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Association of Early post-ECMO lactate-to-albumin Ratio and its Dynamic Changes with Mortality: A Retrospective Cohort Study

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Abstract: Extracorporeal membrane oxygenation is used for severe cardiac or respiratory failure, yet early risk assessment remains difficult. We examined whether the lactate-to-albumin ratio measured early after extracorporeal membrane oxygenation initiation and its change from intensive care unit baseline were associated with adjudicated mortality. This single-center retrospective cohort included adults receiving extracorporeal membrane oxygenation in the intensive care unit between 2022 and 2024. The ratio was calculated as 10 times lactate in millimoles per liter divided by albumin in grams per liter. The primary exposure was the available ratio measured within the first 24 hours after support initiation closest to the 24-hour time point. Missing data were handled using multiple imputation by chained equations with predictive mean matching, yielding five completed datasets. Logistic regression, restricted cubic spline analysis, receiver operating characteristic analysis, and sensitivity analyses were performed. Among 84 patients, 57 were classified as non-survivors and 27 as survivors. In the fully adjusted model, each one-unit increase in the early post-extracorporeal membrane oxygenation ratio was associated with 53.3% higher odds of mortality (odds ratio 1.533, 95% confidence interval 1.136–2.069; P = 0.006). Spline analysis identified an overall association and no statistically significant departure from linearity. The intensive care unit baseline ratio was not associated with mortality, whereas a greater absolute increase in the ratio was associated with higher odds of mortality. In exploratory tertile analysis, the proportion of non-survivors increased from 52.8% to 61.8% and 89.1% across increasing relative-change groups (P for trend = 0.005). The area under the receiver operating characteristic curve for the ratio was 0.794, with no significant difference from lactate alone. Early post-extracorporeal membrane oxygenation lactate-to-albumin ratio and its trajectory were associated with mortality; prospective external validation is needed.

Keywords: Albumin; Extracorporeal Membrane Oxygenation; Lactate; Lactate-to-albumin Ratio.

1. Introduction

Extracorporeal membrane oxygenation (ECMO) provides temporary cardiopulmonary support for patients with refractory cardiac or respiratory failure. The international Extracorporeal Life Support Organization registry has documented expanding ECMO use and more than 100,000 survivors, but mortality remains substantial across adult indications [1]. The Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) and Survival After Veno-Arterial Extracorporeal Membrane Oxygenation (SAVE) scores estimate survival from information available around ECMO initiation [2–3]. Because physiology can change rapidly after support begins, repeatable biomarkers measured during the early post-ECMO period may complement baseline risk assessment.

Blood lactate is routinely measured during shock and reflects the balance between production and clearance. Serial lactate concentrations and lactate clearance after ECMO initiation have been associated with mortality in postcardiotomy and other ECMO populations [4–9]. These observations highlight the importance of both measurement timing and early metabolic trajectory.

Albumin may add information about the systemic inflammatory and illness milieu. Hypoalbuminemia has been associated with adverse outcomes during venoarterial ECMO for cardiogenic shock [10]. The lactate-to-albumin ratio (LAR) combines lactate with albumin and has been studied as a prognostic marker in critical illness [11]. Across sepsis and several other acute critical illnesses, higher LAR has been associated with adverse outcomes [12–20]. Zhao et al. [21] recently reported an association between LAR and 28-day mortality in patients with cardiogenic etiologies receiving venoarterial ECMO. Their analysis used a single ICU-based measurement and identified dynamic lactate and albumin assessment after ECMO initiation as an area for further study.

Whether LAR measured during the early post-ECMO period, and particularly its change from ICU baseline, is prognostically informative remains uncertain. This question is relevant in real-world ECMO populations that include both venoarterial and venovenous support. We examined the association of LAR measured within the first 24 hours after ECMO initiation, closest to the 24-hour time point, with adjudicated mortality. We also assessed the shape and discrimination of this association and explored absolute and relative changes in LAR from ICU baseline.

2. Materials and Methods

2.1. Study Design and Population

This single-center retrospective cohort study included adult patients who received ECMO support in the ICU between January 2022 and December 2024. All ECMO support was initiated and managed by the institutional ECMO team. Venoarterial ECMO was primarily used for severe cardiogenic circulatory failure, whereas venovenous ECMO was mainly used for severe respiratory failure. Patients transferred from another institution while already receiving

ECMO were not included. For patients who received ECMO more than once during the study period, only the first ECMO episode was analyzed.

