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ORIGINAL RESEARCH

Predictive Value of Complete Blood Count Indicators for Short-Term Mortality in Patients with Combined Coronary Artery Disease and Chronic Kidney Disease

Shuoyan An, Wuqiang Che, Yanxiang Gao, Xiaoyan Duo, Xingliang Li, Jiahui Li

Department of Cardiology, China-Japan Friendship Hospital, Beijing, People's Republic of China

Correspondence: Jiahui Li, Department of Cardiology, China-Japan Friendship Hospital, 2 Yinghua Dongjie, Chaoyang District, Beijing, 100029, People's Republic of China, Tel +86 10 84206170, Email veighlee@163.com

Objective: Patients with chronic kidney disease (CKD) and coronary artery disease (CAD) had a poor prognosis. Indicators derived from complete blood count (CBC), like neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), monocyte-lymphocyte ratio (MLR), Systematic Inflammation Response Index (SIRI), systemic immune-inflammation index (SII) and Pan-Immune-Inflammation Value (PIV) had prognostic significance. But which one performed best in patients with CKD and CAD was still unclear.

Methods: CKD Patients with CAD admitted to ICU were retrospectively included. Patients with sepsis, connective tissue disease, tumor and receiving glucocorticoids were excluded. The primary endpoints encompassed in-hospital mortality and 30-day mortality.

Results: The study comprised 694 participants, with 60 patients died during hospitalization, and another 15 died in 30-day follow-up period. Both the admission level and maximal level of CBC-derived indicators were higher in the deceased group. ROC curve analysis demonstrated that maximal NLR had the highest AUCs - 0.795 for in-hospital mortality and 0.754 for 30-day mortality prediction. Furthermore, Net Reclassification Improvement (NRI) and Integrated Discrimination Improvement (IDI) analyses further confirmed that adding maximal NLR to the base model, which included traditional risk factors, significantly improved both NRI and IDI ($p < 0.05$ for both).

Conclusion: The maximum of NLR was with the best predictive value for in-hospital mortality and 30-day mortality in ICU patients with CAD and CKD. Predicting prognosis based on dynamic changes of NLR is more worthy of attention.

Keywords: neutrophil-to-lymphocyte ratio, chronic kidney disease, CKD, coronary artery disease, CAD, mortality, systematic inflammation response index, SIRI

Introduction

Despite significant therapeutic advances, coronary artery disease (CAD) and chronic kidney disease (CKD) still prevail as two major global health problems. Sterile inflammation, triggered by activation of the innate immune system, plays a vital role in the initiation, progression and prognosis of both CAD[1–4] and CKD.[5–7] Chronic inflammation and CKD not only increase the risk of CAD but also serve as key clinical factors in CAD risk assessment.[8] Also, a large proportion of CKD deaths are attributed to cardiovascular mortality. Endogenous and exogenous mediators such as modified lipoproteins, gut microbiome alterations, factors associated with premature ageing, oxidative stress, renin–angiotensin system and disturbances in the calcium–phosphate metabolism induce inflammation, contributing to the progression of CKD and its cardiovascular complications.[5] Given the increasing prevalence of CKD and the growing recognition of anti-inflammatory therapy as a crucial therapeutic strategy, evaluating the inflammatory status is crucial for prognostic assessment in patients with CAD and CKD.

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Complete blood count (CBC) is a low-cost and rapidly available test which can promptly provide a preliminary assessment of the systemic immune-inflammatory status and stress. In addition to commonly used clinical inflammatory biomarkers interleukin (IL)-6, tumor necrosis factor (TNF)-α, high-sensitivity C-reactive protein (hsCRP), and IL-1β, composite indices derived from complete blood count (CBC), such as neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), monocyte-lymphocyte ratio (MLR), Systemic Inflammation Response Index (SIRI), systemic immune-inflammation index (SII), and Pan-Immune-Inflammation Value (PIV), have emerged as new potential proinflammatory predictive or prognostic biomarkers. These indices reflect systemic inflammation and have been demonstrated to correlate with elevated mortality rates and unfavorable prognosis in CAD and CKD.[9–11] However, most prior studies have focused on either CAD or CKD populations separately, while their role in patients with coexisting CAD and CKD remains uninvestigated. Furthermore, existing research has predominantly assessed these markers at a single time point (eg, admission values), without considering their dynamic changes during hospitalization, which may better reflect disease severity and systemic inflammatory responses. To address these gaps, our study systematically evaluates multiple CBC-derived inflammatory markers in patients with both CAD and CKD, comparing both admission and maximal values to determine their predictive value for short-term mortality.

Methods

Data Acquisition

The current study utilized data extracted from the publicly available Medical Information Mart for Intensive Care IV (MIMIC-IV) database,[12] which was compiled by the Massachusetts Institute of Technology (MIT) from Beth Israel Deaconess Medical Center (Boston, Massachusetts).[12] Each admission was packaged in the database with the following information: demographics characteristics, diagnosis of International Classification of Diseases (ICD), vital signs, laboratory tests, treatment and follow-up results. One author (ASY, certification number: 39674606) got certification of this database and collected variables needed in the study.

