

RESEARCH ARTICLE

Prognostic value of glucose-to-lymphocyte ratio in critically ill patients with acute respiratory distress syndrome: A retrospective cohort study

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Abstract

Background: There is need to identify biomarkers for prognosis of acute respiratory distress syndrome (ARDS). This may allow early and accurate identification of patients with high-risk ARDS to guide adjustment of clinical treatment and nursing intervention, which would ultimately improve prognosis of patients with ARDS. Biomarkers based on a combination of fasting glucose and lymphocyte counts to predict prognosis in critically ill patients with ARDS remain undefined. In this study, we investigated the association between glucose-to-lymphocyte ratio (GLR) and in-hospital mortality.

Methods: The study obtained data from Medical Information Mart for Intensive Care-IV (MIMIC-IV Version 1.0) database. We defined the GLR as fasting glucose/lymphocyte count and the patient in-hospital mortality was considered as the outcome. In addition, we employed linear and logistic regression models for analysis.

Results: In total, 1,085 patients with ARDS were included in this study. The eligible participants included 498 female and 587 males, with a mean age of 64.2 ± 17.5 years. Logistic regression analysis demonstrated that higher GLR was an independent risk factor for all-cause mortality (OR =1.67, 95% CI: 1.26–2.22) after adjusting for age, sex, anion gap, white blood cell count, congestive heart failure, sequential organ failure assessment (SOFA), SBP, DBP, and respiratory rate in both the dichotomized group and subgroups. We also analyzed the in-hospital mortality to ROC curves by comparing the value between SOFA + GLR and SOFA. The area under the curve (AUC) was 0.6991 for the SOFA + GLR (95% CI: 0.6634–0.7348), and 0.6613 for the SOFA (95% CI: 0.6238–0.6988).

Conclusion: Our data showed that the GLR was an independent predictor of in-hospital mortality for patients with ARDS. The GLR is an integrated, readily available clinical biomarker for mortality in patients with ARDS.

KEYWORDS

acute respiratory distress syndrome, glucose-to-lymphocyte ratio, intensive care unit, mortality, prognosis

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1 | INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a clinical syndrome characterized by refractory hypoxemia and acute diffuse inflammatory lung injury.^{1,2} Inflammation causes damage to endothelium and capillaries in the lungs.^{3,4} These events cause pulmonary edema, which can lead to fatal respiratory failure.⁵ Despite significant advances in early diagnosis and treatment, there is still no treatment that directly targets the pathologic mechanisms of ARDS.⁶ Mechanical ventilation and supportive therapy are the mainstay treatment options for ARDS.^{6,7} Timely treatment of ARDS can deeply improve outcomes and reduce the fatality rate.⁸ Therefore, risk stratification and reliable prognostic biomarkers are crucial for categorizing patients to help doctors make the best therapeutic management.

Many studies have shown that ligands such as interleukin (IL-1 β), IL-6, and TNF α are related with the prognosis of patients with ARDS.⁹⁻¹¹ However, these parameters are not part of routine tests in hospital laboratories and cannot be detected immediately, thus making the disease risk stratification relatively difficult. Therefore, there is need for novel, simple forecasting, and comprehensive evaluation systems in the management of the diseases. Previous clinical and animal studies have shown that activation of multiple inflammatory cells and release of inflammatory mediators are associated with progression and prognosis of ARDS. In addition, the red blood cells distribution width (RDW),^{12,13} neutrophil to lymphocyte ratio (NLR),¹⁴⁻¹⁶ and platelet to lymphocyte ratio (PLR),¹⁷ which are systemic inflammatory biomarkers were associated with poor prognosis of the ARDS.

Lymphocytes are one of the components of systemic inflammatory response and have been implicated in the development of ARDS disease.¹⁸ Lymphocytes have a profound role in immune surveillance. On the other hand, glucose levels have been shown to be associated with prognosis in patients with ARDS.¹⁹ However, there are no biomarkers that combine glucose and lymphocyte counts to predict prognosis in critically ill patients with ARDS. In this study, we analyzed the association between glucose-to-lymphocyte ratio (GLR) and in-hospital mortality.

