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Preoperative Red Cell Distribution Width-to-Albumin Ratio and In-Hospital Mortality in Patients with Fournier Gangrene Requiring Postoperative Intensive Care: A Retrospective Cohort Study

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Abstract

Background/Objectives: The red cell distribution width-to-albumin ratio (RAR) is associated with mortality in Fournier gangrene, but its value beyond albumin remains uncertain. We examined preoperative RAR in patients requiring postoperative intensive care and compared its performance with its components. **Methods:** This single-center retrospective cohort included 105 adults admitted to intensive care after their first debridement (January 2024–January 2026). RAR was calculated from operative-day preoperative measurements. Logistic regression adjusted for American Society of Anesthesiologists (ASA) physical status. Firth regression, covariate sensitivity analyses, paired discrimination comparisons and bootstrap internal validation were performed. **Results:** Twenty-five patients (23.8%) died during hospitalization. Median RAR was 8.30 (interquartile range 6.74–10.21) in nonsurvivors and 5.04 (4.17–6.19) in survivors. The area under the receiver operating characteristic curve (AUC) was 0.888 for RAR, 0.839 for albumin and 0.799 for red cell distribution width. The adjusted odds ratio per one-unit RAR increase was 1.77 (95% confidence interval [CI] 1.32–2.39); for ASA IV–V versus II–III, it was 10.98 (2.63–45.74). The ASA–RAR model had an optimism-corrected AUC of 0.914 (approximate 95% CI 0.836–0.971) and calibration slope of 0.962. Its corrected AUC difference from ASA plus albumin was 0.015 (−0.019 to 0.045). **Conclusions:** Higher preoperative RAR was associated with in-hospital mortality independently of ASA physical status. A predictive advantage over ASA plus albumin was not demonstrated. External validation against albumin and established severity scores is required before clinical use.

Keywords: Fournier gangrene; necrotizing soft tissue infection; red cell distribution width; serum albumin; blood-based biomarkers; prognosis; intensive care units; hospital mortality

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1. Introduction

Fournier gangrene is a rapidly progressive necrotizing infection of the genital, perineal and perianal tissues that can cause septic shock and organ failure [1,2]. A systematic review of 3646 patients reported a crude mortality of 20.4% [3]. Estimates vary with case mix and disease severity [4,5], and an umbrella review found little improvement over time [6].

Early debridement, antibiotics and organ support remain central to treatment [1,2,6–8]. Patients requiring postoperative intensive care form a clinically distinct, selected population. Evaluating prognosis within this group may help characterize mortality risk after the ICU decision has been made; it cannot establish which patients need ICU admission.

The Fournier Gangrene Severity Index (FGSI) and related scores assess physiological severity, but their performance and thresholds vary [4]. The Fournier's Gangrene Mortality Index incorporates age, creatinine, albumin, lymphocyte percentage and the neutrophil-to-lymphocyte ratio (NLR) [9]. Higher admission NLR has been associated with mortality [10], while initial albumin and postoperative lactate were independent predictors in a postoperative ICU cohort [11].

Routine biomarkers offer readily available alternatives, but their value depends on sampling time and information beyond established predictors. Reviews of C-reactive protein (CRP) and other sepsis biomarkers show heterogeneous performance [12–14]. The CRP-to-albumin ratio (CAR), lactate-to-albumin ratio (LAR), NLR and systemic immune-inflammation index (SII) have also been associated with mortality [15–20]. We examined these as exploratory comparators, rather than assuming that combining measurements necessarily improves prediction.

Red cell distribution width (RDW) is influenced by inflammation, oxidative stress and erythropoiesis [21,22], while albumin reflects inflammatory and metabolic changes [17,18,23]. Their ratio (RAR) has been associated with mortality in cardiovascular and critically ill populations [24–27]. Kayar et al. reported an RAR area under the receiver operating characteristic curve (AUC) of 0.955 in 62 patients with scrotal Fournier gangrene [28]. However, this small study did not establish incremental performance beyond albumin in a postoperative ICU population. Albumin is itself prognostic in Fournier gangrene [9,11], making a direct component comparison essential.

We examined the association between preoperative RAR and in-hospital mortality in adults requiring intensive care after their first debridement. We compared ASA–RAR models with models containing albumin, RDW or both components separately. ASA physical status provided routinely recorded preoperative adjustment with few parameters; it was not considered a substitute for acute severity. Other indices and postoperative ICU length of stay were exploratory outcomes or comparators.

2. Materials and Methods

2.1. Study Design, Setting and Ethics

This single-center retrospective cohort study included adults treated in the anesthesiology intensive care unit (ICU) of Izmir City Hospital, Izmir, Türkiye, between 1 January 2024 and 31 January 2026. The eligibility period was specified in the ethics application before data extraction. Reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement, and the relevant items of the updated reporting guidance for clinical prediction models that use regression or machine learning methods (TRIPOD+AI) were used for the model-performance analyses [29,30]. A completed STROBE checklist is provided as a Supplementary File S1.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Non-Interventional Ethics Committee of Izmir City Hospital on 22 July 2026 (decision number 2026-500). The committee waived the requirement for informed consent because of the retrospective design. After approval, the principal investigator accessed the hospital records on 1 August 2026; records from the prespecified clinical period were screened retrospectively during August 2026, and study data were recorded in anonymized form.

2.2. Participants

Patients were identified by searching the hospital information system for P621470, the institutional procedure code for debridement of Fournier gangrene. Eligible patients were aged at least 18 years, underwent debridement for Fournier gangrene and required

postoperative ICU admission. Duplicate entries were removed at the patient level, and only the first hospital admission within the study period was retained. Operative-note review confirmed Fournier gangrene in every retained patient. No included patient had undergone surgery for Fournier gangrene before the study period. Institutional indications for postoperative ICU admission included hemodynamic instability, vasopressor or inotropic requirements, mechanical ventilation, or impaired consciousness with a Glasgow Coma Scale score below 15. These describe the admission criteria; patient-level frequencies of the individual indications were not available.

Patients who received postoperative ward care without ICU admission were not eligible. Exclusion criteria were advanced liver cirrhosis, a history of hematological malignancy, missing laboratory data, serious inconsistencies in the medical records, and preoperative red blood cell transfusion or albumin administration; the last two criteria were applied because both interventions directly alter the components of the ratio. All eligible patients treated during the study period were included, and no a priori sample-size calculation was performed. The selection process is summarized in Figure 1.

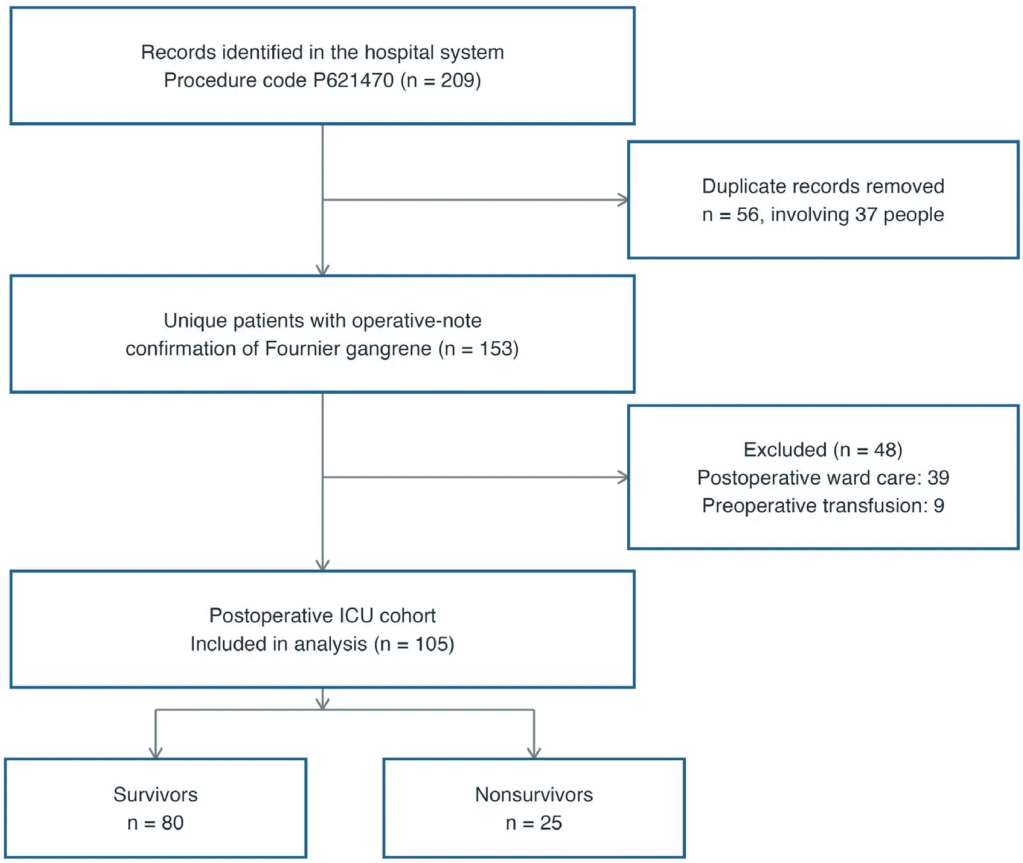


Figure 1. Flow diagram of patient selection. ICU, intensive care unit.

2.3. Clinical and Laboratory Variables

Age, sex, comorbidities, ASA physical status, laboratory measurements, recorded ward and ICU durations, and survival at discharge were obtained from the medical records. ASA status came from the routine preoperative anesthetic assessment. Classes IV–V were grouped as high ASA status and compared with II–III to limit model parameters. Basic demographic, ASA and mortality data were also retrieved for the excluded ward and preoperative-transfusion groups.

The first debridement during the index admission was the index operation; preoperative laboratory measurements and postoperative ICU admission referred to this operation.