Study Cohort and Definition

All individuals diagnosed with both CKD and CAD without missing data in neutrophil, monocyte, lymphocyte, platelet and leukocyte were included in the study. Exclusion criteria: younger than 18 years of age, with missing data exceeding 30%, sepsis, connective tissue disease, tumor and receiving glucocorticoids. Data from the first admission were exclusively included for patients with multiple hospitalizations. Demographic information, comorbidities, laboratory results, vital signs, Sequential Organ Failure Assessment (SOFA) scores at admission, In-hospital and 30-day mortality information were retrieved from the MIMIC-IV database utilizing pgAdmin PostgreSQL tools (version 1.22.1). Moreover, data on commonly prescribed medications used for secondary prevention of CAD were also collected, including aspirin, statin, and beta-blocker. NLR was determined by dividing the number of neutrophils by the number of lymphocytes. MLR was determined by monocyte counts/lymphocyte counts. PLR was computed as platelet counts / lymphocyte counts. SII obtained by multiplying NLR with platelet count. SIRI was computed as NLR * monocyte counts. PIV was derived by SIRI* platelet counts. For the above-mentioned inflammatory markers, both the admission and the maximal values during hospitalization were collected.

Statistical Analysis

Categorical variables were presented as frequencies and percentages and analyzed using Fisher's exact test (or Chi-square tests). Continuous variables were reported as median with interquartile ranges and assessed using the Wilcoxon rank sum test. Receiver operating characteristic (ROC) curves and areas under the ROC curves (AUC) were employed to evaluate the overall discriminative performance of these inflammatory factors. Differences between AUC values were statistically evaluated using DeLong's test, a non-parametric approach for comparing correlated ROC curves. The indicator with the highest predictive value was further assessed for incremental predictive value using Net Reclassification Improvement (NRI) and Integrated Discrimination Improvement (IDI) analyses. The base model included traditional risk factors and new model was constructed by adding the top-performing inflammatory indicators

to the base model. NRI and IDI were calculated to assess the improvement in risk stratification and discrimination. Additionally, logistic and cox regression analysis were conducted to determine the independence association of the indicator with prognosis. Demographics characteristics, laboratory result, vital signs and treatment were included as variables in the multivariate analysis. The optimal cutoff point obtained from the ROC curve were used to group the study subjects and analyze their prognosis. Kaplan-Meier curves were utilized to exhibit the difference in short-term clinical outcomes between different groups. Statistical analyses were carried out using R (version 4.1.3, Austria). A significance level of $p < 0.05$ (two-tailed) was adopted for all tests.

Results

Baseline Characteristics

Following the specified inclusion and exclusion criteria, the study included a total of 694 participants. Flowchart of the selection process was shown in Figure 1. As illustrated in Table 1, the mean age of the whole study population was 74.00 [67.00, 82.00] year, with 71.3% being male. Patients with CKD stage 3 and above accounted for 86.1%. Cardiogenic shock was present in 9.8% of patients, with a higher incidence in the non-survival group (46.7%) compared to the survival group (9.8%, p<0.001). During hospitalization, 44.5% of patients received vasopressors, 42.2% underwent mechanical ventilation, and 12.4% received renal replacement therapy (RRT). The admission levels of inflammatory markers were as follows: NLR 6.86±4.10, MLR 0.47±0.28, PLR156.99±94.63, SII 1287.60±938.52, SIRI 4.04±3.13, PIV 826.07 ±784.92.

Hospital Mortality

During hospitalization, 60 (8.65%) patients deceased. Table 1 illustrates a comparison of characteristics between the groups that survived and those that did not during hospitalization. Patients in the non-survival group were older (80.00 [70.00, 86.00] vs 74.00 [66.25, 81.00], p=0.01) and exhibited poorer renal function. Heart failure (HF) and atrial fibrillation (AF) were more prevalent in this group. In the non-survival group, both the admission and peak levels of the above-mentioned inflammatory markers, NLR, PLR, MLR, SIRI, SI and PIV, were markedly elevated compared to those in the survival group (p<0.001, Supplementary Figure 1). ROC curves were utilized to evaluate the discriminative performance of each inflammatory indicator. As shown in Figure 2A and Table 2, maximal NLR had the highest AUC for predicting in-hospital mortality (AUC = 0.795), followed by maximal SIRI (AUC = 0.773) and maximal MLR (AUC =

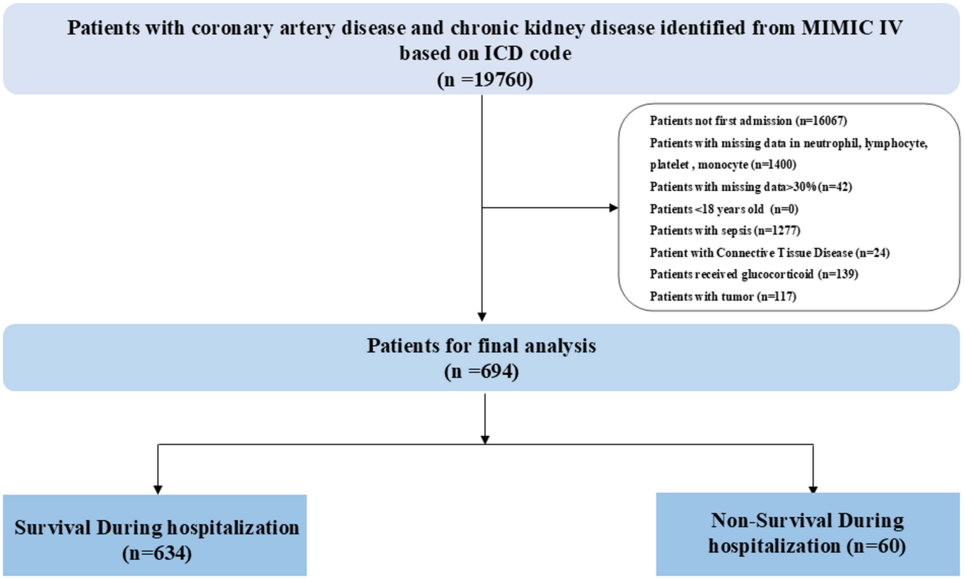

Figure 1 Flowchart of the study design.
Abbreviations: MIMIC-IV, Medical Information Mort for Intensive Care; ICD, International Classification of Diseases.