2 | METHODS

2.1 | Data sources

We obtained data for this study from Medical Information Mart for Intensive Care-IV (MIMIC-IV Version 1.0) database.^{20,21} The MIMIC-IV database is an open and freely available database developed by Massachusetts Institute of Technology (MIT) computational Physiology Laboratory. The database records clinical data of patients admitted to the ICU at Beth Israel Deacon Medical Center from 2008 to 2019. The record includes basic information, vital signs, supplementary tests, medication status, and diagnosis. There was requirement for informed consent from the patients because the current study evaluated data from a clinical database.

2.2 | Selection criteria

Out of more than 50,000 different patients in the database, we included patients aged ≥ 16 years and those with ARDS as prescribed by the Berlin definition²²: (1) acute onset; (2) arterial partial pressure of oxygen (PaO₂)/fraction of inspired oxygen (FiO₂) < 300 mmHg; (3) positive end-expiratory pressure (PEEP) ≥ 5 cm H₂O; and (4) absence of heart failure. Patients younger than 16 years of age, those lacking fasting glucose and lymphocyte count data on the first day of admission to ICU and those with 20% of missing data were excluded from this study.

2.3 | Data collection and extraction

Baseline parameters of patients in ICU such as age, gender, and race were collected. The patients had complications such as congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), pneumonia, renal failure, liver disease, and atrial fibrillation (AF). Laboratory parameters included white blood cell count, serum creatinine, serum urea nitrogen, serum chloride, serum sodium, and anion gap in the first 24 h after admission. In addition, sequential organ failure assessment (SOFA) and acute physiology score III (APSOIII) data were also included. The GLR was defined as fasting glucose/lymphocyte count²³ and the patient in-hospital mortality was defined as the outcome.

2.4 | Statistical analysis

Navicat Premium 15.0 software was used for data extraction, and analysis of statistical data was conducted with the R software (Version 4.01). The normally distributed measurement data are presented as $X \pm S$, whereas the comparison among various groups was performed by means of an independent sample *t*-test. Subsequently, the count data were presented as *N* (%) while the χ^2 test was employed for the purpose of performing comparisons. The most significant parameters for predicting in-hospital mortality were identified with the aid of univariate and multivariate logistic regression models. All probability values are double-sided and statistical significance was established as $p < 0.05$. The predictive power of SOFA + GLR was compared with SOFA by receiver operating characteristic (ROC) curve analysis. Comparison of the AUCs between different models was estimated using DeLong's test.

3 | RESULTS

3.1 | Characteristics of patients

A total of 1,085 patients with ARDS were included in this study. The eligible participants included 498 females and 587 males, with a mean age of 64.2 ± 17.5 years and a mean GLR of $211.7 \pm 262.1 \times 10^{-9}$.

