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ORIGINAL RESEARCH

Association of Lymphocyte to Monocyte Ratio and Risk of in-Hospital Mortality in Patients with Cardiogenic Shock: A Propensity Score Matching Study

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Background: Lymphocyte to monocyte ratio (LMR) has been long implicated in the prediction of many inflammatory-related diseases. However, the possible value as prognostic marker of LMR have not been evaluated in cardiogenic shock (CS) patients. The aim of the study was to assess the relationship between LMR on admission and in-hospital mortality in CS patients.

Methods: Data on patients diagnosed with CS were extracted from the Medical Information Mart for Intensive Care-IV (MIMIC-IV) database. We performed a single-institution, retrospective study of 1487 CS patients and determined the optimal cut-off for LMR by X-tile software. Propensity score matching (PSM) and inverse probabilities of treatment weighting (IPTW) were conducted to control confounders. Cox proportional hazards model was performed to evaluate the relationship between LMR and in-hospital mortality. Kaplan–Meier curves and receiver operating characteristics (ROC) analysis were applied to assess the prognostic value of LMR.

Results: The optimal cut-off value for LMR was 0.9. Cox proportional hazards model demonstrated that lower LMR (< 0.9) was independently associated with in-hospital mortality with hazard ratio (HR) of 1.40 (1.12–1.74, $P = 0.003$). The results were consistent with survival analyses ($P < 0.001$, Log rank test). Adding LMR< 0.9 to the sequential organ failure assessment (SOFA) score improved discrimination and risk stratification for in-hospital mortality.

Conclusion: Lower level of LMR is related to higher risk of in-hospital mortality of patients with CS. As an easily available biomarker, LMR can independently predict the in-hospital mortality in CS patients.

Keywords: lymphocyte to monocyte ratio, cardiogenic shock, mortality, LMR, CS

Introduction

Cardiogenic shock (CS) is a emergency state which determined by severe systemic hypoperfusion,[1,2] CS is reported to occur in about 5–10% patients with coronary heart diseases (CHD).[3,4] It is estimated that the incidence of CS is 40,000–50,000 cases per year in the United States and 60,000–70,000 cases in Europe.[5,6] Currently, the mortality rates of CS still remain unacceptably high exceeding 50%, which is the leading cause of in-hospital mortality despite significant advancements in aggressive guideline-directed medical therapy and early reperfusion therapy.[7,8] Hence, it is clinically significant to identify a novel biomarker to predict in-hospital mortality in CS patients with high accuracy.

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A series of studies reported that CS is not only a hypoperfusion problem but is rather a systemic inflammatory response within the context of multi-organ failure.[9–12] A systemic inflammatory status contributes to the high fatality rates in CS, especially in severe CS patients. Recently, an easily available and non-invasive biomarker based on platelet, neutrophils and lymphocytes counts, called systemic immune-inflammatory index (SII), has been proposed to predict short and long term mortality of CS patients.[13] Accumulating evidence indicates that a biomarker based on lymphocytes and monocyte counts which named as the lymphocyte to monocyte ratio (LMR), becoming as an innovate biomarker of inflammation.

LMR has long been introduced as an inflammatory marker in various clinical conditions, including liver cirrhosis, cerebral venous sinus thrombosis, colorectal cancer and peripheral arterial occlusive disease.[14–17] Moreover, LMR were also reported to be associated with adverse outcome in various cardiovascular diseases including myocardial infarction, heart failure and aortic dissection.[18–20] As mentioned above, a systemic inflammatory status contributes to poor prognosis in CS patients. So it is reasonable to believe that LMR is associated with CS prognosis and LMR maybe an independent prognosis predictor in patients with CS.

However, to our knowledge, whether LMR is associated with in-hospital mortality in CS patients remains unknown. Hence, this study aims to assess the predictive role of LMR on the in-hospital mortality in CS patients.

Methods

Data Source

All data were extracted from the Medical Information Mart for Intensive Care-IV (MIMIC-IV version 1.0) database, which is an updated version of MIMIC-III with pre-existing institutional review board approval, is freely available. A number of improvements have been made, including simplifying the structure, adding new data elements, and improving the usability of previous data elements. Currently, the MIMIC-IV contains comprehensive and high-quality data of patients admitted to intensive care units (ICUs) at the Beth Israel Deaconess Medical Center (BIDMC) between 2008 and 2019 (inclusive), developed by the computational physiology laboratory of Massachusetts Institute of Technology (MIT) and approved by the institutional review boards of MIT and Beth Israel Deaconess Medical Center (BIDMC).[21] The database contains desensitization data for more than 50,000 critically ill patients at BIDMC between 2008 and 2019, including demographics, vital signs, laboratory indicators and medications. After passing the "Protecting Human Research Participants" exam on the website of the National Institutes of Health (NIH), one author (Tianyang Hu) was approved to extract data from the database (Record ID: 37474354).