Patients were excluded if they were younger than 18 years, received ECMO support for less than 6 hours, or had completely missing ICU baseline laboratory data. Completely missing baseline laboratory data were defined as the absence of all prespecified laboratory measurements at ICU baseline; baseline vital signs were not included in this criterion. ECMO duration was calculated in hours as the interval between ECMO initiation and ECMO discontinuation. The study protocol was approved by the Scientific Research Ethics Committee of the First Affiliated Hospital of Jinan University (Approval No. KY-2024-083; May 20, 2024).

2.2. Data Collection

Clinical, laboratory, and ECMO-related data were retrospectively collected from the electronic medical record system, laboratory information system, and ICU electronic information system. Medical records were additionally reviewed manually when necessary to verify clinical information and outcomes. Collected variables included age, sex, ECMO modality, vital signs, hematologic and coagulation indices, biochemical and inflammatory markers, blood gas variables, electrolytes, lactate, albumin, ECMO initiation and discontinuation times, and outcome status.

2.3. Definition of Measurement Time Points

ICU baseline measurements were defined as the first available measurements after ICU admission. The same principle was used for baseline vital signs. Early post-ECMO measurements were defined as the available measurements obtained within the first 24 hours after ECMO initiation that were closest to the 24-hour time point. These values therefore represent early post-ECMO measurements closest to 24 hours rather than protocolized measurements collected at an exact 24-hour timestamp.

2.4. Calculation of LAR and Dynamic LAR Indices

Because albumin was recorded in grams per liter, LAR was calculated as 10 × lactate (mmol/L) / albumin (g/L), corresponding to lactate divided by albumin expressed in grams per deciliter. The primary exposure was early post-ECMO LAR. ICU baseline LAR was evaluated as a secondary exposure. Absolute change in LAR (ΔLAR) was defined as early post-ECMO LAR minus ICU baseline LAR; positive values indicated an increase after ICU baseline.

Relative LAR change was calculated as 100 × (early post-ECMO LAR − ICU baseline LAR) / ICU baseline LAR. Negative values indicated a decrease in LAR, whereas positive values indicated an increase. In an exploratory analysis, relative LAR change was categorized using common tertile cutoffs derived across the five completed imputed datasets. The median of the imputation-specific 33.3rd and 66.7th percentiles was used to define fixed cutoffs of −33.6% and 36.4%, which were then applied identically to all completed datasets. The lowest tertile predominantly represented a marked decrease in LAR, and the highest tertile represented a marked increase. These data-driven cutoffs were not considered clinical thresholds.

2.5. Outcome Definition

The primary outcome was adjudicated mortality. Patients who died during the index hospitalization were classified as non-survivors. Patients who discontinued active treatment and were discharged alive because of an extremely poor clinical condition were also classified as non-survivors when the treating clinical team and expert reviewers considered death to be imminent on the basis of severe physiological deterioration, overall clinical status, medical record review, and available follow-up information. Death occurring after withdrawal of life-sustaining treatment during hospitalization was classified as a mortality outcome. All remaining patients who survived the index hospitalization without meeting the predefined criteria for an adjudicated mortality outcome were classified as survivors.

2.6. Missing Data

Variables with more than 20% missing observations were excluded from the imputation model; these were early post-ECMO C-reactive protein, early post-ECMO chloride, and ICU baseline chloride. Among retained variables, the maximum original missingness was 13.1%. Missing data were handled by multiple imputation by chained equations using predictive mean matching [22–23]. Five imputed datasets were generated over 20 iterations. Lactate and albumin were imputed as component variables; LAR was not directly imputed. Instead, ICU baseline LAR, early post-ECMO LAR, ΔLAR, and relative LAR change were passively recalculated after component imputation in each completed dataset. Analyses were performed separately in each completed dataset and combined using Rubin's rules unless otherwise specified. A detailed missing-data profile and the corresponding imputation approach are provided in Supplementary Table S1.

2.7. Statistical Analysis

Continuous variables were summarized as mean ± standard deviation when approximately normally distributed and as median with the 25th and 75th percentiles otherwise. Categorical variables were summarized as number and percentage. For Table 1, descriptive values represent the average of the corresponding summary statistics across the five completed datasets. Continuous group comparisons were performed separately within each completed dataset and combined using Rubin's rules; non-normally distributed variables were rank-transformed within each completed dataset before pooled comparison. Pearson chi-square or Fisher exact tests were used for categorical variables as appropriate.