TABLE 1 Baseline characteristics of patients with ARDS between GLR groups

Characteristics	GLR		p-Value
	<193.7*10 ⁻⁹	≥193.7*10 ⁻⁹	
N	542	543	
Clinical parameters			
Age, years	63.1 ± 18.2	65.3 ± 16.8	0.042
Sex, n (%)			0.213
Female	259 (47.8)	239 (44.0)	
Male	283 (52.2)	304 (56.0)	
Ethnicity, n (%)			0.017
White	308 (56.8)	322 (59.3)	
Black	59 (10.9)	33 (6.1)	
Other	175 (32.3)	188 (34.6)	
Vital signs			
SBP, mmHg	116.3 ± 16.1	115.0 ± 15.9	0.159
DBP, mmHg	62.3 ± 10.8	62.0 ± 10.9	0.671
MAP, mmHg	77.4 ± 10.6	77.1 ± 10.6	0.571
Heart rate, beats/minute	86.9 ± 16.6	89.6 ± 16.5	0.008
Respiratory rate, times/minute	20.3 ± 4.5	21.0 ± 4.5	0.011
Temperature, °C	36.9 ± 0.7	36.9 ± 0.8	0.657
SpO ₂ , %	96.9 ± 3.4	96.8 ± 3.1	0.646
Comorbidities			
Chronic heart failure	121 (22.3)	119 (21.9)	0.871
Renal failure	103 (19.0)	84 (15.5)	0.123
Liver disease	39 (7.2)	39 (7.2)	0.993
AF	156 (28.8)	170 (31.3)	0.364
COPD	60 (11.1)	74 (13.6)	0.200
Pneumonia	170 (31.4)	202 (37.2)	0.043
Laboratory parameters			
White blood cell, 10 ⁹ /L	11.9 ± 9.0	16.1 ± 7.6	<0.001
Blood glucose, mg/dl	128.9 ± 49.3	187.0 ± 97.6	<0.001
Lymphocyte, 10 ⁹ /L	2.2 ± 6.1	0.6 ± 0.4	<0.001
Serum creatinine, mg/dl	1.3 ± 1.1	1.6 ± 1.5	0.001
Serum urea nitrogen, mg/dl	23.4 ± 18.1	29.3 ± 26.4	<0.001
Serum chloride, mg/dl	104.4 ± 6.5	102.5 ± 6.6	<0.001
Serum sodium, mg/dl	139.0 ± 4.8	138.0 ± 5.4	0.001
Anion gap, mg/dl	15.8 ± 5.2	17.7 ± 6.0	<0.001
Scoring systems			
APSOIII	56.8 ± 28.8	64.0 ± 30.6	<0.001
SOFA	7.0 ± 4.4	7.7 ± 4.7	0.013
Mortality	121 (22.3)	189 (34.8)	<0.001

Abbreviations: AF, atrial fibrillation; APSIII, acute physiology score III; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; GLR the ratio of blood glucose to lymphocyte count; MAP, mean arterial pressure; SBP, systolic blood pressure; SOFA, sequential organ failure assessment.

We analyzed the baseline characteristics of the patients as shown in Table 1. The data showed that patients with higher GLR ($\geq 193.7 \times 10^{-9}$) were older, had faster heart rate, higher SOFA, and APSIII scores as well as higher rate of pneumonia ($p < 0.05$), compared to those with

lower GLR group. Moreover, the patients had higher WBC, serum creatinine, serum urea nitrogen, blood glucose and anion gap, and lower chloride, and serum sodium ($p < 0.05$). In addition, the all-cause mortality rate was higher in the higher GLR group ($p < 0.001$).