The analyzed measurements were the operative-day preoperative results. Exact blood-collection and incision times were unavailable: electronic request, result and approval timestamps did not reliably establish venipuncture time. Intervals from admission, resuscitation or ICU admission to sampling therefore could not be quantified, and samples were not assumed to precede fluids, antibiotics or vasoactive treatment. Seven patients had preoperative ICU care. Complete blood counts were obtained with a Sysmex XN-1000 analyzer (Sysmex Corporation, Kobe, Japan); RDW-CV was derived from the erythrocyte-volume histogram measured by hydrodynamically focused impedance. RDW-CV was reported in percent (laboratory reference interval 11.5–14.5%) and RDW-SD in fL (37–50 fL). Serum albumin was measured by the bromocresol green (BCG) colorimetric method using ALB2 reagent (Roche Diagnostics, Basel, Switzerland) on the cobas c702 module of the cobas 8000 system and reported in g/L. RAR was RDW-CV (%) divided by albumin (g/dL), equivalently 10 × RDW-CV/albumin (g/L). RDW-CV was retained as the primary RDW measure for consistency with the original RAR analysis and preceding RAR studies; RDW-SD-based analyses were exploratory. Other index definitions are provided in Table S1.

Internal quality control used two albumin control levels and three hematology control levels twice daily, with additional checks after reagent changes and maintenance. Levey–Jennings charts and Westgard multirules guided acceptance and corrective action. Monthly cumulative analytical CVs during the study period ranged from 1.6% to 2.2% for albumin and from 1.4% to 2.3% for RDW-CV. Monthly KBUDEK external quality assessment covered both parameters, with absolute peer-group z scores below 2.0 in all assessment cycles. Instruments, measurement methods and reagent types remained unchanged; routine reagent-lot changes underwent verification before patient testing. Control materials, acceptance rules, calibration, lot verification and corrective procedures are detailed in Supplementary Methods S2.

MCV, RDW-SD, erythrocyte count, hematocrit and other red-cell indices were retrieved for hematological sensitivity analyses. Microcytosis was defined as MCV < 80 fL, not as iron deficiency. Ferritin, transferrin saturation, vitamin B12 and folate measurements were unavailable. The simplified FGSI was reconstructed from admission hematocrit, creatinine and potassium using published categories [31,32]. Because acute kidney injury was investigator-classified from creatinine history without complete baseline timing or urine output, scores with and without the acute-renal-failure creatinine weighting were examined separately. Full FGSI, UFGSI and SOFA were not reconstructed.

All core laboratory and model variables were complete for the 105 included patients; no imputation was performed. Source verification and subsequent corrections, including the verified RDW-CV value of 28.3%, are documented in the supplementary correction log. Transfusion and albumin records were reviewed to distinguish preoperative exclusion exposures from postoperative treatment.

2.4. Outcomes

The primary outcome was all-cause death during the index hospitalization; patients discharged alive were classified as survivors. Postoperative ICU length of stay was examined as an exploratory secondary outcome.

2.5. Statistical Analysis

Continuous distributions were assessed within survival groups using histograms, quantile–quantile plots and Shapiro–Wilk tests. Variables compatible with approximate normality were summarized as mean ± standard deviation and compared with Welch's t test; other variables were summarized as median [interquartile range] and compared with the Mann–Whitney U test. Categorical variables were compared using Pearson's chi-square

test or Fisher's exact test when an expected count was below five. Tables show nominal p values; supplementary outputs retain false-discovery-rate adjustment for the original 17 continuous comparisons and separately for the additional laboratory comparisons. No hypothesis-testing family was retrospectively designated as prespecified.

Discrimination was assessed using AUCs with DeLong 95% confidence intervals (CIs). Lower albumin and hemoglobin represented higher risk. Five paired DeLong comparisons of RAR with RDW-CV, albumin, LAR, CAR and NLR formed a Holm correction family. Individual AUC CIs, paired-difference CIs and adjusted p values are reported separately. RAR was selected after exploratory biomarker comparisons; the primary model and its internal validation were conditional on that selection.

Logistic regression estimated odds ratios (ORs) with Wald 95% CIs. The primary model contained continuous RAR and binary high ASA status: two predictor parameters for 25 deaths (12.5 events per parameter, excluding the intercept). Firth regression used profile penalized-likelihood CIs [33]. Separate sensitivity models added age, lactate, hemoglobin, MCV or a simplified severity score, each with three predictor parameters (8.3 events per parameter). Further analyses excluded patients with hemoglobin < 10 g/dL, MCV < 80 fL, preoperative ICU care, or the verified extreme RDW-CV value of 28.3%. Each retained ASA and continuous RAR. Sample sizes, deaths, parameter counts and penalized estimates are reported to make sparse-data uncertainty explicit. These additional analyses were exploratory.

The ASA–RAR model was compared with ASA alone and ASA plus albumin, RDW-CV, both components, or hemoglobin. MCV and the RDW-SD-to-albumin ratio were evaluated in separate exploratory models. Continuous predictors were not categorized in regression. Log(RAR) and a natural cubic spline assessed possible nonlinearity; analogous models evaluated the RDW-SD ratio. Five nested-model likelihood-ratio tests formed a separate Holm family. Spearman correlations and variance inflation factors described the relationship between MCV and the RDW measures.

Internal validation used 1000 patient-level bootstrap resamples, repeating model fitting to estimate optimism-corrected AUCs, Brier scores and calibration slopes [30,34]. Shared resamples allowed paired model comparisons, and a nested bootstrap provided approximate CIs for three fixed models. A separate post hoc procedure repeated selection of the highest-AUC marker among eight original candidates within each resample. Apparent calibration was displayed with a smooth curve and pointwise bootstrap intervals conditional on the development-cohort predictions. Full fitting, selection, correction and convergence procedures are specified in the Supplementary Methods. Every model and calibration fit was checked for separation; Firth-equivalent mean bias reduction provided finite estimates when separation occurred, under one consistent fitting rule.

The Youden index defined an exploratory RAR threshold within this cohort; bootstrap resampling assessed its variability. Sensitivity, specificity and predictive values were described without proposing a clinical decision rule. Mortality across RAR quartiles was summarized overall and by ASA group. ICU-stay analyses were confined to the Supplementary Materials because death truncates follow-up and survivor-only analyses introduce selection. All tests were two-sided; interpretation emphasized effect estimates and uncertainty.

Analyses and figures were generated in R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria). Exact software and package versions are recorded in the accompanying session information. Supplementary File S2 Data and Code provides the anonymized English datasets, complete analysis workflow, numerical outputs and figures.

2.6. Use of Generative Artificial Intelligence

A generative artificial intelligence tool (Claude Opus 5.5; Anthropic, San Francisco, CA, USA) was used solely for English-language editing of the manuscript text. The authors reviewed and edited all suggested changes and take full responsibility for the content of this publication.

3. Results

3.1. Patient Characteristics

Of 209 screened records, 56 duplicate records relating to 37 individuals were removed, leaving 153 unique patients, in all of whom Fournier gangrene was confirmed on operative-note review. After exclusion of 39 patients transferred to a ward after surgery and nine patients who had received a preoperative transfusion, 105 patients were included (Figure 1). No patient had received preoperative albumin, and no patient was excluded for advanced liver cirrhosis, hematological malignancy, missing laboratory data or serious record inconsistencies.

The excluded ward and transfusion groups were younger than the included ICU cohort (mean ages 44.3, 47.4 and 61.1 years, respectively), and neither excluded group had an in-hospital death. ASA IV–V occurred only in the included cohort. Sex, individual ASA classes and mortality are reported separately for all three groups in Table S13; these descriptive data do not remove selection bias.

Twenty-five patients died during hospitalization (23.8%; Wilson 95% CI 16.7–32.8%), and 80 patients (76.2%) were men. Nonsurvivors were older than survivors (67.0 ± 12.5 versus 59.3 ± 15.7 years; $p = 0.015$). High ASA status was present in 13 of 25 nonsurvivors (52.0%) and in 4 of 80 survivors (5.0%; $p < 0.001$); no ASA II patient died. Cardiac disease (52.0% versus 20.0%; $p = 0.002$) and neurological disease (40.0% versus 8.8%; $p < 0.001$) were also more frequent among nonsurvivors, whereas diabetes mellitus, the most common comorbidity, was similarly distributed (68.0% versus 63.8%; $p = 0.698$) (Table 1).

Table 1. Clinical characteristics according to in-hospital survival.

Characteristic	Survivors ($n = 80$)	Nonsurvivors ($n = 25$)	p
Age, years	59.3 ± 15.7	67.0 ± 12.5	0.015
Female sex	16 (20.0)	9 (36.0)	0.101
Diabetes mellitus	51 (63.8)	17 (68.0)	0.698
Hypertension	40 (50.0)	15 (60.0)	0.382
Asthma or COPD	8 (10.0)	3 (12.0)	0.721
Neurological disease	7 (8.8)	10 (40.0)	<0.001
Endocrine disorder	3 (3.8)	1 (4.0)	1.000
Cardiac disease	16 (20.0)	13 (52.0)	0.002
Renal disease	3 (3.8)	2 (8.0)	0.591
Immunosuppressive medication	4 (5.0)	1 (4.0)	1.000
Malignancy	10 (12.5)	2 (8.0)	0.727
ASA physical status [a]			<0.001

Table 1. *Cont.*

Characteristic	Survivors ($n = 80$)	Nonsurvivors ($n = 25$)	p
II	13 (16.3)	0 (0.0)	
III	63 (78.8)	12 (48.0)	
IV	4 (5.0)	11 (44.0)	
V	0 (0.0)	2 (8.0)	

Data are mean ± standard deviation or n (%); p values are nominal and unadjusted for multiplicity. Age was compared with Welch's t test; categorical variables were compared with Pearson's chi-square test or, when any expected count was below five, Fisher's exact test. [a] The p value compares ASA IV–V with ASA II–III, the grouping used in the regression models (Fisher's exact test). ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease.

3.2. Preoperative Laboratory Profile

Median RAR was 8.30 [6.74–10.21] in nonsurvivors and 5.04 [4.17–6.19] in survivors ($p < 0.001$). Nonsurvivors had higher RDW-CV (16.80 [15.20–18.10] versus 13.80 [12.83–15.98] %), lower albumin (22.00 [15.00–25.50] versus 29.00 [25.00–32.75] g/L) and lower hemoglobin (9.70 ± 2.30 versus 12.10 ± 2.30 g/dL; all $p < 0.001$; Figure 2). MCV was similar (85.30 [78.90–89.70] versus 85.90 [81.13–90.58] fL; $p = 0.567$), whereas RDW-SD was higher in nonsurvivors (51.10 [45.40–57.10] versus 42.50 [39.58–48.58] fL; $p < 0.001$). Table 2 also reports NLR, RLR and RPR; additional measurements are in Tables S10 and S14.