Binary logistic regression was used because exact time-to-death information was not available. The primary association between early post-ECMO LAR and mortality was evaluated in progressively adjusted models. Model 0 was unadjusted. Model 1 adjusted for age, sex, and ECMO modality. Model 2 additionally adjusted for ICU baseline creatinine and baseline base excess. Covariates were prespecified on the basis of clinical relevance, temporal precedence, and model parsimony rather than univariable P values. The final adjustment set was intended to account for demographic characteristics, ECMO modality, baseline renal function, and baseline metabolic status while limiting overfitting in the modest sample. LAR, lactate, and albumin were entered into separate parallel models because of mathematical coupling and overlapping biological information.

The shape of the association between early post-ECMO LAR and mortality was evaluated using a three-knot restricted

cubic spline logistic model adjusted as in Model 2. Knot locations were estimated from the observed pre-imputation LAR distribution and subsequently fixed at 0.463, 1.678, and 11.864 to ensure an identical spline basis across all five imputed datasets. The observed median LAR of 1.678 was used as the reference value. Overall association and nonlinearity were evaluated using pooled D1 comparisons of nested multiply imputed models.

Receiver operating characteristic analyses were performed separately in each completed dataset. Areas under the curve were logit-transformed and combined using scalar Rubin pooling with within-imputation DeLong variances. Paired area-under-the-curve differences were pooled using the corresponding within-imputation DeLong variances and covariances [24]. LAR, lactate, and albumin were compared, and a basic clinical model including age, sex, ECMO modality, baseline creatinine, and baseline base excess was compared with models additionally containing lactate or LAR. Holm adjustment was applied to multiple pairwise area-under-the-curve comparisons. Exploratory Youden cutoffs were calculated but were not treated as validated clinical thresholds.

Internal validation used 100 bootstrap repetitions within each of the five completed datasets. The same resampling indices were applied to the three compared clinical models within each completed dataset. Optimism was estimated as the difference between model performance in the bootstrap sample and performance of the bootstrap-fitted model in the original completed dataset. Optimism-corrected areas under the curve were calculated within each imputation and averaged across imputations. Bootstrap optimism correction was used to quantify the degree of apparent-performance optimism, consistent with established approaches to internal validation of logistic regression models [25].

Sensitivity analyses repeated the primary regression in complete cases and among patients supported with ECMO for at least 24 hours. Effect modification by ECMO modality was assessed by an LAR-by-ECMO-modality interaction term. Secondary analyses evaluated ICU baseline LAR, ΔLAR, and relative LAR change tertiles. All tests were two-sided, and $P < 0.05$ was considered statistically significant. Analyses were performed in R (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Study Population and Baseline Characteristics

A total of 104 patients received ECMO in the ICU during the study period. Two patients younger than 18 years, nine patients with ECMO support lasting less than 6 hours, and nine patients with completely missing baseline laboratory data were excluded, leaving 84 patients in the final cohort (Figure 1). According to the predefined outcome adjudication criteria, 57 patients (67.9%) were classified as non-survivors and 27 as survivors. Sixty patients (71.4%) were male. Venoarterial and venovenous ECMO each accounted for 42 patients.

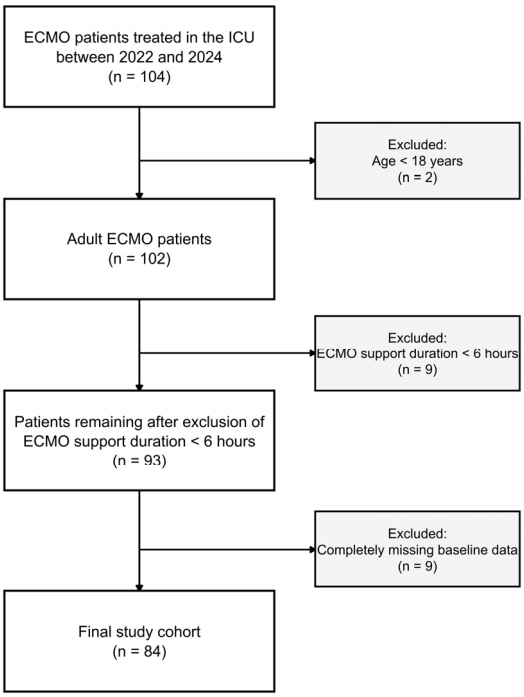

Figure 1. Flowchart of patient selection. ECMO, extracorporeal membrane oxygenation.