Cohort Selection

Patients diagnosed with CS were extracted. CS was defined on the grounds of the Ninth Revision of International Classification of Diseases (ICD-9) and was coded R57.001. CS was defined as systolic blood pressure to be 90 mmHg and signs of hypoperfusion (altered mental status/confusion, cold periphery, oliguria 2 mmol/L).[22]

Patients with one of the following conditions were excluded: 1) less than 16-year-old at first admission to ICU; 2) less than 24 hours of hospital stay; 3) more than 10% of personal data was missing; 4) patients with repeated ICU admissions; and 5) patients with systemic inflammatory disorders and recent received glucocorticosteroid therapies. A number of patients were excluded in our final cohort because they were missing lymphocyte and monocyte counts data at the first day of admission to the ICU.

Date Collection and Outcomes

Baseline characteristics of included patients were recorded within 24 hours on first admission to ICU, including demographics, vital signs, laboratory indicators, comorbidities and scoring systems. Demographics included age, gender, weight and ethnicity. Vital signs included temperature, heart rate, respiratory rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and saturation of percutaneous oxygen (SPO_2) . Laboratory indicators included anion gap, serum bicarbonate, lactate, serum sodium, serum potassium, serum calcium, blood urea nitrogen (BUN), serum creatinine (SCr), hematocrit, hemoglobin, white blood cell (WBC) count, prothrombin time (PT), activated partial thromboplastin time (APTT), international normalized ratio (INR), lymphocyte counts, monocyte counts, platelet counts. Comorbidities included hypertension, diabetes, coronary artery disease (CAD), congestive heart failure (CHF), pneumonia, chronic obstructive pulmonary disease (COPD), chronic liver disease, chronic renal disease, malignancy. Scoring systems included Sequential Organ

Failure Assessment score (SOFA), Simplified Acute Physiology Score II (SAPSII) and oxford acute severity of illness score (OASIS), acute physiology score III (APSIII). All the above scores were calculated with clinical information (Glasgow Coma Score, hypotension, oxygenation index, platelet, serum bilirubin, serum creatinine and so on) according to published recommendations.[23–26] The use of mechanical ventilation and renal replacement therapy were also extracted.

The primary outcome was in-hospital mortality.

Statistical Analysis

LMR was defined as lymphocyte-monocyte ratio counts. SII was defined as platelet*neutrophil/lymphocyte. Continuous data were expressed as mean ± standard deviation (SD). Categorical data were expressed as frequency (percentage). For variables that showed skewed distributions, descriptive statistics are presented as medians with interquartile ranges. Chi-square test or Fisher's test was appropiately performed to compare the differences between groups. The baseline characteristics were reported as original cohort, matched cohort and weighted cohort. The X-tile software was conducted to evaluate the optimal cut-off LMR, the cohort was divided into two groups based on the optimal cut-off LMR (the low-LMR group and high-LMR group).

To control confounding factors between the low-LMR group and high-LMR group, propensity score matching (PSM) was conducted. PSM model was performed to predict probability that an individual has a higher LMR value when given baseline characteristics. All the potential confounding covariates were included in the PSM model. Patients were matched with 1:1 using the nearest-neighbor algorithm with a calliper width of 0.2 was applied in the current study. After PSM, standardized mean differences (SMD) were used to evaluate the balance of characteristics between the two groups. A variable can be considered as an imbalance between groups when its SMD is greater than 0.1. To further reduce the imbalance between groups, an inverse probabilities of treatment weighting (IPTW) model was performed. This method showed a good balancing property and had been approved a preferred approach in PSM.[27] Moreover, we performed a sensitivity analysis to evaluate the robustness of our results. In the original cohort, matched cohort and weighted cohort, we evaluated LMR against in-hospital mortality by Cox proportional hazards models and results were shown as hazard ratio (HR) and 95% confidence interval (CI).

Kaplan-Meier curves were performed in the crude and PSM cohort to evaluate the survival of the low-LMR and high-LMR group. To assess whether LMR improves discrimination beyond sequential organ failure assessment (SOFA) score, the area under the curve (AUC) of the receiver operating characteristics (ROC) curves were calculated. The added value of LMR in the risk prediction model was assessed using the likelihood ratio test of nested models. Discrimination was also assessed by the integrated discrimination index (IDI). Improvement in clinical risk stratification was assessed by calculating net reclassification improvement (NRI). All analyses were performed in X-tile (version 3.6.1) and R software (version 4.1.0). $P < 0.05$ was considered statistically significant.