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Table 1 Baseline Characteristics in Patients with CKD and CAD from MIMIC-IV Database

	Overall	Survival	Non-Survival	P value
n	694	634	60	
Age (median [IQR]) (years)	74.00 [67.00, 82.00]	74.00 [66.25, 81.00]	80.00 [70.00, 86.00]	0.001
Gender Male (n,%)	495 (71.3)	458 (72.2)	37 (61.7)	0.11
Chronic Kidney Disease stage (n,%)				<0.001
1	6 (0.9)	6 (0.9)	0 (0.0)	
2	90 (13.0)	86 (13.6)	4 (6.7)	
3	374 (53.9)	352 (55.5)	22 (36.7)	
4	109 (15.7)	94 (14.8)	15 (25.0)	
5	47 (6.8)	36 (5.7)	11 (18.3)	
Dialysis	68 (9.8)	60 (9.5)	8 (13.3)	
AF (n,%)	306 (44.1)	268 (42.3)	38 (63.3)	0.003
HF (n,%)	403 (58.1)	356 (56.2)	47 (78.3)	0.001
Cardiogenic Shock (n,%)	68 (9.8)	40 (6.3)	28 (46.7)	<0.001
HT (n,%)	651 (93.8)	595 (93.8)	56 (93.3)	>0.99
DM (n,%)	432 (62.2)	395 (62.3)	37 (61.7)	>0.99
$los_{hospital}$ (median [IQR]), days	9.00 [6.00, 13.00]	9.00 [6.00, 13.00]	7.50 [2.00, 17.00]	0.13
los_{icu} (median [IQR]), days	1.92 [1.17, 3.20]	2.00 [1.21, 3.20]	1.31 [0.75, 3.18]	0.007
WBCmean (median [IQR]), K/uL	10.60 [7.98, 13.69]	10.50 [7.90, 13.50]	12.40 [8.62, 16.97]	0.006
NEUmean (median [IQR]), K/uL	8.18 [5.89, 10.96]	8.10 [5.81, 10.75]	10.35 [6.70, 14.12]	0.001
LYMmean (median [IQR]), K/uL	1.34 [0.95, 1.90]	1.40 [1.00, 1.96]	0.96 [0.68, 1.24]	<0.001
MONOmean (median [IQR]), K/uL	0.56 [0.36, 0.83]	0.54 [0.35, 0.81]	0.67 [0.48, 1.09]	0.002
HGBmean (median [IQR]), g/dL	9.30 [8.15, 10.70]	9.30 [8.10, 10.70]	9.53 [8.25, 10.74]	0.66
PLTmean (median [IQR]), K/uL	170.00 [132.00, 228.75]	168.42 [132.00, 228.00]	183.50 [134.50, 244.58]	0.39
NLRadmission (mean (SD))	6.86 (4.10)	6.54 (3.93)	10.24 (4.36)	<0.001
NLRmax (mean (SD))	7.79 (4.88)	7.32 (4.60)	12.76 (5.02)	<0.001
MLRadmission (mean (SD))	0.47 (0.28)	0.45 (0.27)	0.67 (0.27)	<0.001
MLRmax (mean (SD))	0.54 (0.33)	0.51 (0.32)	0.82 (0.32)	<0.001
PLRadmission (mean (SD))	156.99 (94.63)	151.53 (92.41)	214.65 (99.32)	<0.001
PLRmax (mean (SD))	172.37 (104.81)	165.71 (101.73)	242.75 (111.69)	<0.001
SIIadmission (mean (SD))	1287.60 (938.52)	1226.31 (909.93)	1935.22 (997.89)	<0.001
SIImax (mean (SD))	1516.02 (1170.60)	1427.17 (1119.99)	2454.84 (1286.95)	<0.001
SIRIadmission (mean (SD))	4.04 (3.13)	3.81 (3.01)	6.46 (3.37)	<0.001
SIRImax (mean (SD))	4.97 (4.08)	4.60 (3.87)	8.78 (4.32)	<0.001
PIVadmission (mean (SD))	826.07 (784.92)	776.29 (753.92)	1352.03 (911.23)	<0.001
PIVmax (mean (SD))	1050.51 (1038.11)	971.24 (984.23)	1888.06 (1218.24)	<0.001
ALTmean (median [IQR]), U/L	20.90 [14.00, 40.00]	20.00 [14.00, 34.25]	50.47 [20.58, 94.90]	<0.001
ASTmean (median [IQR]), U/L	29.00 [21.00, 48.50]	27.50 [20.00, 42.55]	91.96 [39.94, 104.30]	<0.001
Potassium mean (median [IQR]), mmol/L	4.33 [4.08, 4.59]	4.33 [4.09, 4.58]	4.26 [4.00, 4.66]	0.55
Sodium mean (median [IQR]), mmol/L	138.00 [135.75, 139.88]	138.12 [135.84, 139.87]	137.00 [133.44, 140.88]	0.093
Total calcium mean (median [IQR]), mmol/L	8.61 [8.30, 8.96]	8.60 [8.30, 8.93]	8.74 [8.41, 9.10]	0.06
Magnesium mean (median [IQR]), mmol/L	2.19 [2.03, 2.37]	2.19 [2.03, 2.39]	2.17 [2.02, 2.30]	0.26
Phosphate mean (median [IQR]), mmol/L	3.83 [3.35, 4.43]	3.78 [3.33, 4.36]	5.09 [3.99, 5.53]	<0.001
INRmean (median [IQR])	1.25 [1.14, 1.46]	1.24 [1.13, 1.40]	1.57 [1.25, 2.04]	<0.001
PTmean (median [IQR]), s	13.68 [12.50, 15.98]	13.56 [12.47, 15.41]	17.14 [13.49, 22.18]	<0.001
PTTmean (median [IQR]), s	35.95 [29.29, 55.22]	34.90 [29.06, 52.61]	56.58 [41.51, 68.34]	<0.001
Creatinine baseline (median [IQR]), mg/dL	1.70 [1.30, 2.60]	1.60 [1.30, 2.50]	2.20 [1.80, 3.82]	<0.001
Creatinine mean (median [IQR]), mg/dL	1.74 [1.37, 2.67]	1.70 [1.35, 2.54]	2.64 [1.75, 4.05]	<0.001
BUNmean (median [IQR]), mg/dL	35.32 [25.89, 49.80]	34.03 [25.68, 47.69]	52.52 [32.82, 70.15]	<0.001
SBPmean (median [IQR]), mmHg	117.00 [108.27, 127.99]	117.71 [109.77, 128.08]	105.52 [96.63, 121.64]	<0.001
DBPmean (median [IQR]), mmHg	57.92 [52.84, 64.17]	57.86 [52.91, 64.40]	58.48 [52.18, 61.16]	0.25

