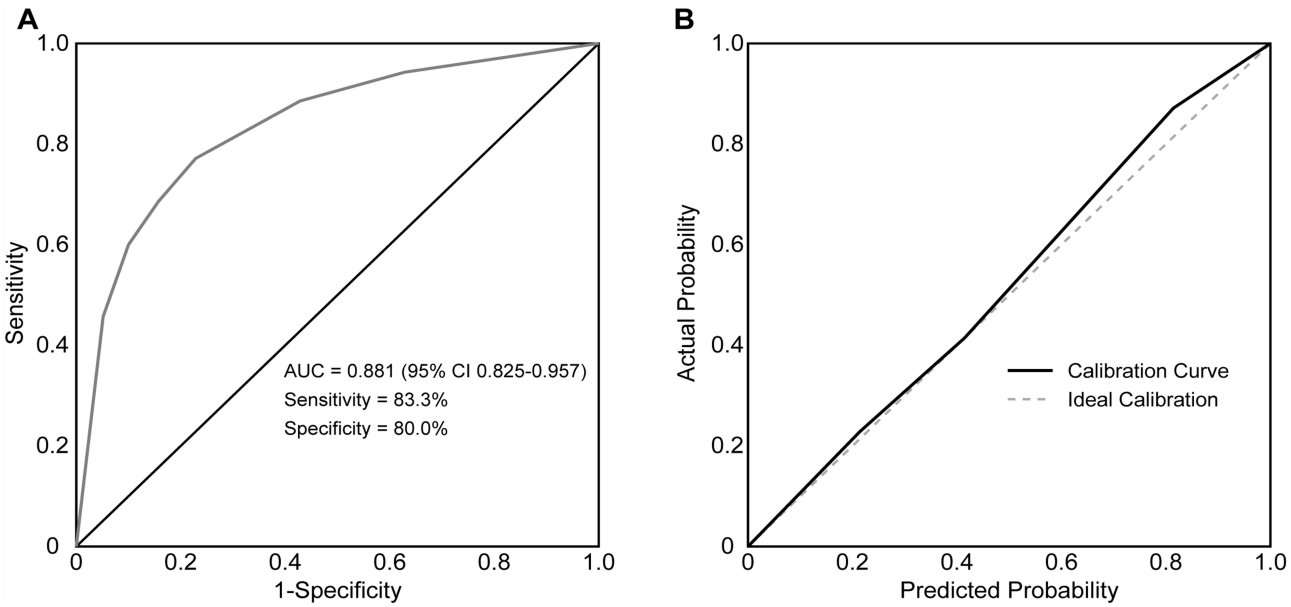


**Figure 3** Performance of the nomogram in the external validation cohort (N=132). (**A**) Receiver operating characteristic (ROC) curve. (**B**) Calibration curve.

## Decision Curve Analysis and Clinical Impact Analysis

As shown in Figure 4, the DCA curve for the nomogram demonstrated a positive net benefit across a wide range of threshold probabilities (approximately 20% to 80%) compared to the strategies of treating all patients or treating no patients. This indicates that using the nomogram to guide clinical decisions would lead to better outcomes than either default strategy. A sensitivity analysis was also performed by rebuilding the model without the oxygenation index to address potential circularity concerns. This alternative model still demonstrated good discrimination, with an AUC of 0.825 in the development cohort and 0.841 in the validation cohort, supporting the robustness of the other four predictors.