Results

Baseline Characteristics

A total of 1487 CS patients were included in our study. The flow chart of the included population was shown in Figure 1. The included patients had a mean (SD) age of 69.3 (14.6) years. Males accounted for 60.3% and the white accounted for 64.0% of the population. The included patients were divided into two groups according to the optimal cut-off value of LMR: 912 in the high-LMR group (≥ 0.9), and 575 in the low-LMR group (< 0.9). Before PSM, 15 of 37 covariates (age, weight, APSIII score, CAD, COPD, liver disease, WBC, hemoglobin, platelet, aniongap, bicarbonate, BUN, sodium, PT and INR) were imbalanced between high-LMR group and low-LMR group. Based on the estimated propensity scores, PSM and IPTW were applied to standardize the differences between the high-LMR group and low-LMR groups. As shown in Table 1 and Figure 2, the imbalance between the high-LMR group and low-LMR group was significantly reduced and all covariates were comparable between the two groups.

Association of LMR with Outcome

The results of the Cox proportional hazards regression were presented in Table 2. For in-hospital mortality, the HR (95% CI) value of low-LMR group was 1.40 (1.12–1.74) compared with the reference of high-LMR group ($P = 0.0003$). When adjusted for age, gender, weight, ethnicity in Model I, the adjusted HR (95% CI) value of low-LMR group was 1.37 (1.10–1.71). When adjusted for model 1 plus comorbidities in Model II, the adjusted

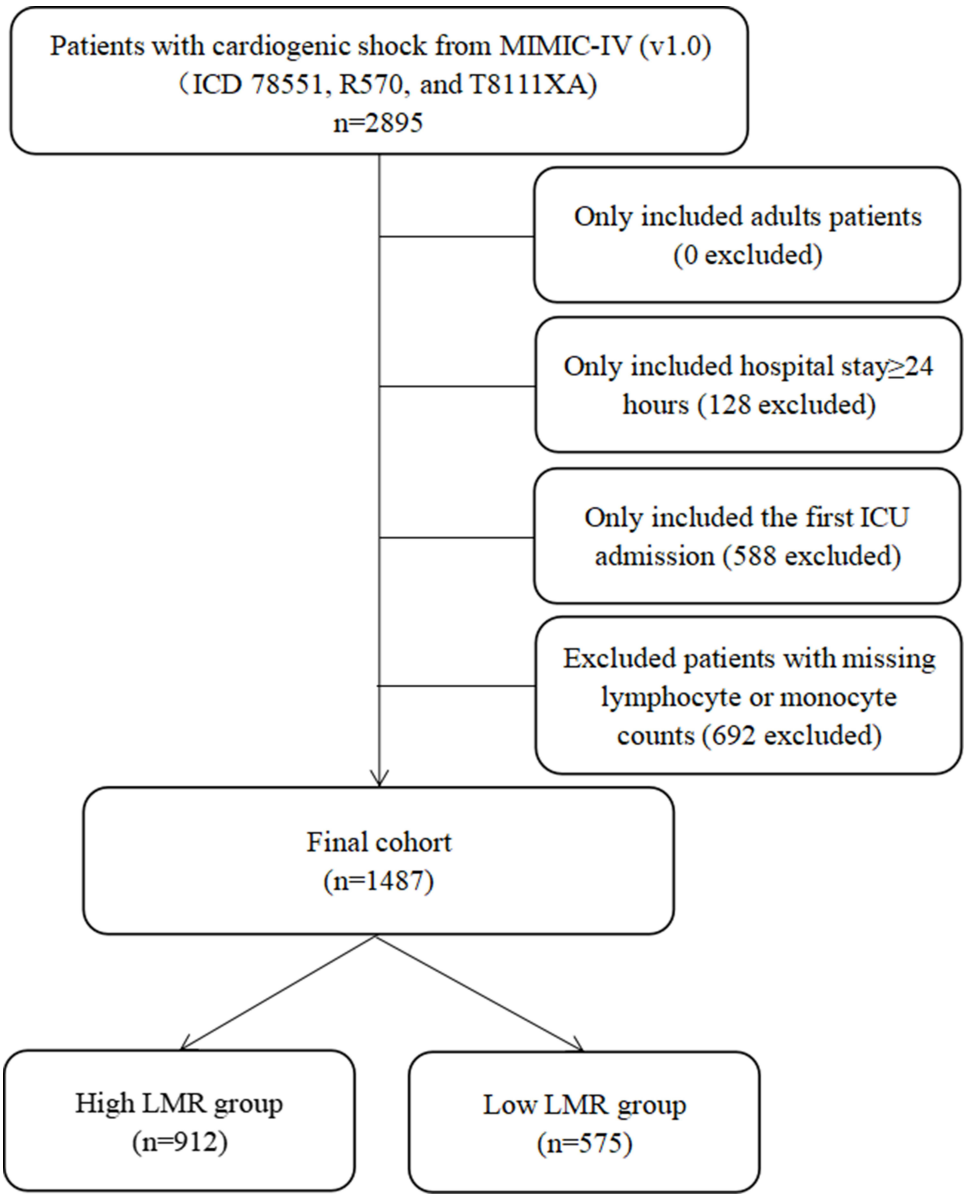

Figure 1 The flow chart of the included population.