Baseline characteristics are summarized in Table 1. Non-survivors had higher ICU baseline creatinine than survivors [165.40 (106.00, 246.70) vs. 105.30 (76.00, 139.30) μmol/L; $P = 0.009$] and more negative baseline base excess (−6.33 ± 9.17 vs. −1.57 ± 6.51 mmol/L; $P = 0.019$). Age, sex, ECMO modality, ICU baseline lactate, albumin, and ICU baseline LAR did not differ significantly between outcome groups.

3.2. Association Between Early Post-ECMO LAR and Mortality

Higher early post-ECMO LAR was associated with greater odds of mortality in all three logistic regression models (Table 2). In the unadjusted model, the odds ratio (OR) per one-unit increase in LAR was 1.515 (95% confidence interval [CI] 1.151–1.993; $P = 0.004$). The estimate remained stable after adjustment for age, sex, and ECMO modality (OR 1.553, 95% CI 1.158–2.082; $P = 0.004$). After further adjustment for ICU baseline creatinine and base excess, early post-ECMO LAR remained independently associated with mortality (OR 1.533, 95% CI 1.136–2.069; $P = 0.006$). Thus, each one-unit increase in LAR corresponded to approximately 53.3% higher odds of mortality in the fully adjusted model. Full coefficients from the fully adjusted model are reported in Supplementary Table S2.

3.3. Dose-Response Association Between Early Post-ECMO LAR and Mortality

Restricted cubic spline analysis showed an overall association between early post-ECMO LAR and mortality (P for overall = 0.005); the test for nonlinearity was not significant (P for nonlinearity = 0.257) (Figure 2). The adjusted odds ratio increased across the observed LAR range, with markedly wider confidence intervals in the upper tail because observations at very high LAR values were sparse.

3.4. Dynamic Changes in LAR and Mortality

ICU baseline LAR was not associated with mortality in the fully adjusted model (OR 0.991 per one-unit increase, 95% CI 0.873–1.125; $P = 0.888$). In contrast, a greater absolute

increase in LAR from ICU baseline to the early post-ECMO measurement was associated with higher odds of mortality (adjusted OR 1.316 per one-unit increase in ΔLAR, 95% CI 1.063–1.629; P = 0.013) (Table 3).