(*Continued*)

Table 1 (Continued).

	Overall	Survival	Non-Survival	P value
MBPmean (median [IQR]), mmHg	74.62 [70.12, 80.30]	74.93 [70.27, 80.58]	71.96 [66.94, 77.31]	0.003
HRmean (median [IQR]), bpm	77.74 [70.42, 85.35]	77.67 [70.55, 84.88]	80.02 [69.66, 95.07]	0.18
Spo_2 mean (median [IQR]), %	96.73 [95.62, 97.72]	96.72 [95.65, 97.70]	96.85 [94.96, 98.12]	0.79
Lactate mean (median [IQR]), mmol/L	1.71 [1.35, 2.20]	1.66 [1.30, 2.05]	3.06 [2.12, 3.06]	<0.001
SOFA (median [IQR])	5.00 [3.00, 7.00]	5.00 [3.00, 6.00]	6.00 [4.00, 10.00]	<0.001
RRT (n,%)	86 (12.4)	72 (11.4)	14 (23.3)	0.013
Ventilation (n,%)	293 (42.2)	270 (42.6)	23 (38.3)	0.62
Vasoactive agents (n,%)	309 (44.5)	274 (43.2)	35 (58.3)	0.034
PCI (n,%)	40 (5.8)	34 (5.4)	6 (10.0)	0.24
CABG (n,%)	215 (31.0)	214 (33.8)	1 (1.7)	<0.001
Aspirin (n,%)	633 (91.2)	582 (91.8)	51 (85.0)	0.12
Statin (n,%)	623 (89.8)	580 (91.5)	43 (71.7)	<0.001
Beta blocker (n,%)	542 (78.1)	505 (79.7)	37 (61.7)	0.002

Abbreviations: MIMIC, Medical Information Mort for Intensive Care; CKD, chronic kidney disease; CAD, coronary artery disease; AF, atrial fibrillation; HF, heart failure, HT, hypertension; DM, diabetes; $los_{hospital}$, length of hospital stay; los_{icu}, length of stay in the intensive care unit; WBCmean, average value of white blood cell; NEUmean, average value of neutrophil; LYMmean, average value of lymphocyte; MONOmean, average value of monocyte; HGBmean, average value of hemoglobin; PLTmean, average value of platelet; NLRadmission, level of neutrophil-lymphocyte ratio at admission; MLRadmission, level of monocyte-lymphocyte ratio at admission; PLRadmission, level of platelet-lymphocyte ratio at admission; SIIadmission, level of systemic immune-inflammation index at admission; SIRIadmission, level of Systemic Inflammation Response Index at admission; PIVadmission, level of Pan-Immune-Inflammation Value at admission; NLRmax, the maximal level of neutrophil-lymphocyte ratio during hospitalization; MLRmax, the maximal level of monocyte-lymphocyte ratio during hospitalization; PLRmax, the maximal level of platelet-lymphocyte ratio during hospitalization; SIImax, the maximal level of systemic immune-inflammation index during hospitalization; SIRImax, the maximal level of Systemic Inflammation Response Index during hospitalization; PIVmax, the maximal level of Pan-Immune-Inflammation Value during hospitalization; ALTmean, average value of alanine transaminase; ASTmean, average value of aspartate aminotransferase; BUNmean, average value of blood urea nitrogen; PTmean, average value of prothrombin time; PTTmean, average value of partial thromboplastin time; INRmean, average value of international normalized ratio; SBPmean, average value of systolic blood pressure; DBPmean, average value of diastolic blood pressure; MBPmean, average value of mean arterial pressure; HRmean, average value of heart rate; Spo_2 mean, average value of pulse oximeter readings of oxygen saturation; SOFA, sequential organ failure assessment, RRT, renal replacement therapy; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

0.754). DeLong's test revealed that the AUC of maximal NLR was not significantly different from maximal SIRI and maximal MLR ($p = 0.093$ and $p = 0.061$, respectively). However, maximal NLR had a significantly higher AUC compared to other indicators (admission SII level, admission PLR level, admission PIV level, maximal SII level, maximal PLR level, maximal PIV level, admission SIRI level, admission MLR level and admission NLR level, all $p < 0.05$).