HR value of low-LMR group was still statistically significant (HR: 1.33, 95% CI: 1.06–1.68, P = 0.015). When further adjusted for model 2 plus score system, interventions, vital signs and laboratory results, the adjusted HR value of low-LMR group was still statistically significant (HR: 1.38, 95% CI: 1.06–1.79, P = 0.018).

After PSM and IPTW, univariate Cox proportional hazard model was performed (Table 2). HR showed that the low-LMR group was associated with in-hospital mortality (HR: 1.20, 95% CI: 1.06–1.51, P = 0.024). For the sensitivity, univariate Cox proportional hazard models were performed in original and matched cohort to estimate the predicting value of LMR for in-hospital mortality. We also adjusted potential confounders in these three models. All results showed a similar tendency ($P < 0.05$) (Table 2).

Kaplan–Meier survival curves were performed to compared the prognosis between low-LMR and high-LMR groups by Log rank test. The data showed that the low-LMR group had a poor prognosis in crude cohort (HR: 1.40, 95% CI: 1.12–1.74, P = 0.003, Figure 2A). After PSM, low-LMR group had a similar poor prognosis in crude cohort (HR: 1.31, 95% CI: 1.08–1.68, P = 0.016, Figure 2B) compared with high-LMR group.

Table 1 Comparisons of Baseline Characteristics Between the Original Cohort, Matched Cohort and Weighted Cohort

