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ORIGINAL RESEARCH

Evaluation of the Prognostic Role of Neutrophil-Lymphocyte Ratio, C-Reactive Protein-Albumin Ratio, and Platelet-Lymphocyte Ratio in Patients with the Co-Presentation of Coronary Artery Disease and COVID-19

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Aim: The purpose of this study was to investigate the role of neutrophil-lymphocyte ratio (NLR), C-reactive protein-albumin ratio (CAR), and platelet-lymphocyte ratio (PLR) in the prognosis of patients with coronary artery disease (CAD) complicated with coronavirus disease 2019 (COVID-19).

Methods: This study included 265 patients. A receiver operating characteristic (ROC) curve analysis was performed to preliminarily evaluate the predictive ability of NLR, CAR, and PLR for all-cause death. The primary outcome was all-cause death during hospitalization, while the secondary outcomes were cardiovascular death and respiratory failure death. The Cox proportional hazard model with adjusted covariates was used to analyze the cumulative risk of outcomes. We also conducted subgroup analyses based on the acute and chronic characteristics of CAD. Propensity score matching (PSM) was used to further evaluate the robustness of the primary outcome.

Results: The ROC curve analysis results showed that the area under curve (AUC) values were 0.686 (95% CI 0.592–0.781, P<0.001) for NLR, 0.749 (95% CI 0.667–0.832, P<0.001) for CAR, and 0.571 (95% CI 0.455–0.687, P=0.232) for PLR. The Cox proportional hazard model showed that trends in NLR and PLR did not affect the risk of all-cause death (P=0.096 and P=0.544 for trend, respectively), but a higher CAR level corresponded to a higher risk of all-cause death (P<0.001 for trend). Similarly, The trends of NLR and PLR did not affect the risk of cardiovascular death and respiratory failure death, while a higher CAR level corresponded to a higher risk of cardiovascular death and respiratory failure death. The results of subgroup analyses and PSM were consistent with the total cohort.

Conclusion: In patients with CAD complicated with COVID-19, a higher CAR level corresponded to a higher risk of all-cause death, cardiovascular death, and respiratory failure death, while trends in NLR and PLR did not.

Keywords: coronary artery disease, coronavirus disease 2019, neutrophil-lymphocyte ratio, C-reactive protein-albumin ratio, platelet-lymphocyte ratio

Introduction

Recently, some randomized controlled trials have demonstrated that targeted inflammatory therapy improves the clinical outcomes for patients with atherosclerosis. The Colchicine Cardiovascular Outcomes Trial (COLCOT),[1] the second Low

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Dose Colchicine trial (LoDoCo-2),[2] and the Canakinumab Thrombosis Outcomes Study (CANTOS)[3] all found that anti-inflammatory treatment reduced the risk of cardiovascular adverse events in patients with coronary artery disease, with both COLCOT and CANTOS included patients showing a slight increase in baseline C-reactive protein (CRP). In contrast, the Cardiovascular Inflammation Reduction Trial (CIRT)[1] did not find any anti-inflammatory benefits of methotrexate for cardiovascular events. However, the baseline CRP of the patients it included was only 1.6mg/L. Therefore, although this study was neutral, it also increased interest in finding simple inflammatory biomarkers widely used in the clinical community. Adamstein et al[4] conducted a meta-analysis that included a series of large-scale clinical studies and found that neutrophil-lymphocyte ratio (NLR) effectively predicted the risk of cardiovascular adverse events. Some studies also found that CRP-albumin ratio (CAR) may be an important indicator for predicting cardiovascular risk.[5–9] Our previous studies[10,11] also confirmed that the combined indicator of CRP and albumin played a similar role in evaluating the prognosis of patients with acute myocardial infarction as the Global Registry of Acute Coronary Events (GRACE) score. In addition, platelet-lymphocyte ratio (PLR) was also found to have good predictive value for cardiovascular events.

With the global pandemic of coronavirus disease 2019 (COVID-19) and the general susceptibility of humans to it, repeated or long-term infections have gradually attracted attention, and at the same time, the number of patients with coronary artery disease (CAD) complicated with COVID-19 has also shown an upward trend. Some studies showed significant increases in CAR, NLR, and PLR levels in patients with COVID-19, which may have an impact on the their prognosis.[12–17] However, few data evaluate the NLR, CAR, and PLR in the context of patients with CAD complicated with COVID-19.

In this study, we aimed to identify the most useful prognostic biomarkers by investigating the predictive value of NLR, CAR, and PLR for all-cause death during hospitalization in patients with CAD complicated with COVID-19.

Methods

Subjects

This is a single-center, retrospective cohort study designed to compare the predictive ability of NLR, CAR, and PLR on the risk of all-cause death, cardiovascular death, and respiratory failure death during hospitalization in patients with CAD complicated with COVID-19. Patients were recruited from the Hangzhou Red Cross Hospital from December 1, 2022, to March 1, 2023. This study was a retrospective cohort study and did not require additional testing or intervention on the subjects. We promised to maintain the confidentiality of all patient information collected in the electronic medical record database. Therefore, an exemption from the informed consent requirement was approved by the ethics committee of Hangzhou Red Cross Hospital (Ethical Application Ref: 2023YS112). This study protocol strictly complied with the requirements of the Helsinki Declaration of the World Medical Association and the international ethics guide for human biomedical research of the Council for International Organizations of Medical Sciences (CIOMS).