Incremental value analysis (Supplementary Table 1) showed that adding maximal NLR to the base model significantly improved both NRI and IDI (NRI = 0.162, $p < 0.05$; IDI = 0.067, $p < 0.001$), while maximal SIRI and maximal MLR improved only IDI but not NRI. Logistic regression confirmed maximal NLR as an independent predictor of in-hospital mortality after adjusting for confounders (Table 3).

30-Day Follow-Up Results

During the 30-day follow-up period after discharge, an additional 15 patients died. As shown in Figure 2B and Table 2, maximal NLR was the strongest predictor of 30-day mortality (AUC = 0.754), followed by maximal MLR (AUC = 0.746) and maximal SIRI (AUC = 0.731). DeLong's test showed no significant differences between maximal NLR and maximal SIRI and maximal MLR ($p = 0.059$ and $p = 0.056$), but maximal NLR had a significantly higher AUC compared to other indicators (admission SII level, admission PLR level, admission PIV level, maximal SII level, maximal PLR level, maximal PIV level, admission SIRI level, admission MLR level and admission NLR level, all $p < 0.05$).

Incremental value analysis (Supplementary Table 1) revealed that only maximal NLR significantly improved both NRI and IDI (NRI = 0.222, $p < 0.05$; IDI = 0.029, $p < 0.05$). Cox regression analysis further validated maximal NLR as

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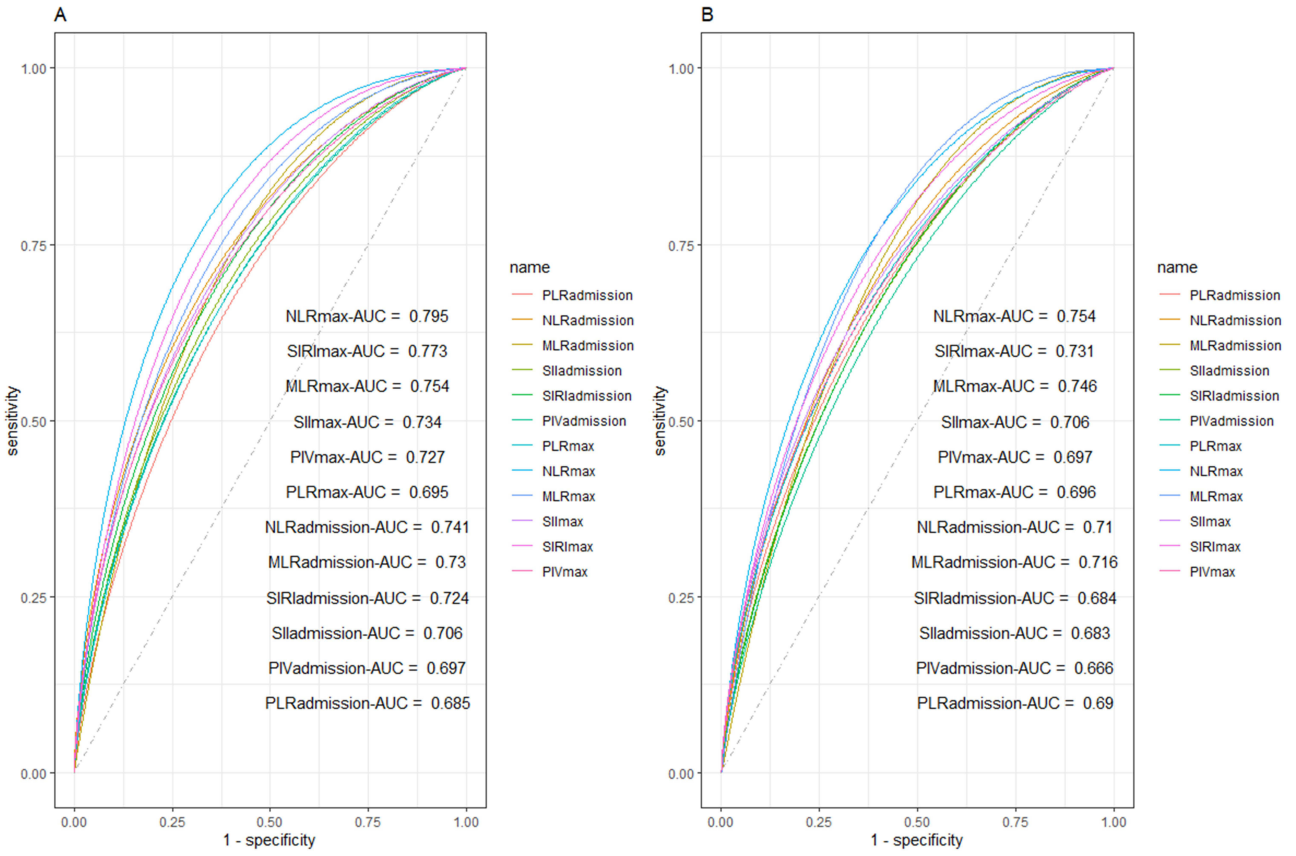

Figure 2 Receiver Operating Characteristic (ROC) curves of CBC derived indicators in predicting clinical outcomes. (**A**) ROC curve of the indicators in predicting in-hospital mortality; (**B**) ROC curve of the indicators in predicting 30-day mortality.