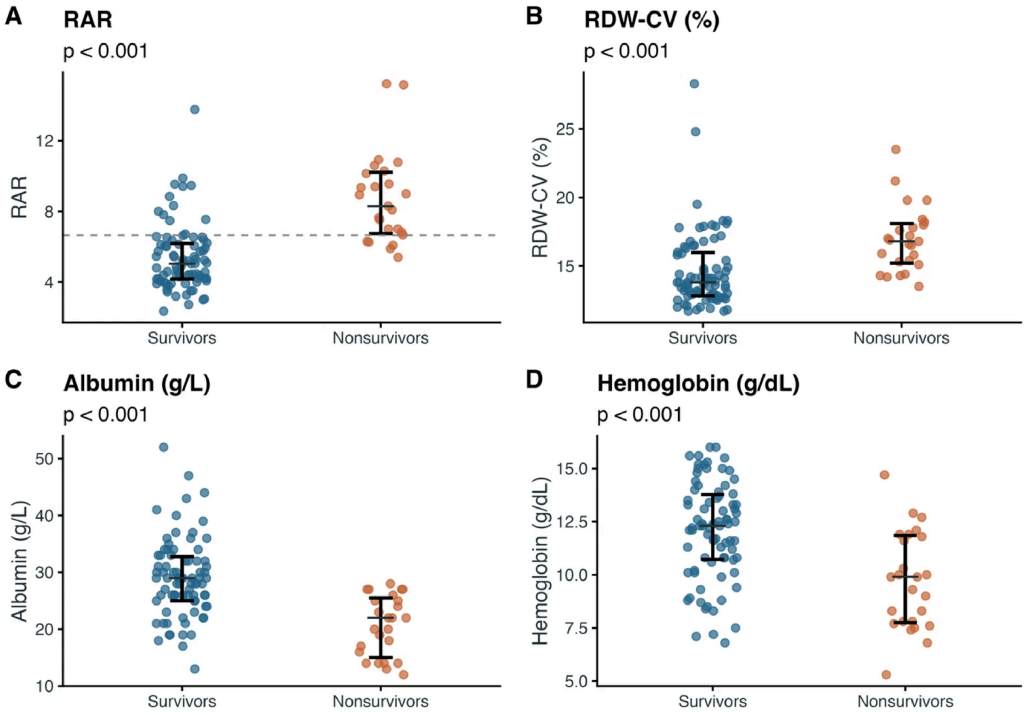


Figure 2. Preoperative laboratory markers. Preoperative RAR (**A**), RDW-CV (**B**), serum albumin (**C**) and hemoglobin (**D**) in survivors and nonsurvivors. Each dot represents one patient; horizontal bars indicate the median and the 25th–75th percentiles. p values are from the Mann–Whitney U test (**A**–**C**) and Welch's t test (**D**). The dashed line in panel (**A**) marks the exploratory Youden threshold (RAR 6.65). RAR, red cell distribution width-to-albumin ratio; RDW-CV, red cell distribution width coefficient of variation.

Table 2. Preoperative laboratory measurements according to in-hospital survival.

Variable	Survivors ($n = 80$)	Nonsurvivors ($n = 25$)	p
Hemoglobin, g/dL	12.10 ± 2.30	9.70 ± 2.30	<0.001
Platelets, $\times 10^9$/L	271.50 [225.00–344.75]	276.00 [161.50–403.00]	0.746
Neutrophils, $\times 10^9$/L	12.85 [9.27–17.18]	16.59 [11.79–23.41]	0.046
Lymphocytes, $\times 10^9$/L	1.14 [0.79–1.89]	0.84 [0.63–1.43]	0.103
Monocytes, $\times 10^9$/L	1.01 [0.70–1.40]	0.80 [0.45–1.19]	0.047
MCV, fL	85.90 [81.13–90.58]	85.30 [78.90–89.70]	0.567
RDW-CV, %	13.80 [12.83–15.98]	16.80 [15.20–18.10]	<0.001
RDW-SD, fL	42.50 [39.58–48.58]	51.10 [45.40–57.10]	<0.001
CRP, mg/L	239.50 [139.00–319.00]	242.00 [154.50–342.50]	0.549
Albumin, g/L	29.00 [25.00–32.75]	22.00 [15.00–25.50]	<0.001
Lactate, mmol/L	2.00 [1.60–2.75]	2.60 [2.15–3.45]	0.030
RAR	5.04 [4.17–6.19]	8.30 [6.74–10.21]	<0.001
NLR	10.82 [6.43–18.19]	18.74 [10.22–26.13]	0.012
RLR	12.94 [7.17–20.14]	19.57 [12.26–26.86]	0.012
RPR	0.051 [0.039–0.065]	0.059 [0.042–0.105]	0.098

Values are mean ± standard deviation when approximately normally distributed and otherwise median [25th–75th percentile]; Welch's t test and Mann–Whitney U test were used, respectively. p values are nominal; the complete statistical outputs identify each test and the separate exploratory multiplicity families. Albumin is shown in g/L; RAR uses albumin in g/dL. MCV, mean corpuscular volume; RDW-CV, red cell distribution width coefficient of variation; RDW-SD, red cell distribution width standard deviation; RLR, RDW-CV-to-lymphocyte ratio; RPR, RDW-CV-to-platelet ratio; other abbreviations are defined in Table S1.

Microcytosis occurred in 7/25 nonsurvivors (28.0%) and 16/80 survivors (20.0%; $p = 0.415$), while hemoglobin < 10 g/dL occurred in 14/25 (56.0%) and 14/80 (17.5%; $p < 0.001$). MCV correlated weakly with RDW-CV (Spearman's rho −0.162; $p = 0.099$) and RAR (rho −0.128; $p = 0.192$). RDW-CV and RDW-SD were correlated (rho 0.763; $p < 0.001$). These results do not support interpreting MCV as the sole explanation for the RDW-CV association (Table S14; Figure S3). No patient in the included cohort was receiving chronic dialysis, and no pre-admission transfusion or recent bleeding was recorded.

3.3. Discrimination of Individual Biomarkers

RAR had an AUC of 0.888 (95% CI 0.825–0.951), compared with 0.839 (0.762–0.917) for lower albumin, 0.799 (0.715–0.884) for RDW-CV and 0.771 (0.668–0.875) for lower hemoglobin. AUCs for the other original derived indices ranged from 0.540 to 0.731 (Figure 3A,C; Table S2). After Holm correction, RAR exceeded RDW-CV, LAR, CAR and NLR in paired comparisons. The RAR-minus-albumin difference was 0.049 (95% CI −0.001 to 0.098; adjusted $p = 0.055$); this neither established an advantage nor demonstrated equivalence (Table S3).

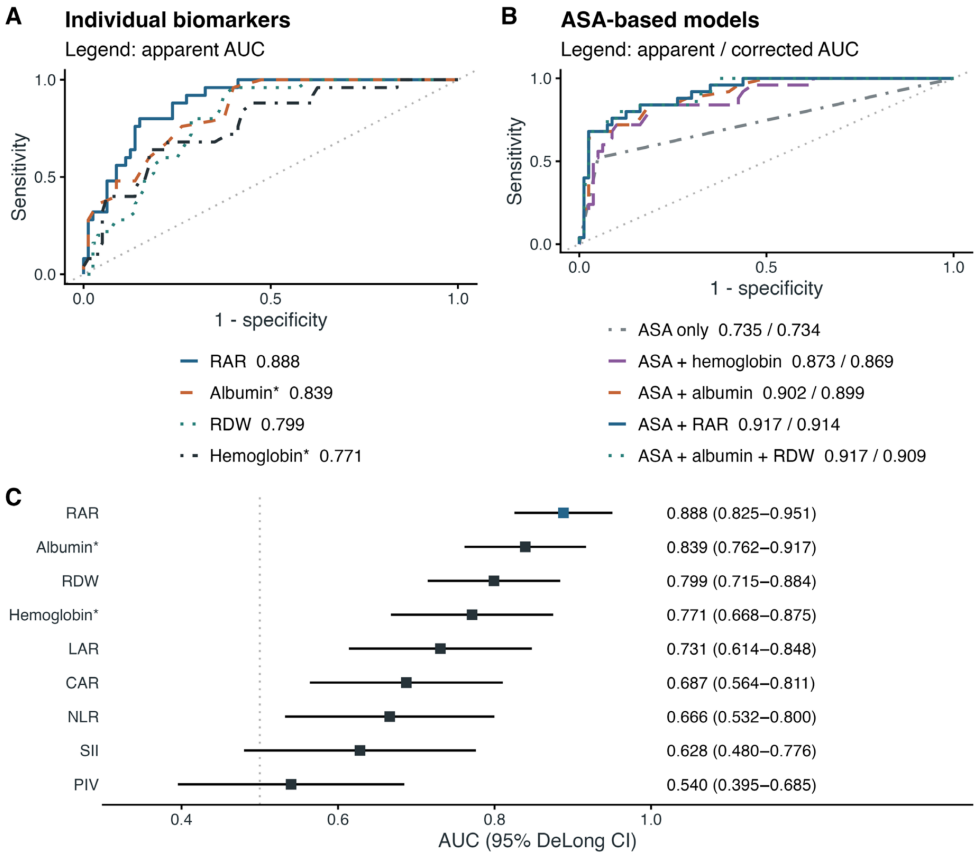


Figure 3. Discrimination for in-hospital mortality. (**A**) Receiver operating characteristic curves of individual biomarkers. (**B**) Receiver operating characteristic curves of the ASA-based models; the curves show apparent performance in the development cohort, and the legend gives apparent and optimism-corrected AUCs. (**C**) AUCs with 95% DeLong confidence intervals for RAR, its components, hemoglobin and the other derived indices. The dotted vertical line in panel (**C**) indicates an AUC of 0.50, representing no discrimination (chance-level performance). * Lower values were assigned the higher-risk direction. ASA, American Society of Anesthesiologists; AUC, area under the curve; CAR, C-reactive protein-to-albumin ratio; LAR, lactate-to-albumin ratio; NLR, neutrophil-to-lymphocyte ratio; PIV, pan-immune-inflammation value; RAR, red cell distribution width-to-albumin ratio; RDW, red cell distribution width; SII, systemic immune-inflammation index.