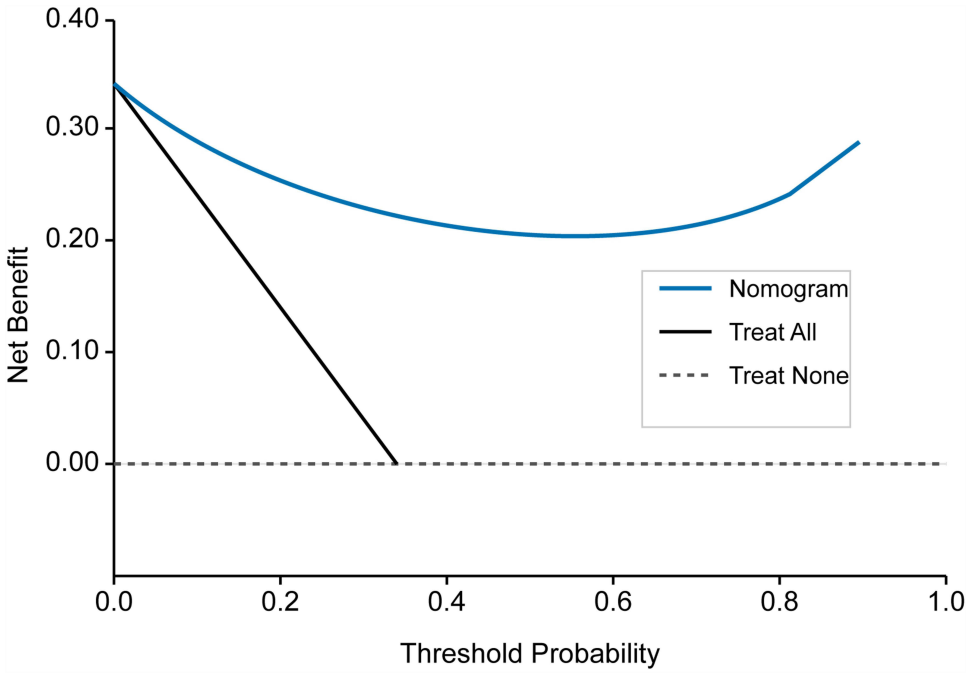


**Figure 4** Decision curve analysis (DCA) for the nomogram. The y-axis represents the net benefit. The blue line (Nomogram) shows a higher net benefit than either the "Treat All" strategy (black solid line) or the "Treat None" strategy (dashed gray line) across a threshold probability range of approximately 20% to 80%.

## Discussion

Sepsis-associated ARDS is a devastating complication. In this study, we developed and externally validated a nomogram for predicting the risk of ARDS in patients with sepsis, incorporating five readily available parameters: APACHE II score, pulmonary infection, PCT, TNF-α, and oxygenation index. The nomogram demonstrated excellent discrimination and calibration in both cohorts, suggesting its utility for early risk stratification.

The predictors identified in our model are strongly supported by the latest evidence. A recent comprehensive meta-analysis by Yin et al confirmed that pulmonary infection and higher APACHE II scores are significant risk factors for ARDS in sepsis patients.[7] Concurrently, a narrative review by Zhang et al underscored the central role of inflammatory biomarkers like PCT and TNF-α in the pathophysiology and early diagnosis of sepsis-related ARDS.[12] Our findings align perfectly with these conclusions, lending substantial external validity to our model. The incidence of ARDS in our sepsis cohorts (33.77% and 31.82%) is consistent with rates reported previously.[15–18] Early identification allows for proactive measures, such as lung-protective ventilation and judicious fluid management, which may mitigate ARDS severity.[19] Furthermore, the clinical utility of the nomogram was confirmed by decision curve analysis, which demonstrated that using the nomogram to guide clinical decisions provides a greater net benefit than treating all or no patients across a wide range of clinically relevant risk thresholds (20% to 80%).

Our analysis confirmed several plausible risk factors. The APACHE II score reflects overall illness severity and is a known predictor of organ dysfunction.[13,20] Pulmonary infection as a sepsis source provides a direct lung insult, making it a strong and intuitive predictor.[6] The biomarkers PCT and TNF-α are well-recognized indicators of bacterial infection severity and systemic inflammation, respectively, and both play central roles in ARDS pathogenesis.[6,21,22] The oxygenation index, measured before ARDS diagnosis, highlights that even subtle early disturbances in gas exchange can herald progression to clinically significant disease.[23]

Notably, several established modifying risk factors for ARDS, such as diabetes mellitus and alcohol consumption, were not retained as independent predictors in our final multivariate model. In our univariate analysis, these factors did not show a strong association with ARDS development ($P > 0.10$) and were therefore excluded from the multivariate stage. This observation is consistent with the findings of the large-scale meta-analysis by Yin et al, which also found no statistically significant association between smoking status and the development of ARDS in septic patients.[7] This could be due to the overwhelming predictive power of acute physiological derangements (APACHE II score) and key biomarkers (PCT, TNF-α) in our cohort, which may have masked the more subtle effects of chronic comorbidities. It is also possible that the sample size was insufficient to detect smaller effect sizes for these variables.

The strength of our study lies in its user-friendly nomogram and its successful external validation. The consistent performance across two different hospital populations enhances confidence in its generalizability. Our model's reliance on both general severity scores like APACHE II and specific inflammatory markers like PCT aligns with other recent prognostic models in critical care. For example, a study by Uluç et al utilized systemic inflammatory markers and composite scores to predict mortality in geriatric patients in the respiratory ICU, similarly highlighting the value of integrating physiological data with biomarker profiles for risk stratification.[24]

Several limitations should be acknowledged. First, the retrospective design is susceptible to bias. Second, the precise timing of ARDS onset can be challenging to pinpoint retrospectively. Third, the sample size, particularly in the validation cohort, is moderate; larger, multicenter prospective studies are needed for further validation. Fourth, our model is based on static variables collected at a single time point and does not account for the dynamic changes in a patient's clinical parameters over time. Finally, the inclusion of TNF-α, which is not a routine test in all centers, may limit the immediate widespread applicability of the nomogram, though its strong mechanistic link to ARDS justifies its inclusion.

## Conclusion

In conclusion, we successfully developed and externally validated a nomogram for predicting the risk of ARDS in patients with sepsis. This nomogram demonstrated good discrimination, calibration, and clinical utility, offering a practical tool to assist clinicians in the early identification of high-risk patients, thereby facilitating timely interventions.

## Ethics Approval and Consent to Participate

The study protocol was approved by the Ethics Committee of Renmin Hospital of Wuhan University. The requirement for informed consent was waived.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that they have no competing interests in this work.

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