Abbreviations: CBC, complete blood count; AUC, the area under the ROC curves; NLRadmission, level of neutrophil-lymphocyte ratio at admission; MLRadmission, level of monocyte-lymphocyte ratio at admission; PLRadmission, level of platelet-lymphocyte ratio at admission; SIIadmission, level of systemic immune-inflammation index at admission; SIRIadmission, level of Systemic Inflammation Response Index at admission; PIVadmission, level of Pan-Immune-Inflammation Value at admission; NLRmax, the maximal level of neutrophil-lymphocyte ratio during hospitalization; MLRmax, the maximal level of monocyte-lymphocyte ratio during hospitalization; PLRmax, the maximal level of platelet-lymphocyte ratio during hospitalization; SIImax, the maximal level of systemic immune-inflammation index during hospitalization; SIRI_max, the maximal level of Systemic Inflammation Response Index during hospitalization; PIVmax, the maximal level of Pan-Immune-Inflammation Value during hospitalization.

an independent predictor of 30-day mortality, with statistical significance maintained after adjusting for potential confounders (Table 3).

Given the superior discriminative ability of the maximal NLR level, we categorized participants into low-NLR and high-NLR groups based on the ROC curve-derived cutoff value. As shown in Figure 3, patients with a maximal NLR level exceeding 6.30 had a significantly higher risk of 30-day mortality ($p < 0.001$).

Table 2 Performance of CBC-Derived Indicators in Predicting Hospital Mortality and 30-Day Mortality in ICU Patients with CKD and CAD

	Hospital Mortality					30-Day Mortality				
	AUC	**95% CI**	**Cut-Off**	**Sensitivity**	**Specificity**	**AUC**	**95% CI**	**Cut-Off**	**Sensitivity**	**Specificity**
NLRmax	0.795	0.741–0.849	7.096	0.614	0.867	0.754	0.699–0.809	6.303	0.544	0.88
SIRImax	0.773	0.715–0.832	5.112	0.685	0.767	0.731	0.672–0.79	4.326	0.616	0.76
MLRmax	0.754	0.693–0.815	0.622	0.692	0.733	0.746	0.692–0.799	0.561	0.645	0.747
NLRadmission	0.741	0.676–0.806	7.143	0.681	0.717	0.710	0.65–0.771	6.303	0.595	0.76
SIImax	0.734	0.669–0.798	1906.535	0.741	0.65	0.706	0.643–0.769	1974.217	0.754	0.587
MLRadmission	0.730	0.667–0.793	0.538	0.683	0.683	0.716	0.66–0.773	0.526	0.682	0.667

(*Continued*)

Table 2 (Continued).

	Hospital Mortality					30-Day Mortality				
	AUC	**95% CI**	**Cut-Off**	**Sensitivity**	**Specificity**	**AUC**	**95% CI**	**Cut-Off**	**Sensitivity**	**Specificity**
PIVmax	0.727	0.66–0.795	1131.773	0.722	0.65	0.697	0.632–0.761	1131.773	0.727	0.613
SIRIadmission	0.724	0.657–0.791	5.126	0.751	0.633	0.684	0.62–0.747	4.326	0.677	0.627
SIIadmission	0.706	0.639–0.773	1156.899	0.637	0.717	0.683	0.62–0.746	1156.899	0.64	0.667
PIVadmission	0.697	0.628–0.766	827.142	0.683	0.65	0.666	0.601–0.731	640.333	0.595	0.68
PLRmax	0.695	0.626–0.764	219.917	0.732	0.617	0.696	0.634–0.759	219.917	0.738	0.6
PLRadmission	0.685	0.615–0.754	171.322	0.655	0.667	0.690	0.627–0.753	122.987	0.525	0.787

Abbreviations: CBC, complete blood count; ICU, intensive care unit; CKD, chronic kidney disease; CAD, coronary artery disease; AUC, the area under the Receiver Operating Characteristic (ROC) curves; CI, confidential interval; NLRadmission, level of neutrophil-lymphocyte ratio at admission; MLRadmission, level of monocyte-lymphocyte ratio at admission; PLRadmission, level of platelet-lymphocyte ratio at admission; SIIadmission, level of systemic immune-inflammation index at admission; SIRIadmission, level of Systemic Inflammation Response Index at admission; PIVadmission, level of Pan-Immune-Inflammation Value at admission; NLRmax, the maximal level of neutrophil-lymphocyte ratio during hospitalization; MLRmax, the maximal level of monocyte-lymphocyte ratio during hospitalization; PLRmax, the maximal level of platelet-lymphocyte ratio during hospitalization; SIImax, the maximal level of systemic immune-inflammation index during hospitalization; SIRImax, the maximal level of Systemic Inflammation Response Index during hospitalization; PIVmax, the maximal level of Pan-Immune-Inflammation Value during hospitalization.