Table 1. Baseline characteristics of survivors and non-survivors

Variable	Overall (n = 84)	Survivors (n = 27)	Non-survivors (n = 57)	P value
Demographic and ECMO characteristics				
Age, years	54.00 (43.00, 65.50)	53.00 (39.00, 62.00)	56.00 (48.00, 66.00)	0.122
Sex, n (%)				0.237
Male	60 (71.4)	17 (63.0)	43 (75.4)	
Female	24 (28.6)	10 (37.0)	14 (24.6)	
ECMO mode, n (%)				0.483
VA-ECMO	42 (50.0)	12 (44.4)	30 (52.6)	
VV-ECMO	42 (50.0)	15 (55.6)	27 (47.4)	
Vital signs at ICU admission				
Heart rate, bpm	117.48 ± 26.18	113.30 ± 24.77	119.45 ± 26.78	0.349
Temperature, °C	36.50 (36.20, 36.70)	36.50 (36.20, 36.76)	36.46 (36.12, 36.60)	0.230
Systolic blood pressure, mmHg	106.70 (88.20, 127.30)	107.20 (94.20, 126.20)	106.00 (87.20, 129.20)	0.592
Diastolic blood pressure, mmHg	63.37 ± 19.54	65.33 ± 15.89	62.44 ± 21.11	0.543
Hematologic and coagulation variables				
White blood cell count, 10^9/L	13.06 (7.73, 19.02)	13.44 (8.53, 19.74)	12.78 (6.95, 18.58)	0.541
Red blood cell count, 10^12/L	3.47 ± 1.12	3.65 ± 0.89	3.39 ± 1.21	0.319
Hemoglobin, g/L	101.34 ± 34.63	106.83 ± 28.57	98.74 ± 37.08	0.335
Platelet count, 10^9/L	119.66 (68.05, 200.05)	141.00 (78.30, 198.00)	110.00 (52.60, 202.10)	0.303
Activated partial thromboplastin time, s	50.80 (38.89, 111.85)	49.10 (37.80, 85.50)	51.40 (39.30, 116.10)	0.458
Prothrombin time, s	18.50 (15.27, 25.80)	17.50 (15.10, 21.90)	18.70 (15.60, 26.20)	0.389
Fibrinogen, g/L	3.55 (1.97, 5.03)	3.71 (1.59, 6.96)	3.55 (2.14, 5.00)	0.642
D-dimer, ng/mL	6991.00 (2710.00, 18299.00)	9353.20 (3142.00, 20000.00)	5684.00 (2684.00, 16936.00)	0.357
Biochemical and inflammatory variables				
Alanine aminotransferase, U/L	64.70 (31.50, 417.00)	57.00 (24.00, 122.00)	72.40 (33.00, 511.00)	0.384
Aspartate aminotransferase, U/L	111.00 (53.00, 472.50)	80.00 (46.00, 272.00)	158.00 (61.00, 943.00)	0.143
Total protein, g/L	51.73 ± 9.75	52.05 ± 10.16	51.58 ± 9.63	0.838
Albumin, g/L	28.82 ± 6.64	28.66 ± 6.31	28.90 ± 6.84	0.878
Creatinine, μmol/L	135.30 (89.95, 222.50)	105.30 (76.00, 139.30)	165.40 (106.00, 246.70)	0.009
C-reactive protein, mg/L	93.33 (28.62, 164.35)	85.30 (25.24, 143.12)	97.15 (32.58, 173.52)	0.294
Procalcitonin, ng/mL	5.20 (0.94, 25.17)	4.03 (0.76, 59.62)	5.63 (1.09, 14.35)	0.946
Blood gas and electrolyte variables				
pH	7.34 (7.20, 7.42)	7.35 (7.26, 7.44)	7.33 (7.18, 7.41)	0.468
PaCO2, mmHg	39.19 (31.04, 49.28)	42.80 (35.60, 63.00)	36.50 (30.56, 47.38)	0.157
PaO2, mmHg	84.69 (57.62, 154.00)	73.30 (56.00, 118.00)	91.52 (60.76, 157.40)	0.289
Bicarbonate, mmol/L	21.11 ± 6.83	23.07 ± 5.03	20.18 ± 7.40	0.071
Base excess, mmol/L	−4.80 ± 8.66	−1.57 ± 6.51	−6.33 ± 9.17	0.019
Potassium, mmol/L	3.85 (3.40, 4.37)	3.90 (3.34, 4.10)	3.83 (3.40, 4.48)	0.538
Sodium, mmol/L	143.26 (139.50, 148.50)	142.28 (138.40, 149.00)	143.44 (140.80, 147.60)	0.910
Calcium, mmol/L	1.05 (0.95, 1.16)	1.03 (0.93, 1.14)	1.10 (0.98, 1.16)	0.194
Lactate and lactate-to-albumin ratio				
Lactate, mmol/L	6.80 (2.33, 15.60)	5.10 (1.80, 15.68)	7.14 (3.92, 15.64)	0.181
Lactate-to-albumin ratio	2.44 (0.87, 5.58)	2.19 (0.56, 5.36)	2.52 (1.36, 5.57)	0.228

Notes: Values are mean ± standard deviation, median (25th percentile, 75th percentile), or n (%). Descriptive summaries were averaged across five imputed datasets; continuous comparisons were pooled using Rubin's rules, with rank transformation for non-normally distributed variables. Categorical comparisons used Pearson chi-square or Fisher exact tests. Measurements are the first available after ICU admission. LAR = 10 × lactate (mmol/L) / albumin (g/L). ECMO, extracorporeal membrane oxygenation; LAR, lactate-to-albumin ratio; VA, venoarterial; VV, venovenous

Table 2. Association between early post-ECMO LAR and mortality

Model	Adjustment	OR per 1-unit increase in LAR (95% CI)	P value
Model 0	Unadjusted	1.515 (1.151–1.993)	0.004
Model 1	Age, sex, and ECMO modality	1.553 (1.158–2.082)	0.004
Model 2	Model 1 + ICU baseline creatinine and ICU baseline base excess	1.533 (1.136–2.069)	0.006

Notes: Outcome: adjudicated mortality. Model 1 adjusted for age, sex, and ECMO modality; Model 2 additionally adjusted for ICU baseline creatinine and base excess. Estimates from five imputed datasets were combined using Rubin's rules. OR, odds ratio; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; LAR, lactate-to-albumin ratio.

In exploratory relative-change analysis, fixed tertile cutoffs of −33.6% and 36.4% were applied. The mean proportion of non-survivors across completed imputed datasets was 52.8%, 61.8%, and 89.1% in the lowest, middle, and highest tertiles, respectively (Figure 3).