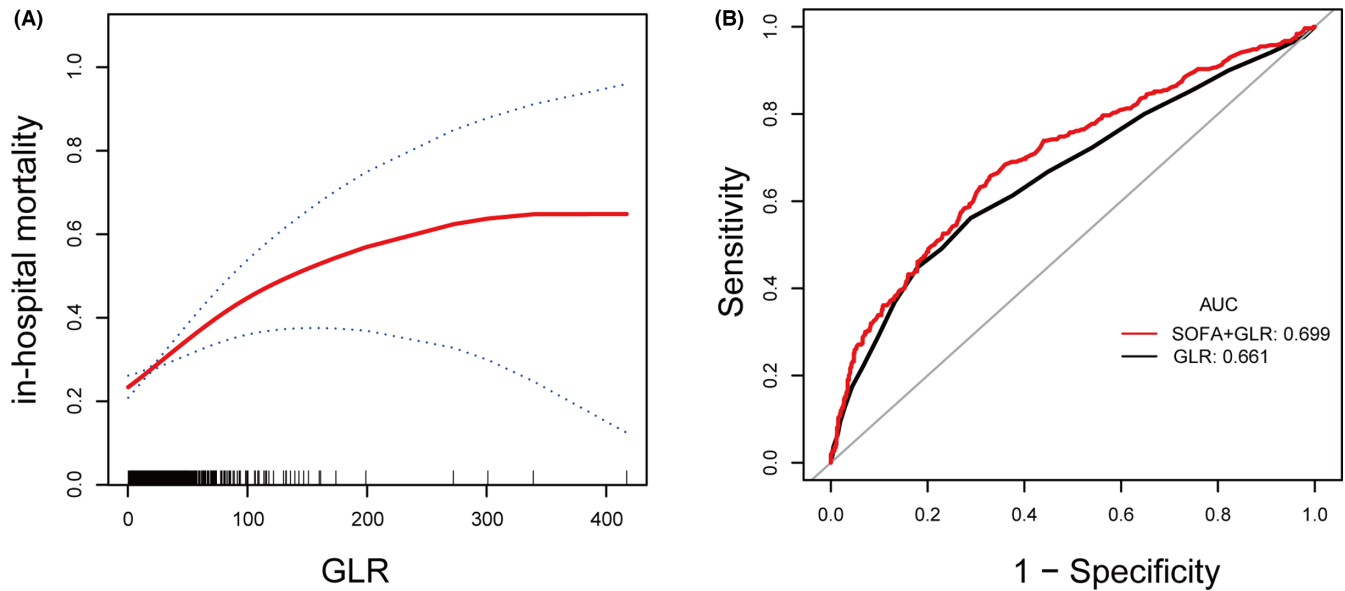


FIGURE 1 (A) The relationship between GLR and the mortality of ARDS; (B) Receiver operator characteristic curve analysis for mortality of patients with ARDS. ARDS, acute respiratory distress syndrome; AUC, area under the curve; GLR: glucose-to-lymphocyte ratio

TABLE 2 OR (95% CIs) for all-cause mortality across groups of GLR level

GLR(*10 ⁻⁹)	Model 1 ^a		Model 2 ^b		Model 3 ^c	
	OR (95% CIs)	p Value	OR (95% CIs)	p Value	OR (95% CIs)	p Value
Continuous variable	1.01 (1.00, 1.01)	0.0003	1.01 (1.00, 1.01)	0.0003	1.01 (1.00, 1.01)	0.0020
Dichotomized groups						
<193.7	1.0		1.0		1.0	
≥193.7	1.86 (1.42, 2.43)	<0.0001	1.81 (1.38, 2.39)	<0.0001	1.67 (1.26, 2.22)	0.0004
Tertile groups						
<90.9	1.0		1.0		1.0	
90.9–190.6	1.23 (0.88, 1.73)	0.2224	1.21 (0.85, 1.71)	0.2847	1.20 (0.84, 1.71)	0.3133
>190.6	1.81 (1.31, 2.51)	0.0004	1.75 (1.25, 2.45)	0.0011	1.60 (1.13, 2.26)	0.0082

Notes: Models 1, 2, and 3 were derived from logistic regression models.

Abbreviations: CI, confidence interval; GLR, the ratio of blood glucose to lymphocyte count; OR, odds ratio.

^aModel 1 covariates were adjusted for nothing.

^bModel 2 covariates were adjusted for age, sex, and race.

^cModel 3 covariates were adjusted for age, sex, anion gap, white blood cell count, congestive heart failure, SOFA, SBP, DBP, and respiratory rate.

3.2 | Association between GLR and in-hospital mortality

To demonstrate linearity of GLR and in-hospital mortality of patients with ARDS, we performed smooth curve fitting and evaluated linear relationships (Figure 1A).

We constructed different models after adjusting for possible covariates to assess independent impact of GLR on patients with ARDS. We determined the relationship between GLR (Continuous variable,

dichotomized groups, and tertile groups) and in-hospital mortality as shown in Table 2. Model 1 shows that there was significant association between higher GLR ($\geq 193.7 \times 10^{-9}$) and high all-cause mortality (compared to the first dichotomized groups, $< 193.7 \times 10^{-9}$) (OR = 1.86, 95% CI: 1.42–2.43, $p < 0.0001$). In model 3, higher GLR ($\geq 193.7 \times 10^{-9}$) was still an independent predictor of all-cause mortality in patients with ARDS (OR = 1.67, 95% CI: 1.26–2.22, $p = 0.02509$), after adjusting for age, sex, anion gap, white blood cell count, congestive heart failure, SOFA, SBP, DBP, and respiratory rate. A similar relationship was also observed in tertile groups.