3.4. Adjusted Associations and Sensitivity Analyses

The unadjusted OR per one-unit increase in RAR was 1.91 (95% CI 1.45–2.53). In the ASA–RAR model, the OR was 1.77 (1.32–2.39; $p < 0.001$), and the OR for ASA IV–V versus II–III was 10.98 (2.63–45.74; $p = 0.001$). Firth estimates were 1.71 (1.32–2.34) and 9.68 (2.60–41.34), respectively (Table 3). Separate adjustment for age, lactate, hemoglobin or MCV yielded RAR ORs of 1.77, 1.80, 1.65 and 1.80, respectively (Table S8; Figure 4). MCV adjustment produced an RAR CI of 1.34–2.43; variance inflation factors did not suggest substantial collinearity in that model (Table S14). These models assess robustness, not causality or absence of residual confounding.

Excluding preoperative ICU patients left 98 patients and 22 deaths; the Firth RAR OR was 1.66 (95% CI 1.26–2.31). Excluding the patient with verified RDW-CV 28.3% left 104 patients and 25 deaths (OR 1.73; 1.33–2.36). After excluding microcytosis, 82 patients and 18 deaths remained (OR 1.62; 1.22–2.26). Excluding hemoglobin < 10 g/dL left 77 patients but only 11 deaths (OR 3.12; 1.81–8.23); this estimate was imprecise and differed substantially between penalized and unpenalized fits. It should not be interpreted as evidence of a stronger biological effect. Full sample sizes and both estimation methods are provided in Table S15.

Table 3. Unadjusted and adjusted associations with in-hospital mortality.

Predictor	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	*p* (Adjusted Model, Wald)	Firth OR (95% CI)
RAR, per 1-unit increase	1.91 (1.45–2.53)	1.77 (1.32–2.39)	<0.001	1.71 (1.32–2.34)
ASA IV–V versus II–III	20.58 (5.75–73.69)	10.98 (2.63–45.74)	0.001	9.68 (2.60–41.34)

Unadjusted ORs are from separate univariable models. The adjusted maximum-likelihood and Firth models include ASA status and RAR (25 deaths). Maximum-likelihood CIs and *p* values are Wald estimates; Firth CIs use profile penalized likelihood (both Firth $p < 0.001$). Both unadjusted *p* values were <0.001. The model equation is provided in Supplementary Methods S3. ASA, American Society of Anesthesiologists; CI, confidence interval; OR, odds ratio; RAR, red cell distribution width-to-albumin ratio.

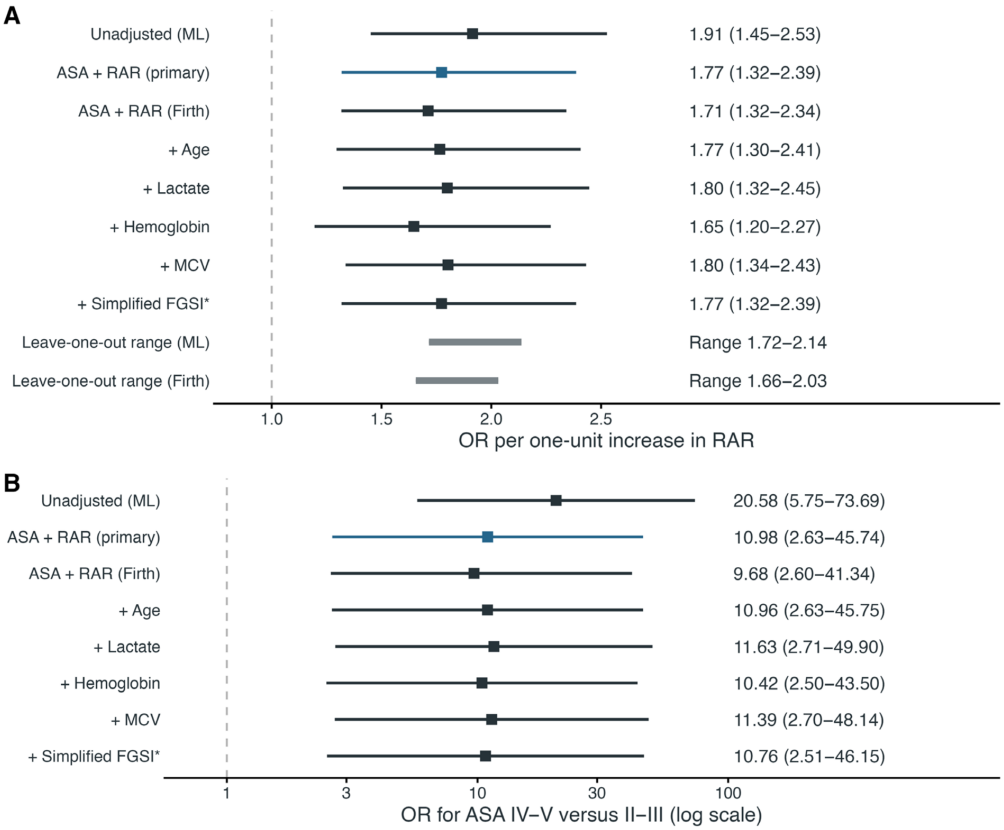


Figure 4. Associations across model specifications. Estimates for RAR (**A**) and ASA IV–V versus II–III (**B**). Squares and lines show ORs and 95% CIs: Wald for maximum likelihood (ML), profile penalized likelihood for Firth. The vertical dashed lines in panels (**A**,**B**) indicate an odds ratio of 1, representing no association with in-hospital mortality. Gray bars show leave-one-out ranges. Blue denotes the primary model. Sensitivity models add the indicated covariate to ASA and RAR. ASA, American Society of Anesthesiologists; CI, confidence interval; OR, odds ratio; RAR, red cell distribution width-to-albumin ratio. * Simplified FGSI uses creatinine-point doubling for investigator-recorded acute kidney injury; the no-doubling variant is reported in Table S18.

Admission hematocrit, creatinine and potassium permitted an exploratory simplified-FGSI sensitivity analysis. RAR remained associated with mortality after adding the score (ML OR 1.77; 95% CI 1.32–2.39), with similar results when the creatinine doubling rule was omitted. This limited score did not replace full physiological severity adjustment (Table S18).

3.5. Model Performance, Internal Validation and Comparison with the Components

The ASA–RAR model had an apparent AUC of 0.917 and an optimism-corrected AUC of 0.914 (approximate 95% CI 0.836–0.971), with a corrected Brier score of 0.101 and calibration slope of 0.962 (Table 4; Figure 5). Adding RAR or albumin to ASA improved model fit (Holm-adjusted $p < 0.001$ for both). The corrected ASA–RAR minus ASA–albumin AUC difference was 0.015 (approximate 95% CI −0.019 to 0.045); the Brier-score difference was −0.007 (−0.021 to 0.008). A predictive advantage over albumin was therefore not demonstrated (Table S12).

Table 4. Discrimination, overall accuracy and calibration with bootstrap internal validation.

Model	Apparent AUC	Corrected AUC (95% CI)	Apparent Brier	Corrected Brier	Corrected Slope
ASA only	0.735	0.734	0.128	0.134	1.003
ASA + RDW-CV	0.870	0.866	0.122	0.133	0.918
ASA + hemoglobin	0.873	0.869	0.115	0.124	0.946
ASA + albumin	0.902	0.899 (0.816–0.960)	0.100	0.109	0.950
ASA + RAR (primary)	0.917	0.914 (0.836–0.971)	0.093	0.101	0.962
ASA + albumin + RDW-CV	0.917	0.909 (0.845–0.968)	0.093	0.104	0.914
ASA + log(RAR)	0.918	0.915	0.092	0.100	0.958
ASA + natural cubic spline of RAR	0.920	0.911	0.093	0.105	0.872

Optimism-corrected estimates are based on 1000 bootstrap resamples (seed 20260922); values were rounded half up, and between-model differences quoted in the text were computed from unrounded values; the apparent calibration slope is 1 for every model. Predictor counts (excluding intercepts) are one for ASA alone, two for the linear two-variable models and log(RAR), and three for separate components or the spline. Approximate 95% CIs for the corrected AUC were obtained with a nested bootstrap (300 outer × 100 inner resamples) for the three principal comparison models; these intervals do not account for the uncertainty of biomarker selection. Lower Brier scores indicate better overall accuracy, and calibration slopes close to 1 indicate little overfitting. ASA, American Society of Anesthesiologists; AUC, area under the receiver operating characteristic curve; CI, confidence interval; RAR, red cell distribution width-to-albumin ratio; RDW, red cell distribution width.

Adding RDW-CV to ASA plus albumin improved model fit (likelihood-ratio statistic 5.01; Holm-adjusted $p = 0.030$), but the separate-component model had a corrected AUC of 0.909. Its paired difference from ASA–RAR remained uncertain (Table S12). Figure 3B compares the apparent ROC curves and corrected AUCs of the ASA-based models, including ASA plus hemoglobin; Figure 3C shows the individual-marker AUCs and their uncertainty. The smooth calibration curve in Figure 5C describes apparent performance, with widening pointwise uncertainty where predicted risks are sparse; it is not an optimism-corrected calibration curve.

The ASA–hemoglobin model had an apparent AUC of 0.873 and a corrected AUC of 0.869, compared with 0.735 and 0.734 for ASA alone (Table 4; Figure 3B). Repeating an explicit maximum-AUC biomarker-selection rule within resampling selected RAR in 969/1000 samples and produced a corrected AUC of 0.913, Brier score of 0.102 and calibration slope of 0.955 (Table S17). This post hoc operationalization assesses one source of selection optimism; it does not reproduce every judgment that informed the original exploratory analysis.