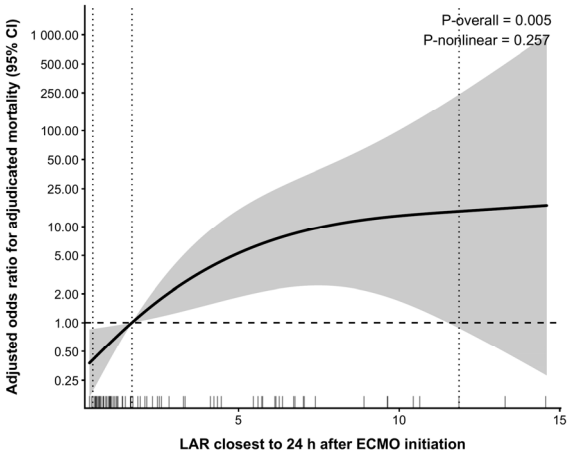

Figure 2. Adjusted restricted cubic spline association between early post-ECMO LAR and adjudicated mortality. Odds ratios are shown on a logarithmic scale relative to LAR 1.678; the model adjusted for age, sex, ECMO modality, ICU baseline creatinine, and base excess. P for overall = 0.005; P for nonlinearity = 0.257.

Compared with the lowest tertile, the highest tertile had higher adjusted odds of mortality (OR 11.579, 95% CI 2.194–61.125; P = 0.005); the middle-tertile estimate was imprecise (OR 2.760, 95% CI 0.707–10.776; P = 0.142). Mortality odds increased across tertiles (OR 3.332 per level, 95% CI 1.473–7.541; P for trend = 0.005).

Table 3. Baseline and dynamic LAR analyses

Exposure or comparison	Model	OR	95% CI	P value
ICU baseline LAR, per 1 unit	Model 2	0.991	0.873–1.125	0.888
ΔLAR, per 1 unit	Model 2	1.316	1.063–1.629	0.013
Middle vs. lowest relative-change tertile	Model 2	2.760	0.707–10.776	0.142
Highest vs. lowest relative-change tertile	Model 2	11.579	2.194–61.125	0.005
Relative-change tertile score, per 1 level	Trend	3.332	1.473–7.541	0.005

Notes: Model 2 adjusted for age, sex, ECMO modality, ICU baseline creatinine, and base excess. Relative-change cutoffs were −33.6% and 36.4%; tertile scores 1–3 were used for trend analysis. CI, confidence interval; ICU, intensive care unit; LAR, lactate-to-albumin ratio; OR, odds ratio.

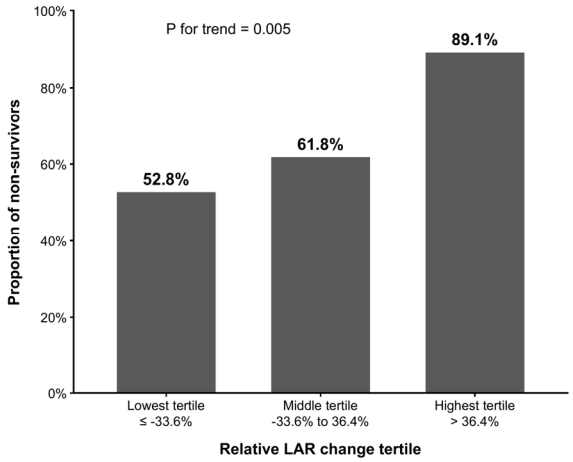

Figure 3. Proportion of non-survivors by tertile of relative LAR change. Bars show mean proportions across five imputed datasets. Cutoffs were ≤−33.6%, >−33.6% to ≤36.4%, and >36.4%; P for trend = 0.005.

3.5. Discriminative Performance of Early Post-ECMO LAR

The pooled area under the receiver operating characteristic curve for early post-ECMO LAR was 0.794 (95% CI 0.671–0.879), compared with 0.809 (95% CI 0.688–0.891) for lactate and 0.578 (95% CI 0.444–0.701) for albumin (Figure 4; Supplementary Table S4A). The area-under-the-curve difference between LAR and lactate was not statistically significant (ΔAUC −0.015, 95% CI −0.046 to 0.015; P = 0.312). LAR had a higher area under the curve than albumin (Holm-adjusted P = 0.009). An exploratory LAR cutoff of 1.90 yielded a mean sensitivity of 65.3% and specificity of 85.2% across imputations; this data-derived cutoff was not considered a validated clinical threshold.