TABLE 3 Subgroup analysis of the associations between all-cause mortality and the GLR

	N	GLR		p Value
		<193.7*10 ⁻⁹	≥193.7*10 ⁻⁹	
Clinical parameters				
Age, years				0.9441
≤58	1127	1	1.72 (1.03, 2.87)	
58–73	1125	1	1.93 (1.20, 3.10)	
≥73	1129	1	1.88 (1.22, 2.90)	
Sex				0.2224
Female	498	1	1.56 (1.06, 2.31)	
Male	587	1	2.18 (1.50, 3.17)	
Ethnicity, n (%)				0.1145
White	630	1	1.63 (1.12, 2.36)	
Black	92	1	0.60 (0.21, 1.71)	
Other	363	1	2.19 (1.20, 4.00)	
Vital signs				
Heart rate, beats/min				0.9254
≤79	360	1	1.96 (1.21, 3.17)	
79–94	359	1	1.71 (1.05, 2.79)	
≥94	360	1	1.85 (1.19, 2.88)	
SBP, mmHg				0.8215
≤107	358	1	1.81 (1.15, 2.83)	
107 – 119	358	1	2.15 (1.29, 3.56)	
≥119	359	1	1.75 (1.10, 2.76)	
DBP, mmHg				0.1170
≤56	358	1	2.21 (1.41, 3.46)	
56 – 65	358	1	1.62 (1.24, 1.99)	
≥65	359	1	2.34 (1.46, 3.75)	
MAP, mmHg				0.7070
≤71	360	1	1.64 (1.05, 2.57)	
72 – 80	358	1	1.84 (1.13, 2.97)	
≥80	361	1	2.16 (1.35, 3.46)	
Respiratory rate, bate/min				0.1370
≤18	359	1	2.09 (1.25, 3.50)	
18 – 21	359	1	2.34 (1.44, 3.78)	
≥21	359	1	1.97 (1.62, 2.45)	
SPO2,%				0.3195
≤96.3	360	1	1.58 (1.02, 2.45)	
96.3– 98.4	359	1	2.54 (1.54, 4.19)	
≥98.4	360	1	1.65 (1.03, 2.65)	
Comorbidities				
Chronic heart failure				0.5409
NO	845	1	1.56 (1.12, 2.16)	
Yes	240	1	2.19 (1.20, 4.00)	
Renal failure				0.2630
NO	898	1	1.75 (1.30, 2.35)	
Yes	187	1	2.59 (1.38, 4.86)	

(Continues)

TABLE 3 (Continued)

	N	GLR		p Value
		<193.7*10 ⁻⁹	≥193.7*10 ⁻⁹	
Liver disease				0.2256
NO	1007	1	1.98 (1.49, 2.63)	
Yes	78	1	1.11 (0.46, 2.70)	
AF				0.0753
NO	759	1	1.56 (1.12, 2.16)	
Yes	326	1	2.63 (1.63, 4.25)	
COPD				0.5553
NO	951	1	1.83 (1.38, 2.43)	
Yes	134	1	2.40 (1.01, 5.70)	
Pneumonia				0.9935
NO	713	1	1.88 (1.35, 2.60)	
Yes	372	1	1.87 (1.17, 3.01)	

Notes: ORs (95% CIs) were derived from logistic regression models. Covariates were adjusted as in model a (Table 2).

TABLE 4 Receiver operating curve for in-hospital mortality

	AUC	95% CI	p
SOFA	0.6613	0.6238–0.6988	
SOFA + PNI	0.6991	0.6634–0.7348	<0.001

Abbreviation: AUC, area under the curve.