Covariate	Original Cohort			Matched Cohort			Weighted Cohort		
	High LMR	Low LMR	SMD	High LMR	Low LMR	SMD	High LMR	Low LMR	SMD
N	912	575	–	547	547	–	528.4	536.2	–
Age, years	68.5(14.6)	70.2(14.6)	0.122	69.8(14.3)	70.0(14.7)	0.023	69.8(14.5)	70.0(14.7)	0.013
Gender, male, n(%)	554(60.7)	343(59.7)	0.022	330(60.3)	327(59.8)	0.011	317.1(60.0)	320.8(59.8)	0.004
Weight (kg)	83.2(22.2)	80.7(21.7)	0.117	80.6(20.8)	80.7(21.8)	0.008	81.0(21.4)	81.0(21.9)	0.002
Ethnicity, n(%)									
White	569(62.4)	383(66.6)	0.093	368(67.3)	363(66.4)	0.029	351.1(66.4)	355.6(66.3)	0.006
Black	119(13.0)	71(12.3)		63(11.5)	68(12.4)		63.5(12.0)	65.5(12.2)	
Other	224(24.6)	121(21.0)		116(21.2)	116(21.2)		113.8(21.5)	115.1(21.5)	
Interventions, n(%)									
MV use	612(67.1)	366(63.7)	0.073	336(61.4)	352(64.4)	0.061	334.8(61.4)	342.0(63.8)	0.009
RRT use	129(14.1)	86(15.0)	0.023	80(14.6)	79(14.4)	0.005	73.2(13.9)	75.7(14.1)	0.008
Score Systerm									
SOFA	9.0(4.0)	8.9(4.1)	0.022	8.8(4.0)	8.9(4.1)	0.029	8.9(4.0)	8.9(4.1)	0.007
OASIS	38.0(9.9)	38.5(10.2)	0.048	38.3(9.9)	38.4(10.1)	0.010	38.4(9.9)	38.3(10.2)	0.001
APSIII	66.3(27.0)	69.8(28.6)	0.126	68.9(27.0)	69.1(28.4)	0.008	69.1(27.5)	68.9(28.2)	0.006
SAPSII	46.4(15.0)	47.4(15.8)	0.064	46.6(15.0)	47.1(15.5)	0.032	47.0(15.2)	47.1(15.6)	0.005
Comorbidities, n(%)									
Hypertension	362(39.7)	222(38.6)	0.022	195(35.6)	208(38.0)	0.049	198.6(37.6)	208.3(38.9)	0.026
Diabetes	333(36.5)	214(37.2)	0.015	203(37.1)	204(37.3)	0.004	193.2(36.6)	197.2(36.8)	0.004
CKD	351(38.5)	231(40.2)	0.035	231(42.2)	221(40.4)	0.037	212.8(40.3)	214.6(40.0)	0.005
CAD	591(68.5)	340(59.1)	0.117	328(60.0)	327(59.8)	0.004	320.4(60.6)	326.5(60.9)	0.006
CHF	721(79.1)	461(80.2)	0.028	443(81.0)	437(79.9)	0.028	420.2(79.5)	427.1(79.7)	0.003
COPD	248(27.2)	192(33.4)	0.135	176(32.2)	175(32.0)	0.004	164.6(31.1)	168.2(31.4)	0.005
Liver disease	109(12.0)	100(17.4)	0.154	82(15.0)	89(16.3)	0.035	82.6(15.6)	86.7(16.2)	0.015
Malignancy	75(8.2)	48(8.3)	0.005	50(9.1)	47(8.6)	0.019	47.5(9.0)	44.8(8.4)	0.022
Vital signs									
MAP, mmHg	105.7(33.0)	103.5(31.8)	0.069	103.1(27.6)	103.5(32.4)	0.013	103.9(28.5)	103.9(32.3)	0.001
Heart rate, bpm	89.6(18.0)	88.7(18.4)	0.053	89.3(18.1)	88.6(18.4)	0.037	89.0(18.4)	88.9(18.4)	0.007
RR, bpm	29.9(6.9)	29.5(6.3)	0.070	29.7(6.4)	29.5(6.3)	0.033	29.6(6.5)	29.5(6.3)	0.009
Temperature, °C	36.1(1.0)	36.0(1.0)	0.053	36.1(1.0)	36.1(1.0)	0.021	36.1(1.0)	36.1(1.0)	0.007
SpO2, %	99.5(1.4)	99.5(1.4)	0.006	99.5(1.5)	99.5(1.4)	0.001	99.6(1.4)	99.5(1.4)	0.012
Laboratory Results									
WBC, × 109/L	15.0(11.0, 19.5)	15.8(11.0,21.3)	0.122	14.9(11.1, 19.6)	14.3(10.2, 20.0)	0.035	15.4(12.0, 20.1)	15.6(11.2, 21.1)	0.010
HGB, g/dL	9.9(2.4)	10.3(2.4)	0.180	10.3(2.4)	10.3(2.4)	0.025	10.3(2.4)	10.3(2.4)	0.008
PLT, × 109/L	171(92.7)	190.4(98.4)	0.203	187.5(94.3)	188.4(98.6)	0.010	188.5(99.4)	187.6(95.8)	0.010
Bilirubin, mmol/L	1.1(1.5)	1.1(1.4)	0.037	1.1(1.3)	1.1(1.5)	0.011	1.1(1.4)	1.1(1.4)	0.007
Aniongap, mEq/L	14.7(3.8)	15.1(4.6)	0.106	15.1(3.9)	15.1(4.6)	<0.001	15.1(3.8)	15.0(4.5)	0.011
Bicarbonate, mEq/L	23.2(4.4)	23.7(4.9)	0.122	23.7(4.7)	23.6(4.8)	0.015	23.6(4.7)	23.6(4.8)	0.003
BUN, mg/dL	30.0(19.0, 48.0)	27.0(18.0, 29.0)	0.114	30.0(19.0, 47.0)	29.0(20.0, 49.0)	0.010	33.0(21.0, 48.0)	34.0(22.0, 49.0)	0.018
Creatinine, mg/dL	1.7(1.3)	1.9(1.4)	0.099	1.9(1.4)	1.9(1.4)	0.016	1.9(1.5)	1.9(1.4)	0.013
Potassium, mmol/L	4.0(0.6)	3.9(0.7)	0.036	4.0(0.6)	3.9(0.7)	0.017	4.0(0.6)	3.9(0.7)	0.011
Sodium, mmol/L	135.4(5.8)	134.7(5.5)	0.124	134.8(5.9)	134.8(5.4)	0.006	134.8(6.1)	134.8(5.4)	0.001
Calcium, mg/dL	8.1(0.9)	8.0(0.9)	0.070	8.0(0.9)	8.0(0.9)	0.008	8.0(0.9)	8.0(0.9)	0.004
PT, s	14.9(12.8, 20.3)	14.1(12.5, 18.1)	0.165	14.9(12.7, 19.9)	14.6(13.2, 19.9)	0.011	15.6(14.5, 22.3)	16.8(14.3, 23.1)	<0.001
APTT, s	35.5(16.2)	36.7(16.6)	0.072	36.2(16.9)	36.5(16.2)	0.018	36.7(17.6)	36.6(16.6)	0.006
INR	1.6(1.0)	1.8(1.0)	0.154	1.7(1.1)	1.7(1.0)	0.005	1.7(1.1)	1.7(1.0)	0.001

Note: For all continuous covariates, the mean values and standard deviations are reported.