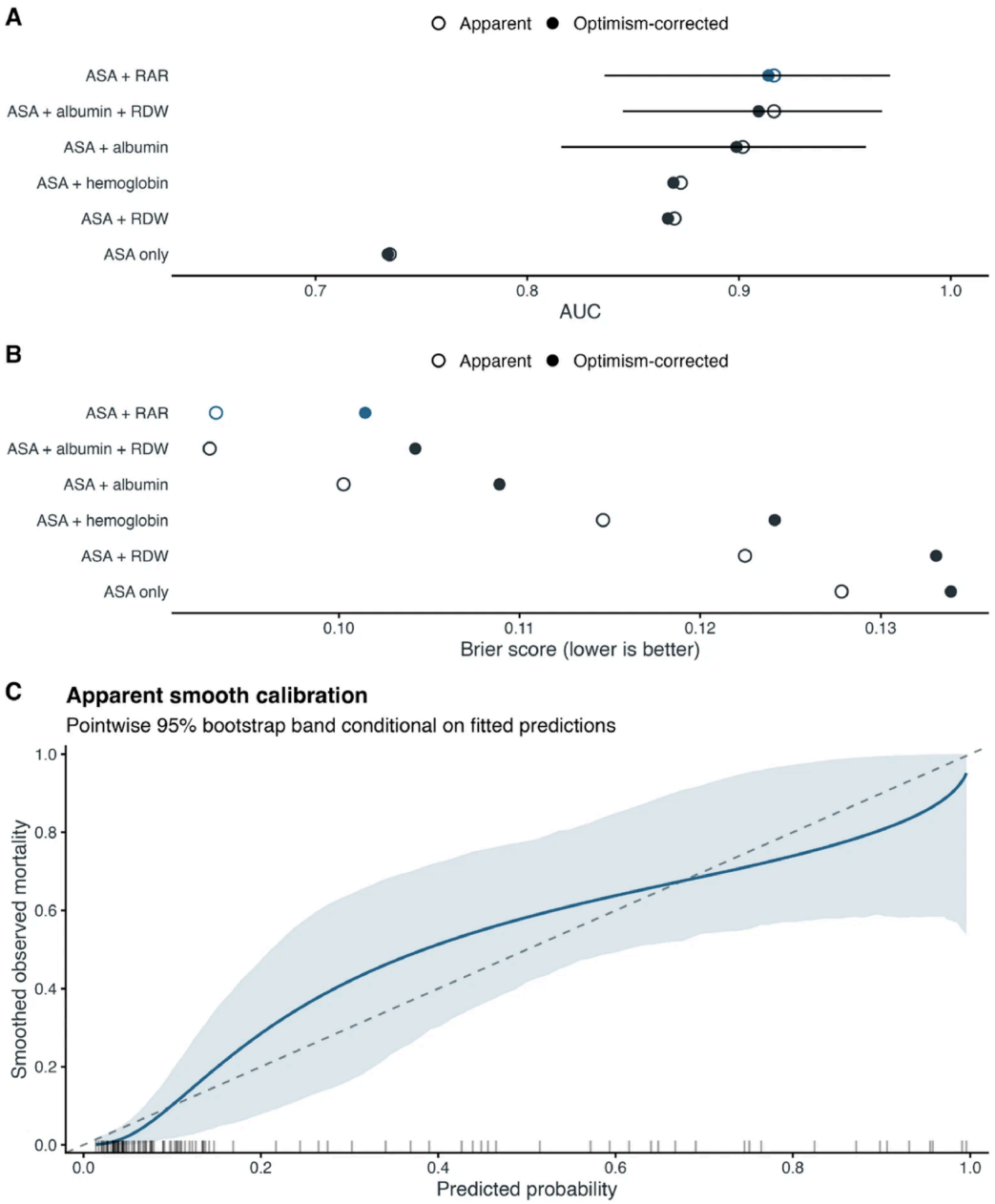


Figure 5. Internal validation and calibration. (**A**) Apparent and optimism-corrected AUCs; intervals are approximate nested-bootstrap 95% CIs for the three principal comparison models. (**B**) Apparent and corrected Brier scores. Blue symbols in panels (**A**,**B**) highlight the primary ASA–RAR model. (**C**) The solid blue curve shows the apparent calibration of the ASA–RAR model, estimated using a two-degree-of-freedom natural cubic logistic smoother; the light blue shaded area represents the pointwise 95% bootstrap confidence band conditional on the original predicted risks. The dashed line indicates perfect calibration. The corrected calibration slope and Brier score are reported in Table 4; the curve and band are apparent estimates. ASA, American Society of Anesthesiologists; AUC, area under the curve.

3.6. Functional Form and Risk Gradient

The natural cubic spline suggested a possible departure from linearity and improved apparent fit relative to linear RAR (likelihood-ratio statistic 5.94; Holm-adjusted $p = 0.030$). Its apparent AUC was 0.920, corrected AUC 0.911 and corrected calibration slope 0.872. Log(RAR) had a corrected AUC of 0.915 and Brier score of 0.100; each relative 10% RAR increase had an OR of 1.53 (95% Wald CI 1.24–1.89). Repeating AIC-style form selection within each bootstrap sample gave a corrected AUC of 0.911 (Table S5). Thus, improved

apparent fit did not establish improved performance after internal validation. Predicted risk rose across RAR, with substantial uncertainty where observations were sparse (Figure 6).

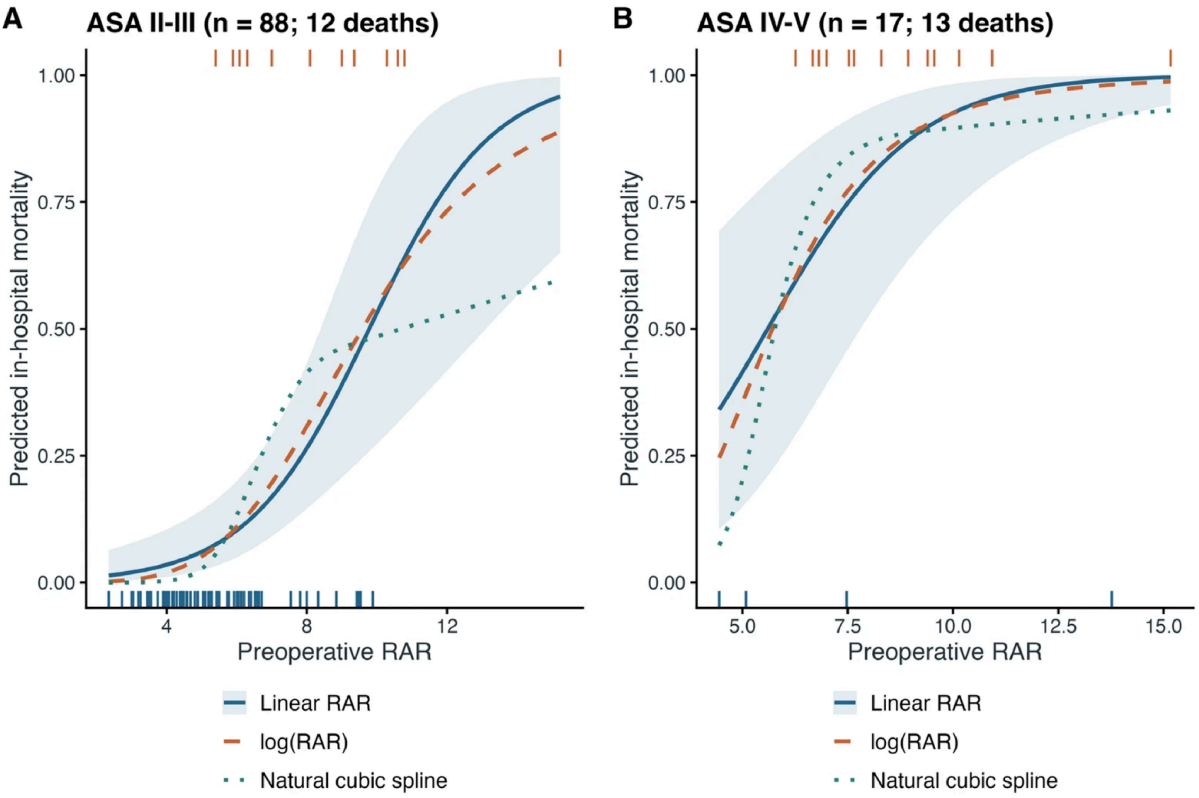


Figure 6. Predicted mortality across RAR values. Predicted in-hospital mortality according to preoperative RAR in ASA II–III (**A**) and ASA IV–V (**B**) patients. Curves are from models containing ASA status and linear RAR, log(RAR) or a natural cubic spline of RAR; the shaded area is the pointwise 95% Wald confidence band of the linear model. Curves are restricted to the observed RAR range in each group, and rug marks show individual survivors (bottom) and nonsurvivors (top). In panel A, only one observation lies above RAR 10.79, so curve shapes beyond this value should not be interpreted. ASA, American Society of Anesthesiologists; RAR, red cell distribution width-to-albumin ratio.

The RDW-SD-to-albumin ratio also showed discrimination (AUC 0.883) and an ASA-adjusted association (OR 1.21 per unit; 95% CI 1.10–1.34). Its functional-form and internally validated comparisons are exploratory and are reported in Table S16 and Figure S2. Paired comparisons with the additional individual biomarkers are reported in Table S19. Its scale differs from RDW-CV-based RAR, so numerical cutoffs and per-unit effects are not interchangeable.

Observed mortality increased across RAR quartiles, from 0 of 28 patients (0%; 95% CI 0–12.3%) in the lowest quartile (RAR 2.35–4.40) to 1 of 25 (4.0%), 8 of 26 (30.8%) and 16 of 26 (61.5%; 95% CI 40.6–79.8%) in the second, third and highest quartiles, respectively (Cochran–Armitage trend $p < 0.001$). The gradient was also present within ASA II–III patients (0%, 4.3%, 19.0% and 43.8%; trend $p < 0.001$), whereas mortality among ASA IV–V patients was 80.0% and 90.0% in the third and highest quartiles (Figure 7; Supplementary Table S11).