3.3 | Subgroup analyses

We performed subgroup analyses as shown in Table 3. The common diseases associated with patients with ARDS were analyzed in the subgroup analysis, and the results showed no significant interaction.

3.4 | ROC curve analysis

The in-hospital mortality was analyzed with ROC curves to compare the value between SOFA + GLR, and SOFA (Figure 1B, Table 4) The area under the curve (AUC) was 0.6991 for the SOFA + GLR (95% CI: 0.6634–0.7348), which was significantly high than the AUC of (0.6613, 95% CI: 0.6238–0.6988) ($p < 0.0001$).

4 | DISCUSSION

Our data showed that GLP was significantly higher in patients who succumbed to ARDS than those who survived. Thus, GLP was an independent risk factor for in-hospital mortality. Furthermore, we compared SOFA + GLR and GLR, and showed that GLR was a predictor of death in ARDS patients.

Lungs are one of the most important organs in the human body.²⁴ They play several physiological functions, and thus their dysfunction directly affects the health of humans. Acute respiratory distress

syndrome is characterized by alveolar epithelial cell injury, increased permeability of pulmonary capillaries and increased exudate in alveolar cavity as well as interstitial lung, which is often accompanied by alveolar hemorrhage.²⁵

Acute respiratory distress syndrome is a complex clinical condition with limited therapeutic approaches and a high mortality rate in severely sick patients requiring invasive mechanical ventilation. In earlier human and animal research, it has been demonstrated that the stimulation of poly inflammatory cells, as well as the secretion of inflammatory mediators, have a function in the occurrence and progression of ARDS. Uncertainty exists, nevertheless, regarding the correlation between unfavorable prognosis and elevated GLP levels. Our study showed that GLR independently acted as a prognostic indicator for critically ill ARDS patients.

Recent studies have shown the feasibility of combining inflammatory indicators such as lymphocytes and blood glucose levels to predict the prognosis of some diseases.^{26,27} GLR is an independent prognostic factor in patients with pancreatic duct adenocarcinoma undergoing radical resection. Another study showed that GLR was a prognostic indicator in patients with gallbladder cancer.²⁷

Acute respiratory distress syndrome is a heterogeneous clinical disease with limited treatment options,²⁸ which often exhibit fatal outcomes in critically ill patients receiving invasive mechanical ventilation. Previous clinical and animal studies showed that activation of poly inflammatory cells and release of inflammatory mediators contribute to the development and progression of ARDS. However, data on the relationship between poor prognosis and higher GLP levels remain scant. Our study showed that GLR is an independent prognostic indicator for the critically ill patients with ARDS.

It has been demonstrated that metabolic abnormalities are positively correlated with the severity and prognosis of patients with ARDS. Furthermore, elevated blood glucose level is an independent risk factor for predicting the prognosis of ARDS patients.^{29,30} Moreover, hyperglycemia at admission is positively associated with poor outcomes

of patients in ICU.³¹ On the other hand, lymphocytes are indicators of immunity and their suppression shows a damaged immune system. With related systemic complications caused by disturbance of the immune system, activation in the initial seepage stages of lung injury, innate immune cells such as single cells and neutrophils are recruited to alveolar airspace. This recruitment causes vascular endothelial boundaries and albino epithelium as well as increased permeability of edema fluid, protein accumulation in alveoli, and interstitial in lung injury. Macrophages in the alveoli secrete inflammatory cytokines that help recruit circulating single cells and neutrophils into the lungs, which leads to persistent inflammation and tissue damage. Therefore, lymphocytes protect endothelial cells, thus reducing inflammation.

Although we highlight important findings, this was a single-center retrospective study with a small sample size. Therefore, there was potential of selection bias, which would make it difficult to generalize the results to all patients with ARDS. Secondly, the study was limited by lack of clinical information. Therefore, there is need to validate our findings in multicenter studies. Third, our study did not consider nonlinearity for the relationship between confounding factors and outcome. Clearly, ensemble modeling will be required to fully address these questions.³²

CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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