Abbreviations: LMR, lymphocyte-to-monocyte ratio; SMD, standardized mean difference; MV, mechanical ventilation; RRT, renal replacement therapy; SOFA, sequential organ failure assessment; OASIS, oxford acute severity of illness score; APSIII, acute physiology score III; SAPS II, Simplified Acute Physiology Score II; CKD, chronic kidney disease; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; MAP, mean arterial pressure; RR, respiratory rate; WBC, white blood cell; HGB, hemoglobin; PLT, platelet; BUN, blood urea nitrogen; PT, prothrombin time; APTT, activated partial thromboplastin time; INR, international normalized ratio.

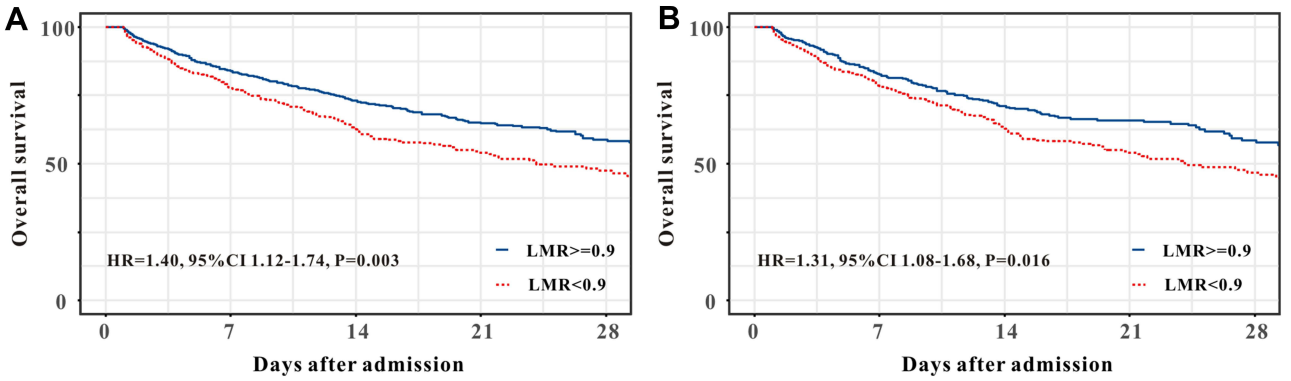

Figure 2 Overall survival of high-LMR and low-LMR groups. Kaplan–Meier curve (**A**) before and (**B**) after PSM.

Additional Analysis

We assessed model performance based on NRI, IDI, and AUC by adding LMR to a clinical model composed of age, gender, weight, ethnicity, comorbidities, interventions, vital signs and laboratory results, and combined biomarker and clinical model (Table 3). As shown in Table 3, adding LMR to these models improved the prediction of in-hospital mortality, as indicated by the significant increase in the AUC. Reclassification adding LMR also showed an IDI of 0.021 ($P = 0.02$) with significantly improvement in NRI (0.121, $P < 0.001$). Replacing LMR with the SOFA score showed a poor prognostic accuracy for in-hospital mortality (AUC:0.658). Reclassification adding SOFA score to the combined biomarker and clinical model did not show a significantly increase in AUC, IDI and NRI. Moreover, combining the LMR and the SOFA score to these models also showed a good prognostic accuracy for in-hospital mortality ($P = 0.001$). Combining the LMR and the SOFA score provided incremental discrimination of risk for in-hospital mortality as assessed by IDI ($P = 0.045$) and NRI ($P = 0.03$). We additionally evaluated the predictive ability for in-hospital mortality after PSM, results are similar as for the results before PSM, adding LMR or combining the LMR and the SOFA score to these models both showed good discrimination for in-hospital mortality as assessed by increased AUC, IDI and NRI (Table 3).

A previous study[13] reported that SII is associated with short- and long-term mortality in CS patients. So we tried to compared the predictive abilities between LMR and SII by using ROC analysis. As shown in Table 4, LMR exhibited better predictive ability than SII in predicting in-hospital mortality in CS patients before and after PSM (all $P < 0.05$).

Discussion

In the present study, we investigated whether LMR could be an independent predictor of in-hospital mortality in CS patients. The main findings are as follows: 1) Lower LMR on admission was significantly associated with an increased risk of in-hospital mortality in CS patients; 2) A LMR cut-off of 0.9 that provides excellent discriminative properties for early risk stratification in CS patients; 3) LMR is an independent predictor of in-hospital mortality in CS patient, overall survival was significantly lower in the LMR < 0.9 group compared with the LMR ≥ 0.9 group; and 4) LMR showed better predictive abilities than SII in predicting in-hospital mortality in CS patients.