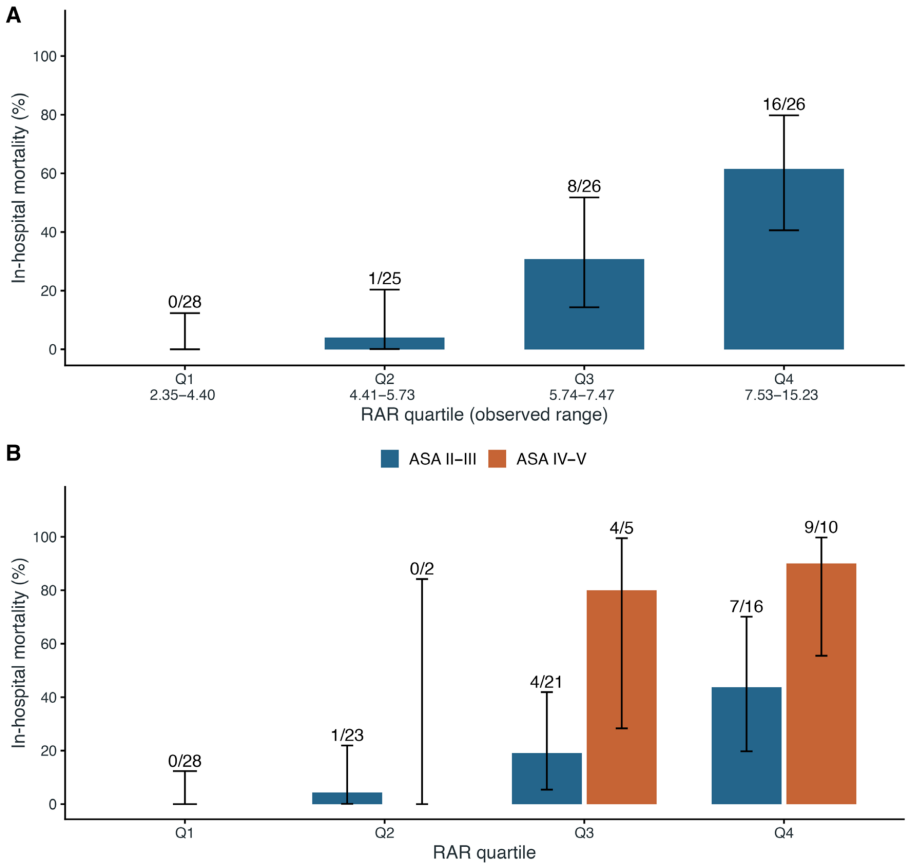


Figure 7. Mortality across RAR quartiles. Observed in-hospital mortality across quartiles of preoperative RAR in the whole cohort (**A**) and according to ASA group (**B**). Bars show proportions with exact binomial 95% confidence intervals; the numbers above the bars are deaths/patients. Quartile limits were derived from the whole cohort, and no ASA IV–V patient was in the lowest quartile. ASA, American Society of Anesthesiologists; RAR, red cell distribution width-to-albumin ratio.

3.7. Exploratory Threshold

In the development cohort, the exploratory Youden threshold was RAR 6.65, with an apparent sensitivity of 80.0% (95% CI 59.3–93.2%), a specificity of 85.0% (75.3–92.0%), a positive predictive value of 62.5% (43.7–78.9%) and a negative predictive value of 93.2% (84.7–97.7%). Across 1000 bootstrap resamples, the median Youden threshold was 6.23, with 2.5th–97.5th percentiles of 5.34–6.86 (Supplementary Table S6; Supplementary Figure S1B). These are apparent estimates from the same cohort used to select the threshold. Positive and negative predictive values depend on mortality prevalence; no clinical decision threshold was validated.

The exploratory ICU-stay analyses, including the survivor-only correlations, are reported in Tables S7 and S9. They were not interpreted as time-to-discharge or causal analyses.

4. Discussion

Higher preoperative RAR was associated with in-hospital mortality in adults requiring intensive care after debridement for Fournier gangrene. The association persisted in parsimonious ASA-adjusted models and after separate assessment of hemoglobin, MCV, preoperative ICU care and the verified extreme RDW-CV observation. These findings agree with prior reports linking RAR and its components to adverse outcomes. However, the central component comparison did not establish a predictive advantage over albumin.

4.1. Findings Consistent with Previous Studies

The direction of the RAR association is consistent with the study by Kayar et al., who evaluated preoperative RDW-derived indices in 62 patients undergoing surgery for scrotal Fournier gangrene [28]. They reported higher mortality risk with RAR and lower albumin and hemoglobin concentrations among nonsurvivors. Our cohort showed the same laboratory pattern: nonsurvivors had higher RAR and lower albumin and hemoglobin. Agreement across these cohorts supports further investigation of preoperative RAR, while our restriction to patients requiring postoperative intensive care defines a more specific population than the broader surgical cohort.

The findings for albumin also agree with evidence from postoperative intensive care. Shin et al. studied 41 patients with Fournier gangrene admitted to the ICU after surgery and identified initial albumin and postoperative lactate as independent mortality predictors [11]. Albumin alone discriminated survivors from nonsurvivors well in our cohort, with an AUC of 0.839; the internally corrected AUC of the ASA–albumin model was 0.899. Albumin is also included in the Fournier's Gangrene Mortality Index [9]. These observations make albumin an essential comparator when assessing an albumin-containing ratio, rather than simply another laboratory variable to be adjusted for or omitted.

The association is also consistent with evidence outside Fournier gangrene. Jin et al. found an adjusted association between admission RAR and 28-day mortality in 24,568 ICU patients [26]. Jeong et al. reported an association with 28-day mortality in patients with pneumonia receiving invasive mechanical ventilation [27]. Meta-analyses in cardiovascular populations likewise associated higher RAR with mortality, including a dose–response relationship [24,25]. Together, these studies support the direction of the association observed here. They do not establish that the strength of discrimination, optimal threshold or added value of RAR will be the same in different clinical settings.

Inflammation, oxidative stress and altered erythropoiesis may contribute to the RAR signal, alongside albumin changes caused by inflammation, capillary leakage and protein metabolism [17,18,21–23]. These mechanisms are plausible rather than demonstrated by the present observational data. Low albumin is not a diagnosis of malnutrition; the nutritional assessment recommended in critical illness includes clinical and functional information that was not collected here [35].

RDW-CV is the standard deviation of erythrocyte volume divided by MCV and multiplied by 100. Its value therefore reflects mean cell volume as well as dispersion. RDW-SD, an analyzer-derived distribution-width measure in fL, is not normalized by MCV in the same way and should not be reconstructed as RDW-CV × MCV/100. Both measures may change with erythropoiesis, nutritional deficiencies, renal disease, bleeding or transfusion. Their biological interpretations and numerical ratios are complementary rather than interchangeable.

Diabetes was present in 64.8% of this cohort. In a cross-sectional study of type 2 diabetes, Babker et al. reported associations between RDW and hemoglobin and erythrocyte indices [36]. This supports considering pre-existing red-cell changes rather than attributing RDW-CV solely to acute inflammation; it does not establish the mechanism in Fournier gangrene. Hemoglobin and MCV adjustment and exclusions for marked anemia or microcytosis assess robustness but cannot identify anemia etiology without appropriate nutritional, iron and longitudinal data.

4.2. Differences from Previous Reports and Added Predictive Value

Kayar et al. reported an RAR AUC of 0.955 and mortality of 17.7%, compared with 0.888 and 23.8% here [28]. RDW alone was not substantially associated with mortality in their cohort, whereas our RDW-CV AUC was 0.799. Their broader surgical population,

anatomical eligibility and strong association between postoperative ICU admission and mortality differ from our ICU-only selection. Case mix, severity, measurement methods and sampling variation in two small cohorts may explain the differences; neither AUC establishes superiority across settings.

RAR discrimination was lower in broader critical-care cohorts: AUCs were 0.66 in Jin et al. and 0.694 in mechanically ventilated pneumonia patients studied by Jeong et al. [26,27]. Jeong et al. used measurements on the day of MICU admission and invasive ventilation, while our results were obtained before the index debridement; Shin et al.'s prognostic lactate was postoperative [11]. Treatment before sampling, outcome horizon and severity can change discrimination. Outcome prevalence also changes predictive values, so thresholds should not be transferred solely because two studies use the same ratio. Jin et al. and Jeong et al. used albumin in g/dL but did not specify an albumin assay method; a method-specific comparison with Kayar et al. could not be established from the accessible report.

The variable performance of CAR, LAR, NLR and SII is consistent with heterogeneous sepsis literature [15–20,37]. CRP was markedly elevated in both survival groups without a clear between-group difference. This does not establish that CRP lacks prognostic relevance: restricted inflammatory range, timing and limited sample size could obscure an association [12–14]. Exploratory comparisons within one cohort control case mix across markers, but choosing a marker after these comparisons can still create optimism.

The component comparisons are central. Adding RDW-CV to ASA plus albumin improved fit, but the separate-component model did not improve corrected discrimination over RAR. The corrected ASA–RAR minus ASA–albumin AUC difference was 0.015 (approximate 95% CI −0.019 to 0.045), and the Brier difference was uncertain. These results support neither superiority nor equivalence. Improved model fit does not necessarily mean better prediction.

4.3. Clinical Interpretation

RAR has no additional assay cost when RDW and albumin are already available. However, albumin is also readily available, and the present data did not show a reliable predictive advantage for replacing it with RAR. ASA reflects preoperative physical status rather than acute organ dysfunction. Jin et al. compared RAR with SOFA [26]; our limited simplified-score sensitivity cannot substitute for a full FGSI or SOFA comparison. Statistical association and discrimination are not clinical utility. No decision-curve analysis or external validation was performed, and net benefit for any treatment decision remains unknown.

Within this dataset, the simple two-predictor model had a corrected calibration slope of 0.962. Although the spline improved apparent fit, it showed more optimism and no advantage after internal validation. Sparse observations at high RAR values further limit interpretation of the curve shape. The observed quartile gradient is clinically understandable, but does not establish a safe low-risk group: despite no deaths in the lowest quartile, its upper 95% confidence limit was 12.3%. The bootstrap Youden threshold ranged from 5.34 to 6.86 between the 2.5th and 97.5th percentiles. Neither the quartiles nor the threshold should determine ICU admission or treatment escalation.

An albumin-containing prognostic marker is not a treatment target. Albumin and resuscitation guidelines address clinical indications [23,38]; trial and meta-analytic evidence on albumin replacement does not evaluate RAR-guided care [39,40]. Our results provide no basis for administering albumin or red cells to change the ratio. Nor can an ICU-only cohort determine whether RAR should guide ICU admission. Any decision threshold would require external validation, calibrated absolute risks and assessment of consequences for patients.

4.4. Strengths and Limitations

Strengths include operative-note confirmation, retention of the first admission and first debridement, direct comparison with both ratio components, and retrieval of basic characteristics for the excluded groups. Added erythrocyte indices, penalized estimates and reduced-cohort analyses broadened assessment of hematological confounding. Complete anonymized datasets, correction logs, code and numerical outputs support independent reproduction.

The retrospective, single-center ICU selection limits generalizability and may induce selection bias through relationships among comorbidity, acute severity, treatment and ICU admission. Describing the 39 ward patients and nine preoperative-transfusion recipients clarifies selection but does not eliminate it. The results apply to patients already selected for postoperative intensive care, not all patients with Fournier gangrene or prediction of ICU need. Only 25 deaths occurred; parameter restriction and Firth penalization cannot fully overcome sparse data, especially in the anemia-exclusion analysis.