The basic clinical model had an area under the curve of 0.718 (95% CI 0.582–0.823). Adding LAR numerically increased the area under the curve to 0.811 (95% CI 0.695–0.890), but the paired area-under-the-curve difference did not reach statistical significance (ΔAUC 0.093, 95% CI −0.011 to 0.197; P = 0.079). The model containing lactate had an area under the curve of 0.812 (95% CI 0.699–0.890), and its discrimination was virtually identical to that of the LAR-enhanced model (P = 0.908). Complete clinical-model AUC comparisons are provided in Supplementary Table S4B, and the corresponding receiver operating characteristic curves are shown in Supplementary Figure S1.

Bootstrap internal validation demonstrated optimism in all three clinical models. The multiple-imputation-averaged optimism-corrected area under the curve was 0.636 for the basic clinical model, 0.747 for the clinical model plus lactate, and 0.745 for the clinical model plus LAR. The corrected areas under the curve remained numerically higher for both biomarker-augmented models than for the basic clinical model, although formal paired area-under-the-curve comparisons were not statistically significant.

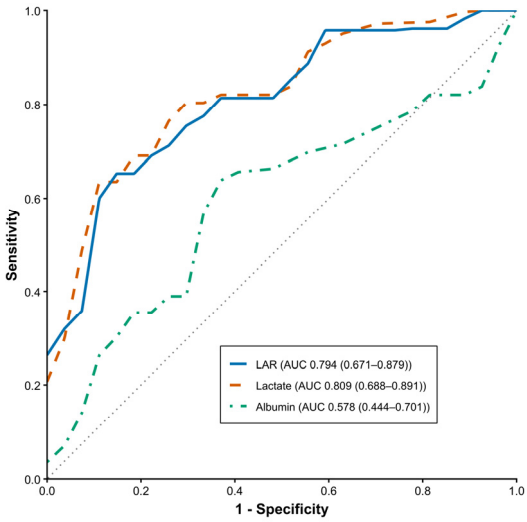

Figure 4. Receiver operating characteristic curves for early post-ECMO LAR, lactate, and albumin. Pooled areas under the curve were 0.794, 0.809, and 0.578, respectively; LAR versus lactate, P = 0.312.

3.6. Sensitivity Analyses

The primary association was consistent in complete-case analysis. Among 75 complete cases, early post-ECMO LAR remained associated with mortality after full adjustment (OR 1.521, 95% CI 1.132–2.043; P = 0.005). Similar results were obtained after restricting the cohort to the 73 patients who received ECMO support for at least 24 hours (OR 1.453, 95% CI 1.065–1.984; P = 0.019). There was no statistically significant evidence that ECMO modality modified the association between LAR and mortality (P for interaction = 0.154). A consolidated summary of sensitivity analyses is provided in Supplementary Table S6.

The relative-change tertile findings were also directionally consistent in the complete-case dynamic cohort of 73 patients. The proportion of non-survivors was 47.8% in the lowest tertile, 56.0% in the middle tertile, and 92.0% in the highest tertile. In the fully adjusted complete-case model, the highest tertile had substantially higher odds of mortality than the lowest tertile (OR 19.341, 95% CI 3.122–119.819; P = 0.001), with a significant trend across tertiles (P for trend = 0.001). The wide confidence intervals reflected limited precision in this small exploratory analysis.

4. Discussion

In this single-center cohort of adults receiving ECMO, higher early post-ECMO LAR closest to the 24-hour time point was associated with adjudicated mortality after multivariable adjustment. Spline modeling did not identify a statistically significant departure from linearity. ICU baseline LAR was not associated with mortality, whereas ΔLAR and

relative-change tertiles showed concordant associations with outcome. The primary association was similar in complete-case and ECMO-duration-restricted analyses.

Several studies have linked serial lactate concentrations or lactate clearance after ECMO initiation with adverse outcomes [4–9]. RESP and SAVE, by contrast, use information available around the time of ECMO initiation [2–3]. Our findings are consistent with the view that metabolic measurements obtained after support has begun can complement, rather than replace, baseline risk assessment by capturing early physiological evolution.

Our findings should also be viewed alongside the recent ECMO-LAR study by Zhao et al. [21]. That study linked a single ICU-based LAR measurement with 28-day mortality in patients receiving venoarterial ECMO for cardiogenic etiologies and called for dynamic measurements aligned with ECMO initiation. We focused on early post-ECMO LAR and change from ICU baseline. The contrasting results for ICU baseline LAR, early post-ECMO LAR, and ΔLAR suggest that timing may influence the prognostic information carried by LAR. Because this was an observational study, the pattern should not be interpreted causally.