Table 2 Summary of Results of Primary Outcome and Sensitivity Analysis

	Original Cohort		Matched Cohort		Weighted Cohort	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Unadjusted	1.40(1.12–1.74)	**0.003**	1.31(1.08–1.68)	**0.016**	1.20(1.06–1.51)	**0.024**
Model 1	1.37(1.10–1.71)	**0.006**	1.30(1.06–1.64)	**0.018**	1.20(1.05–1.52)	**0.032**
Model 2	1.33(1.06–1.68)	**0.015**	1.26(1.02–1.63)	**0.037**	1.22(1.04–1.55)	**0.038**
Model 3	1.38(1.06–1.79)	**0.018**	1.38(1.03–1.84)	**0.030**	1.31(1.01–1.72)	**0.045**

Notes: Model 1 adjusted for age, gender, weight, ethnicity. Model 2 adjusted for model 1 plus comorbidities. Model 3 adjusted for model 2 plus score system, interventions, vital signs and laboratory results. It would be better if significant p values were expressed in bold characters.

Table 3 NRI and IDI Analyses for Risk Reclassification of in Hospital Mortality in Original Cohort and Matched Cohort

Outcome	Sensibility (%)	Specificity (%)	AUC				IDI		NRI[a]	
			Biomaker	Biomaker +Clinical Model	Clinical Model[b]	P value[c]	Value (95% CI)	P value	Value (95% CI)	P value
Original Cohort										
LMR	65.0	67.3	0.706	0.795	0.751	<0.001	0.021(0.003–0.045)	**0.020**	0.121(0.014–0.214)	**<0.001**
SOFA	60.8	62.9	0.658	0.793		0.086	−0.002(−0.007–0.005)	0.515	−0.023(−0.124–0.062)	0.614
LMR+SOFA	60.6	72.0	0.710	0.798		0.001	0.018(0.001–0.045)	**0.045**	0.110(0.001–0.216)	**0.030**
Matched Icohort										
LMR	56.7	75.7	0.707	0.785	0.770	0.017	0.032(0.007–0.058)	**<0.001**	0.124(0.007–0.246)	**0.031**
SOFA	60.9	65.5	0.671	0.777		0.054	0.012(−0.002–0.035)	0.109	0.055(−0.060–0.176)	0.259
LMR+SOFA	63.3	69.4	0.714	0.799		0.013	0.032(0.010–0.057)	**0.011**	0.104(0.001–0.249)	**0.045**

Notes: [a]The NRI is calculated through two-way category by using the event rate of in hospital mortality, [b]The clinical model for predicting in hospital mortality are composed of age, gender, weight, ethnicity, comorbidities, interventions, vital signs and laboratory results, [c]Biomarker+clinical model versus clinical model. It would be better if significant p values were expressed in bold characters.

Abbreviations: AUC, area under the receiver-operating characteristic curve; IDI, integrated discrimination improvement; NRI, net reclassification index; LMR, lymphocyte-to-monocyte ratio, SOFA, sequential organ failure assessment.

CS is a severe state of systemic hypoperfusion, which is a fatal complication of cardiac diseases. Systemic impairment of cellular oxygenation, additional drivers of tissue malperfusion and cytotoxicity were reported to play important roles in the pathophysiological process of CS.[28,29] However, due to the complex, and incompletely understood the pathophysiological mechanisms of CS. Currently, the mortality rates of CS still remain unacceptably high (17–51%), which was the leading cause of in-hospital mortality.[28] Recently, several studies have ireported that systemic inflammation is closely related to poor outcome in CS patients. Increased plasma levels of CRP and inflammatory cytokines, primarily interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) were found in CS patients, the levels of these inflammatory cytokines were positively correlated with the severity of CS.[30–32] Cuinet et al studied 24 consecutive CS patients and found that CS induced elevated levels of IL-6, IL-10 and macrophage chemoattractant protein-1 (MCP-1) at the first day, correlating with shock severity, patients with the most severe shock had reduced lymphocytes and monocytes, showed an acute pro-inflammatory response of CS patients.[33] The IABP-SHOCK trial found that inflammatory cytokines IL-8, IL-10 and IL-7 were also significantly associated with mortality of CS patients.[34]