Table 3 Logistic and Cox Regression Analysis of the Association Between Maximal NLR and Both Hospital Mortality and 30-Day Mortality

	Hospital Mortality			30-Day Mortality		
	OR	**95% CI**	**P value**	**HR**	**95% CI**	**P value**
Model 1	1.21	1.15–1.27	<0.001	1.04	1.03–1.05	<0.001
Model 2	1.21	1.15–1.28	<0.001	1.05	1.03–1.06	<0.001
Model 3	1.27	1.15–1.44	<0.001	1.10	1.05–1.16	<0.001

Notes: Model 1: unadjusted. Model 2: adjusted for age and gender. Model 3: adjusted for age, gender, atrial fibrillation; heart failure; cardiogenic shock; PCI, CABG, aspirin; beta blocker; renal replacement therapy; vasoactive agents; mean level of HGB; mean level of sodium; mean level of calcium; mean level of platelet; mean level of BUN; mean level of INR; SOFA score; lactate; mean level of SBP; mean level of DBP; mean level of HR.
Abbreviations: NLR, neutrophil-lymphocyte ratio; OR, odd ratio; CI, confidence interval; HR, hazard ratio; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; HGB, hemoglobin; BUN, blood Urea Nitrogen; INR, International Normalized Ratio; SOFA, sequential organ failure assessment; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

Subgroup Analysis

Subgroup analysis was conducted to explore the relationship between the maximum NLR and 30-day mortality across different demographic and clinical conditions. As shown in Supplementary Figure 2, no significant interactions were observed among different subgroups, including age, gender, CKD stage, hypertension, diabetes, atrial fibrillation, heart failure, and cardiogenic shock.

Discussion

In the present study, we explored the prognostic significance of six parameters derived from CBC for assessing systemic immune inflammation among ICU patients with CAD and CKD. Among them, maximal NLR had the best prognostic property for in-hospital and 30-day mortality with the highest AUC followed by SIRI and MLR. However, the overlapping confidence intervals (CI) of NLR, SIRI, and MLR suggested that their discriminatory abilities were not statistically different. To address this, we performed the incremental predictive value of these markers. Our results indicate that while the AUCs of NLR, SIRI, and MLR were comparable, only NLR significantly improved risk stratification when added to conventional risk factors. This is one of the first studies to comprehensively assess the prognostic utility of these markers in this high-risk population, providing clinically relevant insights into their role in risk stratification.

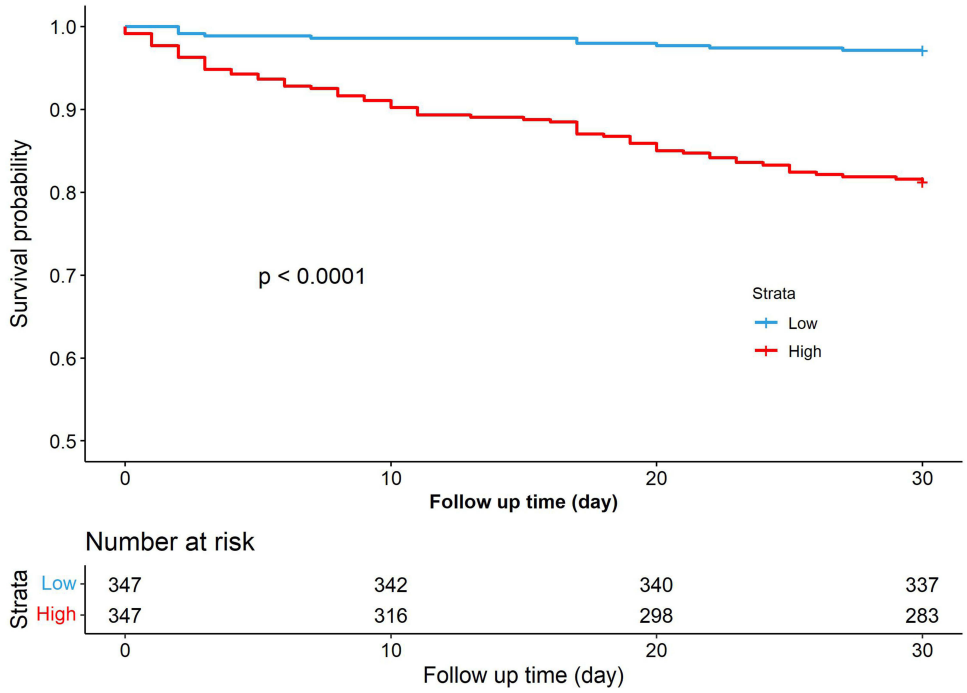

Figure 3 Kaplan-Meier survival curves illustrating the 30-day survival probability for the high-NLR and low-NLR groups.
Abbreviation: NLR, neutrophil-lymphocyte ratio.