The dynamic findings are consistent with this timing hypothesis. Patients in the lowest relative-change tertile, which predominantly represented a marked decline in LAR, had a lower proportion of non-survivors than those in the highest tertile, which represented a marked increase. The tertile trend and the association of continuous ΔLAR with mortality pointed in the same direction. LAR is derived from two time-varying components, and albumin concentrations during critical illness may reflect changing synthesis and peripheral kinetics rather than a fixed nutritional trait [26]. The observed trajectory may therefore summarize concurrent changes in metabolic stress and the systemic illness milieu. A ratio, however, cannot identify the mechanism responsible for an individual patient's change, and relative percentage change remains sensitive to low baseline values. For these reasons, the tertile analysis should be considered exploratory.

The comparison with lactate is particularly important because lactate is a direct component of LAR. Prior critical-care studies have associated higher LAR with adverse outcomes across several conditions [12–20], and some reported better discrimination for LAR than for lactate or albumin alone [14–15]. In our cohort, LAR and lactate were each associated with mortality in separate, identically adjusted models, whereas albumin was not. Their areas under the curve were statistically comparable. These data therefore do not show that LAR is superior to lactate; LAR may instead serve as a simple composite that places lactate burden in the context of albumin status.

Adding LAR to the clinical model increased the area under the curve numerically from 0.718 to 0.811, but the paired difference was not statistically significant. Bootstrap optimism correction reduced apparent performance in all models, and corrected areas under the curve remained numerically higher for the LAR- and lactate-augmented models than for the basic clinical model. These results are compatible with additional prognostic information but do not establish incremental predictive superiority. Bootstrap validation was used to quantify optimism, not as a substitute for external validation [25].

Half of the cohort received venoarterial ECMO and half received venovenous ECMO, extending the clinical context beyond cardiogenic venoarterial support. The LAR-by-modality interaction was not statistically significant. However, the sample was too small to establish equivalent associations in the two modalities, and stratum-specific estimates were imprecise. The results should therefore be viewed as evidence from a mixed ECMO cohort, not as separate validation in venoarterial and venovenous ECMO.

Clinically, our data do not support using a single LAR cutoff to trigger treatment. Early post-ECMO LAR and its direction of change may instead be useful as adjuncts to repeated physiological reassessment. The tertile boundaries of −33.6% and 36.4% were data-derived and were used to display the risk gradient; they are not validated intervention thresholds. Prospective studies with protocolized serial lactate and albumin sampling are needed to determine whether dynamic LAR adds reproducible information to established ECMO risk assessment and whether specific trajectories can support clinical decision-making.

Several limitations warrant consideration. The retrospective, single-center design and small sample limited generalizability and precision, particularly for interaction and tertile analyses. The mixed venoarterial and venovenous cohort was clinically heterogeneous, and power to detect effect modification by ECMO modality was limited. Early post-ECMO measurements were available values within the first 24 hours closest to the 24-hour time point rather than protocolized samples obtained at exact timestamps. The mortality outcome also incorporated clinical adjudication for selected critically ill patients who discontinued active treatment and left the hospital in a moribund condition; despite review of physiological status, medical records, and available follow-up information, some outcome misclassification remains possible. Multiple imputation depends on assumptions about the missing-data mechanism. Relative percentage change in LAR is sensitive to low baseline values, so the tertile analysis was exploratory. Receiver operating characteristic cutoffs were data-driven, and no external validation cohort was available. ECPR status and several established severity and ECMO-related variables, including validated ECMO risk scores and detailed pre-ECMO organ-support information, were unavailable. Residual confounding by illness severity and other unmeasured factors therefore cannot be excluded.

5. Conclusion

Early post-ECMO LAR closest to the 24-hour time point was independently associated with adjudicated mortality in this retrospective ECMO cohort. Spline analysis did not identify a statistically significant departure from linearity. ICU baseline LAR showed no clear association, whereas increasing ΔLAR and higher relative-change tertiles were associated with worse outcomes. LAR had moderate discrimination that was comparable to lactate alone, and adding LAR to a basic clinical model did not produce a statistically significant paired area-under-the-curve improvement. These findings support further evaluation of early LAR trajectory in prospective multicenter cohorts with protocolized serial measurements and external validation.

Ethics Statement

The study was approved by the Scientific Research Ethics Committee of the First Affiliated Hospital of Jinan University (Approval No. KY-2024-083; May 20, 2024). The study was conducted in accordance with the approved research protocol

and institutional ethical requirements.

Conflict of Interest

The authors declare no conflicts of interest.

Data Availability

The datasets are not publicly available because of patient privacy and institutional restrictions but may be available from the corresponding author upon reasonable request and with appropriate institutional approval.

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