In recent years, some investigators studied the relationship between integrated inflammation indicators such as the neutrophil-to-lymphocyte ratio (NLR),[35] and the SII[13] with mortality in CS patients. However, until recently, there was no study reported the predictive effect of LMR in CS patients. LMR is an innovative biomarker reflects systemic inflammation which combined with lymphocyte and monocyte counts into a single index. Accumulating studies have demonstrated that LMR was a readily available and independent prognostic biomarker in predicting the poor prognosis of patients with various clinical conditions, including liver cirrhosis, cerebral venous sinus thrombosis, colorectal cancer and peripheral arterial occlusive disease.[14–17] Moreover, numerous investigators have detected the predictive effect of LMR in predicting the clinical outcomes in some inflammatory diseases. Cherfane et al explored the predictive value of LMR in ulcerative colitis (UC) and found that low LMR might be effective, readily available, and low-cost biomarkers to identify disease activity in UC patients.[36] The present study also demonstrated a predictive value of LMR on CS patients, which further verified that CS is a not only a severe state of systemic hypoperfusion, but also a systemic inflammatory state. We also compared the predictive abilities between LMR and SII by using ROC

Table 4 Compared the Predictive Effect of LMR with SII Inin Hospital Mortality in Original Cohort and Matched Cohort

	Sensibility (%)	Specificity (%)	AUC (95% CI)	P value
Original Cohort				**<0.001**
SII	56.5	61.6	0.612(0.587–0.637)	
LMR	65.0	67.3	0.706(0.684–0.731)	
Matched Cohort				**0.018**
SII	62.7	64.5	0.671(0.642–0.699)	
LMR	56.7	75.7	0.707(0.677–0.732)	

Note: It would be better if significant p values were expressed in bold characters.
Abbreviations: AUC, area under the receiver-operating characteristic curve; LMR, lymphocyte-to-monocyte ratio; SII, systemic immune-inflammatory index.

analysis. The results showed that LMR exhibited better predictive abilities than SII in predicting in-hospital mortality in CS patients before and after PSM, the SII seems exhibit worse predictive abilities in predicting in-hospital mortality in CS patients before [AUC: 0.612 (0.587–0.637)] and after PSM [AUC: 0.671 (0.642–0.699)]. Previous study[13] reported that SII is associated with short- and long-term mortality in CS patients. A possible reason for this difference is our study focused on in-hospital mortality (mean hospitalization stay: 13 days) in CS patients but Peng et al[13] focused on 30-day, 90-day and 365-day mortality SII seems showed better predictive abilities in predicting longer-term mortality in CS patients and the difference deserve further research.

Although we found that LMR is an independent predictor of in-hospital mortality in CS patient, the mechanisms to explain the association between a lower LMR and a higher in-hospital mortality in CS patients remains unclear. Lymphocytes are indicators of immunity and decrease lymphocytes counts demonstrates immunity injury,[37] evidence indicated that some subtypes of lymphocytes (regulatory T cells and Th2 cells) promote the secretion of anti-inflammatory cytokine IL-10 and inhibit the secretion of pro-inflammatory cytokine IL-6 and TNF-α.[38] Moreover, monocyte have a pivotal role in the systemic inflammatory response which can release pro-inflammatory cytokine IL-1β, IL-6 and TNF-α.[38] So low LMR may indicate the activation of the both immune system and systemic inflammatory response with increased release of plasma pro-inflammatory cytokine. And these pro-inflammatory cytokine were reported to play important role in hypoperfusion[39] and muti-organ failure.[40] Taken together, low LMR reflects the in-hospital mortality as well as the activation of the both immune system and systemic inflammatory response in patients with CS. The precise mechanism still needs to be clarified in the future.

There were several limitations to our study. First, this was a retrospective study based on a the MIMIC-IV database, the results of our study require further validation by prospective studies in the future. Second, although we had performed the PSM to control the confounding, there might exist some residual confounders that would not be measured in this study. Moveover, due to different drug may have different influence on lymphocyte count, monocyte count and LMR, these drug cocktails may have an effect on the accuracy of LMR as a in-hospital mortality predictor in CS patients, future prospective studies are needed to remove these confounders. Finally, although the sample size of this study was not small, future larger multicenter prospective studies are warranted to validate these findings.

Conclusions

The present study demonstrated that LMR is an independent predictor of in-hospital mortality in CS patient. As a simple and easily accessible prognostic biomarker, LMR provides excellent predictive ability for early risk stratification in CS patients.

Data Sharing Statement

The datasets used are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

The MIMIC-IV database was approved by the Massachusetts Institute of Technology (Cambridge, MA) and Beth Israel Deaconess Medical Center (Boston, MA), and consent was obtained for the original data collection. Therefore, the ethical approval statement and the need for informed consent were waived for this manuscript.

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Disclosure

The authors declare that they have no conflicts of interest.

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