Acute severity and treatment remained incompletely characterized. Temperature, heart rate and respiratory rate were unavailable from the study records, while sodium and bicarbonate were not retrieved for this study; full FGSI and UFGSI therefore could not be calculated. Oxygenation, vasopressor doses and other organ-specific measures needed for SOFA were also unavailable. The reconstructed simplified score was limited to recorded hematocrit, creatinine and potassium, and its acute-renal-failure weighting depended on an incompletely verifiable clinical classification. ASA adjustment and these sensitivity analyses do not establish independence from acute disease severity. Actual support exposures, initial fluids, antibiotics, venipuncture and incision times were unavailable. Operative-day preoperative measurements may already reflect resuscitation, including among the seven patients with preoperative ICU care; excluding those patients cannot remove all timing-related confounding.

The BCG method may overestimate albumin in hypoalbuminemic inflammatory samples through nonspecific binding to other proteins. A method-comparison study found higher BCG results than immunoturbidimetric or capillary-electrophoretic measurements, particularly with inflammatory protein changes [41]. At a given RDW, higher measured albumin lowers the numerical RAR. We did not perform a parallel BCP or immunoassay measurement, so neither the magnitude nor the net effect on discrimination can be quantified. This limits comparison of numerical cutoffs across methods. The reported internal-control CVs and external quality-assessment results characterize routine analytical performance but do not quantify BCG-specific bias in these inflammatory samples.

The absence of iron studies and vitamin measurements leaves possible hematological confounding. A negative MCV group comparison does not exclude it, and microcytosis alone does not diagnose iron deficiency. Calendar dates and summed stay segments were not validated event times; they cannot establish exact treatment-to-sampling intervals, location of death or time-to-event outcomes. In-hospital mortality also depends partly on discharge practices.

Analytical limitations remain. The primary fixed-model bootstrap did not repeat the exploratory biomarker selection. An additional resampling analysis operationalized selection by maximum univariable AUC, but does not reconstruct all original analytical choices; corrected performance may therefore retain optimism [30,34]. The nested-bootstrap intervals are approximate, and the smooth calibration band describes apparent conditional uncertainty rather than external calibration. Neither internal validation nor a high AUC establishes transportability. No decision-curve analysis was performed, so clinical net benefit has not been shown. Multicenter validation should standardize sampling and compare RAR directly with albumin and established severity scores.

5. Conclusions

Higher preoperative RAR was associated with in-hospital mortality among patients with Fournier gangrene requiring postoperative intensive care. The association persisted in parsimonious ASA-adjusted and exploratory hematological sensitivity analyses, but a predictive advantage over ASA plus albumin was not demonstrated. RAR is an inexpensive candidate prognostic marker, not a validated clinical decision threshold. External validation with standardized sampling and established acute severity scores is needed before clinical implementation.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/diagnostics16233959/s1, Supplementary Methods; Tables S1–S12: biomarker definitions, discrimination, paired comparisons, model forms, threshold performance, ICU stay, covariate sensitivities, recorded stays, additional indices, quartiles and nested-bootstrap uncertainty; Table S13: included and excluded groups; Table S14: hematological measurements, correlations and collinearity; Table S15: reduced-cohort analyses; Table S16: extended models and RDW-SD functional forms; Table S17: repeated biomarker-selection validation; Table S18: simplified FGSI reconstruction and sensitivities; Table S19: paired comparisons with additional biomarkers; Figures S1–S3: case deletion and threshold variability, RDW-SD ratio curves, and MCV–RDW relationships. Supplementary File S1: The STROBE checklist is separate. Supplementary File S2: Data and Code include anonymized English datasets, a data dictionary, correction log, reproducible R scripts and numerical outputs.

Author Contributions: Conceptualization, M.K. and G.G.Ç.; methodology, M.K. and G.G.Ç.; investigation, M.K. and G.G.Ç.; data curation, M.K.; formal analysis, M.K.; visualization, M.K.; writing—original draft preparation, M.K.; writing—review and editing, M.K. and G.G.Ç.; project administration, M.K. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Non-Interventional Ethics Committee of Izmir City Hospital (decision number 2026-500; date of approval 22 July 2026).

Informed Consent Statement: Patient consent was waived by the Non-Interventional Ethics Committee of Izmir City Hospital because of the retrospective design of the study and the use of anonymized data.

Data Availability Statement: Anonymized patient-level datasets for the included and excluded groups, the English data dictionary, correction log, reproducible R analysis and figure code, software information and numerical outputs are provided in Supplementary File S2 Data and Code (File S2. Data_and_Code.zip). Institutional file numbers, patient names and exact calendar dates are excluded from the public files.

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Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript: AIC, Akaike information criterion; ASA, American Society of Anesthesiologists; AUC, area under the receiver operating characteristic curve; CAR, C-reactive protein-to-albumin ratio; CI, confidence interval; CRP, C-reactive protein; FGSI, Fournier Gangrene Severity Index; ICU, intensive care unit; IQR, interquartile range; LAR, lactate-to-albumin ratio; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; PIV, pan-immune-inflammation value; RAR, red cell distribution width-to-albumin ratio; RDW, red cell distribution width; RDW-CV, red cell distribution width coefficient of variation; SII, systemic immune-inflammation index;

SOFA, Sequential Organ Failure Assessment; UFGSI, Uludag Fournier Gangrene Severity Index. BCG, bromocresol green; BCP, bromocresol purple; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW-SD, red cell distribution width standard deviation; RLR, RDW-to-lymphocyte ratio; RPR, RDW-to-platelet ratio; SFGSI, simplified Fournier Gangrene Severity Index.

References

1. Tarasconi, A.; Perrone, G.; Davies, J.; Coimbra, R.; Moore, E.; Azzaroli, F.; Abongwa, H.; De Simone, B.; Gallo, G.; Rossi, G.; et al. Anorectal emergencies: WSES-AAST guidelines. *World J. Emerg. Surg.* **2021**, *16*, 48. [CrossRef] [PubMed]
2. Kranz, J.; Cai, T.; Geerlings, S.; Köves, B.; Lambregts, M.M.C.; Mantica, G.; Pilatz, A.; Medina-Polo, J.; Schneidewind, L.; Schubert, S.; et al. European Association of Urology Guidelines on Urological Infections: Summary of the 2026 Guidelines. *Eur. Urol.* **2026**, *90*, 413–429. [CrossRef] [PubMed]
3. Shet, P.; Mustafa, A.D.; Varshney, K.; Rao, L.; Sawdagar, S.; McLennan, F.; Ansari, S.; Shet, D.; Sivathamboo, N.; Campbell, S. Risk Factors for Mortality Among Patients With Fournier Gangrene: A Systematic Review. *Surg. Infect.* **2024**, *25*, 261–271. [CrossRef] [PubMed]
4. Tufano, A.; Dipinto, P.; Passaro, F.; Anceschi, U.; Franco, G.; Flammia, R.S.; Proietti, F.; Antonelli, L.; Di Pierro, G.B.; Prata, F.; et al. The Value of Fournier's Gangrene Scoring Systems on Admission to Predict Mortality: A Systematic Review and Meta-Analysis. *J. Pers. Med.* **2023**, *13*, 1283. [CrossRef] [PubMed]
5. El-Qushayri, A.E.; Khalaf, K.M.; Dahy, A.; Mahmoud, A.R.; Benmelouka, A.Y.; Ghozy, S.; Mahmoud, M.U.; Bin-Jumah, M.; Alkahtani, S.; Abdel-Daim, M.M. Fournier's gangrene mortality: A 17-year systematic review and meta-analysis. *Int. J. Infect. Dis.* **2020**, *92*, 218–225. [CrossRef] [PubMed]
6. Müssgens, C.; Wimmer, L.; Fankhauser, C.D.; Schneidewind, L.; Aschwanden, F.J. Defining the Standard of Care in Fournier's Gangrene—An Umbrella Review. *Eur. Urol. Open Sci.* **2026**, *83*, 64–71. [CrossRef] [PubMed]
7. Nawijn, F.; Smeeing, D.P.J.; Houwert, R.M.; Leenen, L.P.H.; Hietbrink, F. Time is of the essence when treating necrotizing soft tissue infections: A systematic review and meta-analysis. *World J. Emerg. Surg.* **2020**, *15*, 4. [CrossRef] [PubMed]
8. Prescott, H.C.; Antonelli, M.; Alhazzani, W.; Møller, M.H.; Alshamsi, F.; Azevedo, L.C.P.; Belley-Cote, E.; De Waele, J.; Derde, L.; Dionne, J.C.; et al. Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock 2026. *Intensive Care Med.* **2026**, *52*, 863–936. [CrossRef] [PubMed]
9. Yönder, H.; Çelik, M.; Berhuni, M.S.; Genç, A.C.; Elkan, H.; Tatlı, F.; Özgönül, A.; Çiftçi, F.; Erkmen, F.; Karabay, O.; et al. Fournier's Gangrene Mortality Index (FGMI): A New Scoring System for Predicting Fournier's Gangrene Mortality. *Diagnostics* **2024**, *14*, 2732. [CrossRef] [PubMed]
10. Seretis, K.; Bounas, N.; Sfaelos, K.; Gaitanis, G.; Bassukas, I. The Neutrophil-to-Lymphocyte Ratio as a Prognostic Biomarker of Fournier's Gangrene Severity: A Meta-Analysis. *Infect. Dis. Rep.* **2025**, *17*, 55. [CrossRef] [PubMed]
11. Shin, I.S.; Gong, S.C.; An, S.; Kim, K. Biomarkers to predict mortality in patients with Fournier's gangrene admitted to the intensive care unit after surgery in South Korea. *Acute Crit. Care* **2023**, *38*, 452–459. [CrossRef] [PubMed]
12. Silvinato, A.; dos Santos, C.L.; Amorim, E.; Floriano, I.; Paciência, L.E.M.; Tristão, L.S.; Bernardo, W.M. C-reactive protein in adult sepsis: Systematic review and meta-analysis. *Clinics* **2026**, *81*, 100848. [CrossRef] [PubMed]
13. Molano-Franco, D.; Arevalo-Rodriguez, I.; Muriel, A.; del Campo-Albendea, L.; Fernández-García, S.; Alvarez-Méndez, A.; Simancas-Racines, D.; Viteri, A.; Sanchez, G.; Fernandez-Felix, B.; et al. Basal procalcitonin, C-reactive protein, interleukin-6, and presepsin for prediction of mortality in critically ill septic patients: A systematic review and meta-analysis. *Diagn. Progn. Res.* **2023**, *7*, 15. [CrossRef] [PubMed]
14. Imamura, M.; Duggan, S.N.; Vadiveloo, T.; Cooper, J.G.; Kaye, C.T.; Manson, P.; Virgili, G.; Aucott, L.; Clarke, M.; Brazzelli, M. Clinical utility of biomarkers for outcomes prediction in adults with suspected sepsis presenting to the emergency department: A synthesis of current evidence. *Health Technol. Assess.* **2026**, *30*, 73–162. [CrossRef] [PubMed]
15. Liu, Y.; Gao, Y.; Liang, B.; Liang, Z. The prognostic value of C-reactive protein to albumin ratio in patients with sepsis: A systematic review and meta-analysis. *Aging Male* **2023**, *26*, 2261540. [CrossRef] [PubMed]
16. Zhao, X.; Peng, Q.; Li, W.; Hu, D.; Guan, Y.; Wang, J. Elevated lactate/albumin ratio is associated with poor prognosis in sepsis patients: A systematic review and meta-analysis. *J. Med. Biochem.* **2024**, *43*, 334–349. [CrossRef] [PubMed]
17. Kurt, Z.E.; Yumrutepe, S. Prognostic value of the lactate-to-albumin ratio in adult sepsis: An updated systematic review of prognostic evidence. *Respir. Med.* **2026**, *262*, 109119. [CrossRef] [PubMed]
18. Karampela, I.; Kounatidis, D.; Vallianou, N.G.; Panagopoulos, F.; Tsilingiris, D.; Dalamaga, M. Kinetics of the Lactate to Albumin Ratio in New Onset Sepsis: Prognostic Implications. *Diagnostics* **2024**, *14*, 1988. [CrossRef] [PubMed]
19. Gao, Z.; Wang, X.; Wang, W.; Kang, Z.; Chen, X. Association between neutrophil to lymphocyte ratio and the mortality of patients with sepsis: An update systematic review and meta-analysis. *Front. Med.* **2025**, *12*, 1637365. [CrossRef] [PubMed]