Various markers derived from complete blood count (CBC) have demonstrated effectiveness in predicting adverse outcomes in patients with either CAD, CKD, or both. An elevated SII level was independently correlated with major cardiovascular events in patients with acute coronary syndrome and concurrent CKD (adjusted hazard ratio [HR]: 1.865, 95% CI: 1.197–2.907, p = 0.006).[13] Increased SII levels upon admission were also identified as an independent risk factor for all-cause mortality among patients with CKD.[11] In hemodialysis patients, NLR was predictive of mortality and cardiovascular events.[14] However, it is not clear which marker has the highest predictive power. Several studies focused on this issue. In ST-segment elevation myocardial infarction, PIV outperformed NLR, PLR, and SII in predicting mortality.[15] While in CHD patients at low residual inflammatory risk (hsCRP levels <2 mg/L), SIRI exhibited superior predictive capability compared to other neutrophil-derived indicators and robustly forecasted all-cause mortality, independently of hsCRP.[9] Heterogeneity existed mainly due to the population selection, types and severity of CAD and/or CKD, as well as the timing of inflammatory index assessments. In our study, we specifically targeted patients with concurrent CAD and CKD admitted to ICU, representing a high-risk population where prognosis merits significant consideration. In these patients, CBC should be routinely monitored and the follow-up of its absolute values and dynamic variation tendency was necessary. We separately compared both admission and maximum values of different inflammatory indexes. The maximal NLR had better predictive ability compared to its admission value and other indexes.

NLR has been proposed and widely used as a reliable hematologic marker of systemic inflammatory, oxidative stress, and endothelial damage in immune inflammation response to various infectious and non-infectious factors. It represents a ratio between two opposing yet complementary immune pathways: neutrophils, which play a role in nonspecific immune response during inflammation, and lymphocytes, crucial for specific immune response.[16]

Besides, NLR is an activity measure of granulocytic myeloid-derived suppressor cells released from the bone marrow secondary to disease impairment, which are morphologically similar to granulocytes and monocytes, increase up to 10% of the peripheral blood leukocytes and concomitantly suppressing the lymphocyte response.[17] NLR is closely linked to the complexity and severity of many diseases including both CAD and CKD, which can predict adverse events and all-cause mortality.[9,14–16,18] NLR can help differentiate more severe clinical conditions and higher NLR has been associated with worse prognosis in patients with various forms of CVD, which is a convenient, inexpensive and easily accessible marker of inflammation and stress with high sensitivity and should be tested routinely in ICU patients.

While several CBC-derived markers have demonstrated prognostic value in CAD patients with concomitant CKD,[13] our study focused on ICU patients with both CAD and CKD, representing a population at an exceptionally high risk of mortality. Among these patients, maximal NLR emerged as the most prominent predictor compared to other markers. Moreover, this advantage of NLR continued until 30 days after discharge. In ICU patients diagnosed with both CAD and CKD, maximal NLR exceeding 6.30 were correlated with a markedly elevated risk of mortality within 30 days ($p<0.001$). NLR can offer valuable early warning signs before clinical conditions worsen, particularly in ICU patients. Future studies with larger cohorts and external validation are warranted to further confirm these findings.

Several studies have explored the association between inflammatory indices and complications beyond mortality, such as acute kidney injury (AKI) and bleeding. AKI is a frequent complication in critically ill patients with CAD and CKD, often driven by systemic inflammation, hemodynamic instability, and oxidative stress. Elevated inflammatory markers including NLR have been linked to a higher risk of AKI and worse renal outcomes.[19] Similarly, systemic inflammation plays a critical role in coagulation disorders, contributing to an increased risk of bleeding events in patients with CAD.[20] Some studies have reported that elevated inflammatory indices correlate with higher bleeding risk, particularly in patients undergoing anticoagulation therapy or coronary invasive procedures.[21] Although our study did not specifically evaluate these complications, the strong association between inflammatory markers and adverse outcomes suggests that these indices may also serve as potential predictors for AKI and bleeding. Future research should investigate these relationships further to provide a more comprehensive risk assessment framework for CAD patients with CKD.

Limitations

The present study relied on retrospective analysis utilizing data sourced solely from a single center's public database, thereby introducing an inherent selection bias. A notable limitation of this study is the relatively small number of in-hospital and 30-day mortality events. However, we have performed rigorous statistical analyses, including multivariable adjustments and sensitivity analyses, to mitigate this limitation. Future studies with larger sample sizes and multicenter validation are needed to confirm the prognostic value of these inflammatory markers in patients with CAD and CKD. Due to the utilization of state death records for follow-up outcomes, the study was limited to examining all-cause mortality, as specific causes of death remained undisclosed. We were unable to account for certain unmeasured variables, such as specific treatment strategies, differences in ICU interventions and physician decision-making, all of which may have influenced patient outcomes. Although we adjusted for multiple confounders in our multivariable analyses, residual confounding cannot be entirely ruled out.

Conclusion

Among ICU patients with CAD and CKD, the maximum NLR exhibited the highest predictive value for both in-hospital mortality and 30-day mortality post-discharge. Monitoring prognosis through dynamic changes in NLR deserves greater consideration.

Data Sharing Statement

The data supporting this study's findings are available from the MIMIC IV (https://physionet.org/content/mimiciv/0.4/).

Statement of Ethics

The MIMIC-IV dataset comprises a vast repository of medical records, encompassing ICU admissions spanning from 2008 to 2019 at Beth Israel Deaconess Medical Center (Boston, Massachusetts). The first author Shuoyan An got the certification to access to the MIMIC-IV database (Record ID: 39674606). Our study upheld ethical standards in accordance with the principles outlined in the Declaration of Helsinki. This study was conducted using the publicly available MIMIC-IV database, which provides fully de-identified patient data. According to the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects (2023, China), Article 32, Items 1 and 2, research utilizing de-identified publicly available data does not require formal ethical approval. Therefore, our study was exempt from ethical review.

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Disclosure

The authors report no conflicts of interest in this work.

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