20. Liang, L.; Su, Q. Systemic immune-inflammation index and the short-term mortality of patients with sepsis: A meta-analysis. *Biomol. Biomed.* **2025**, *25*, 798–809. [CrossRef] [PubMed]
21. Agnello, L.; Giglio, R.V.; Bivona, G.; Scazzone, C.; Gambino, C.M.; Iacona, A.; Ciaccio, A.M.; Lo Sasso, B.; Ciaccio, M. The Value of a Complete Blood Count (CBC) for Sepsis Diagnosis and Prognosis. *Diagnostics* **2021**, *11*, 1881. [CrossRef] [PubMed]
22. Zhang, L.; Yu, C.H.; Guo, K.P.; Huang, C.Z.; Mo, L.Y. Prognostic role of red blood cell distribution width in patients with sepsis: A systematic review and meta-analysis. *BMC Immunol.* **2020**, *21*, 40. [CrossRef] [PubMed]
23. Callum, J.; Skubas, N.J.; Bathla, A.; Keshavarz, H.; Clark, E.G.; Rochwerg, B.; Fergusson, D.; Arbous, S.; Bauer, S.R.; China, L.; et al. Use of Intravenous Albumin: A Guideline From the International Collaboration for Transfusion Medicine Guidelines. *Chest* **2024**, *166*, 321–338. [CrossRef] [PubMed]
24. Arba, I.F.; Multazam, C.E.C.Z.; Widiarti, W.; Siahaan, P.P.; Oktaviono, Y.H.; Setyobudi, D.; Saputra, P.B.T.; Lamara, A.D.; Arnindita, J.N. A systematic review and dose-response meta-analysis of red blood cell distribution width to albumin ratio as mortality predictor in cardiovascular disease. *Sci. Rep.* **2025**, *15*, 32053. [CrossRef] [PubMed]
25. Ye, L.; Jiang, W. Red blood cell distribution width-albumin ratio as predictor of mortality in patients with cardiac disease: A systematic review and meta-analysis. *BMC Cardiovasc. Disord.* **2026**, *26*, 430. [CrossRef] [PubMed]
26. Jin, C.; Hao, R.; Ren, X.; Shen, J. Red cell distribution width to albumin ratio (RAR) as a prognostic marker for mortality in critical care patients: A large-scale retrospective cohort study. *Eur. J. Med. Res.* **2025**, *30*, 658. [CrossRef] [PubMed]
27. Jeong, J.H.; Heo, M.; Lee, S.J.; Jeong, Y.Y.; Lee, J.D.; Yoo, J.-W. Clinical Usefulness of Red Cell Distribution Width/Albumin Ratio to Discriminate 28-Day Mortality in Critically Ill Patients with Pneumonia Receiving Invasive Mechanical Ventilation, Compared with Lacate/Albumin Ratio: A Retrospective Cohort Study. *Diagnostics* **2021**, *11*, 2344. [CrossRef] [PubMed]
28. Kayar, R.; Kayar, K.; Artuk, İ.; Demir, S.; Tokuc, E.; Öztürk, M. Diagnostic Accuracy of Red Cell Distribution Width-Derived Indices for Predicting In-Hospital Mortality in Scrotal Fournier's Gangrene: A Retrospective Cohort Study. *Surg. Infect.* **2026**, *27*, 201–207. [CrossRef] [PubMed]
29. von Elm, E.; Altman, D.G.; Egger, M.; Pocock, S.J.; Gøtzsche, P.C.; Vandenbroucke, J.P. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. *PLoS Med.* **2007**, *4*, e296. [CrossRef] [PubMed]
30. Collins, G.S.; Moons, K.G.M.; Dhiman, P.; Riley, R.D.; Beam, A.L.; Van Calster, B.; Ghassemi, M.; Liu, X.; Reitsma, J.B.; van Smeden, M.; et al. TRIPOD+AI statement: Updated guidance for reporting clinical prediction models that use regression or machine learning methods. *BMJ* **2024**, *385*, e078378. [CrossRef] [PubMed]
31. Lin, T.Y.; Ou, C.H.; Tzai, T.S.; Tong, Y.C.; Chang, C.C.; Cheng, H.L.; Yang, W.H.; Lin, Y.M. Validation and simplification of Fournier's gangrene severity index. *Int. J. Urol.* **2014**, *21*, 696–701. [CrossRef] [PubMed]
32. Shiratori, T.; Nakamura, M.; Naito, A.; Yamamoto, M.; Okura, Y.; Yamakawa, J.; Kume, H.; Suzuki, M. Clinical features and treatment outcomes of Fournier's gangrene in a single tertiary emergency hospital: Simplified Fournier's Gangrene Severity Index score is a predictor for death. *Glob. Health Med.* **2023**, *5*, 362–365. [CrossRef] [PubMed]
33. Heinze, G.; Schemper, M. A solution to the problem of separation in logistic regression. *Stat. Med.* **2002**, *21*, 2409–2419. [CrossRef] [PubMed]
34. Moons, K.G.M.; Damen, J.A.A.; Kaul, T.; Hooft, L.; Andaur Navarro, C.; Dhiman, P.; Beam, A.L.; Van Calster, B.; Celi, L.A.; Denaxas, S.; et al. PROBAST+AI: An updated quality, risk of bias, and applicability assessment tool for prediction models using regression or artificial intelligence methods. *BMJ* **2025**, *388*, e082505. [CrossRef] [PubMed]
35. Singer, P.; Reintam Blaser, A.; Berger, M.M.; Calder, P.C.; Casaer, M.; Hiesmayr, M.; Mayer, K.; Montejo-Gonzalez, J.C.; Pichard, C.; Preiser, J.-C.; et al. ESPEN practical and partially revised guideline: Clinical nutrition in the intensive care unit. *Clin. Nutr.* **2023**, *42*, 1671–1689. [CrossRef] [PubMed]
36. Babker, A.M.; Suliman, R.S.; Farajallah, N.A.M.; Al-Qahtani, F.; Alhadeb, D.M.; Elzubair, Q.A.; Gopinath, K.S.; Abbas, A.M. Association of the Red Cell Distribution Width with Complete Blood Count, Glycated Hemoglobin and Vitamin D in Patients with Type 2 Diabetes Mellitus—Across Sectional Study. *Biomed. Pharmacol. J.* **2024**, *17*, 881–888. [CrossRef]
37. Xie, C.; Sun, P.; Zhang, M.; Fan, H.; Li, Z.; Tong, X. The prognostic value of the CALLY index in sepsis: A systematic review and meta-analysis. *Front. Med.* **2026**, *13*, 1812568. [CrossRef] [PubMed]
38. Arabi, Y.M.; Belley-Cote, E.; Carsetti, A.; De Backer, D.; Donadello, K.; Juffermans, N.P.; Hammond, N.; Laake, J.H.; Liu, D.; Maitland, K.; et al. European Society of Intensive Care Medicine clinical practice guideline on fluid therapy in adult critically ill patients. Part 1: The choice of resuscitation fluids. *Intensive Care Med.* **2024**, *50*, 813–831. [CrossRef] [PubMed]
39. Sakr, Y.; Nierhaus, A.; Schumacher, U.; Utzolino, S.; Jaschinski, U.; Petros, S.; Fichtner, F.; Eimer, C.; Putensen, C.; Tanev, I.; et al. Albumin Replacement Therapy in Septic Shock: A Randomized Clinical Trial. *JAMA Netw. Open* **2026**, *9*, e2559297. [CrossRef] [PubMed]

40. Mendes, H.; Wen, H.K.; de Souza, H.; Peng, Y.; Deshpande, K.; Blok, S.G.; Tuinman, P.R.; Serpa Neto, A.; Schultz, M.J.; Malbrain, M.L.N.G.; et al. Mortality effect of albumin fluid resuscitation in adults with septic shock: A systematic review and dual frequentist–Bayesian meta-analysis of randomised trials. *Crit. Care* **2026**, *30*, 372. [CrossRef] [PubMed]
41. Penickova, S.; Benyaich, S.; Ambar, I.; Cotton, F. Reliability of albumin bromocresol green colorimetric method and clinical impact. *Scand. J. Clin. Lab. Investig.* **2024**, *84*, 452–458. [CrossRef] [PubMed]

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