Patient Selection

Inclusion criteria: coronary artery diseases included acute coronary syndrome (ACS) and chronic coronary syndrome (CCS). In short, ACS included acute myocardial infarction and unstable angina. The former refered to the fourth universal definition of myocardial infarction,[18] which first needed to clarify the basis of acute myocardial injury. At the same time, one of the following conditions exists: symptoms of myocardial ischaemia; new ischaemic electrocardiogram changes; development of pathological Q waves; imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology; identification of a coronary thrombus by angiography or autopsy. Unstable angina was considered to have the potential for acute myocardial infarction upon admission, but there was no dynamic change in cTn values during hospitalization. CCS referred to the the 2019 European Society of Cardiology (ESC) Guidelines for the diagnosis and management of chronic coronary syndromes,[19] including stable angina pectoris and asymptomatic coronary heart disease patients found during screening, among others.

The diagnosis of COVID-19 referred to the expert consensus on the clinical prevention and treatment scheme of novel coronavirus pneumonia in the People's Republic of China.[20] In short, all patients with COVID-19 included were confirmed cases and must meet the following conditions: ① epidemiological history, ② corresponding clinical manifestations, such as fever or respiratory symptoms, and ③ COVID-19 nucleic acid positive or IgM antibody positive. The specific diagnostic criteria are detailed in Appendix 1.

Data Collection

This collection of baseline data for patients referred to the age-adjusted Charlson comorbidities index,[21] including age, gender, previous myocardial infarction (MI), congestive heart failure (CHF), peripheral vascular disease (PVD), cerebrovascular disease (CBVD), hemiplegia, dementia, chronic obstructive pulmonary disease (COPD) or asthma, connective tissue disease (CTD), ulcer disease (UD), diabetes, moderate or severe kidney disease, liver disease, tumor, leukemia, lymphoma, and acquired immune deficiency syndrome (AIDS). The diagnostic criteria are detailed in Appendix 1. The raw data supporting the results of this study was uploaded to zenodo (https://www.zenodo.org/record/8320786), and accessed upon reasonable request.

Risk Stratification of Inflammation Scores

The risk stratification of NLR, CAR, and PLR was divided into four levels according to the quartile, with the low-risk group being less than the first quartile (Q1), the risk level increasing sequentially, and the highest-risk group being greater than or equal to the fourth quartile (Q4).

Outcomes

This study retrospectively observed that patients were in a survival state during hospitalization, with the primary outcome was all-cause death. The secondary outcomes were cardiovascular death and respiratory failure death. The diagnostic criteria could be found in Appendix 1.

Statistical Analysis

We compared baseline features grouped by the risk levels of different main study variables (NLR, CAR, and PLR) using the following method. The median and quartile of continuous variables were tested using the Kruskal–Wallis test, and the Pearson chi-square was used for categorical variables. The missing values of continuous variables are filled in using the expectation maximization (EM) method. The analysis of the receiver operating characteristic (ROC) curve was completed to calculate the area under curve (AUC) to determine the predictive value of each main study variable for the primary outcome. The included baseline indicators were used as covariates in the relationship between the main study variables and outcome events, and a multivariate Cox proportional hazard model using the forward likelihood ratio method was used to estimate the timing of event occurrences. Obtain the hazard ratio (HR) and corresponding 95% confidence interval (CI) from the Cox proportional hazard model, and establish a cumulative risk standard chart for outcomes based on this model. The hypothesis of the Cox model was validated by visually evaluating the logarithm of the negative logarithm of the Cox survival function and the standard plot of cumulative risk to confirm the absence of time-dependent effects on the main study variables. In addition, we conducted subgroup analyses the predictive value of the three scores on the primary outcome based on the acute and chronic characteristics of CAD. To further verify the robustness of the Cox model results, propensity score matching (PSM) was performed to adjust for the inter-group baseline data level bias of the main study variables. By generating propensity scores for each patient with the main study variables as the dependent variable and the independent variable including all included baseline indicators. The C-statistic was calculated for the propensity model. Once generated, patients were matched 1 to 1 on their propensity score without replacement using the "nearest neighbor" matching method with a fixed caliper width of 0.2. After matching, standardized differences were used, with a general balance reflecting a standardized difference of <25% and a high balance reflecting a standardized difference of <10%. Then, a univariate Cox proportional hazard model was used to obtain HR and corresponding 95% CI.

Other confounding variables of concern include percutaneous coronary intervention (PCI), aspirin, P2Y12 receptor inhibitor, ACEI (angiotensin converting enzyme inhibitor)/ARB (angiotensin receptor blocker), beta-blocker, calcium-channel blocker, and lipid-lowering agent were also considered to have an impact on the above Cox model. Therefore, we conducted a post hoc analysis to include these confounding variables and evaluate the predictive ability of NLR, CAR, and PLR for all-cause mortality during hospitalization in patients with coronary artery disease complicated with COVID-19. The HR (95% CI), percentages, and median (quartile) were used as summary statistics in the corresponding cases. Bilateral P values <0.05 were considered statistically significant. The data was analyzed using SPSS 26.0 (SPSS, Inc., Chicago, IL).

Results

Baseline Patient Characteristics

A total of 265 consecutive patients were ultimately included in this study (Supplementary Figure 1). The median age was 87 years old, 39.2% of whom were female, with a median observation time of 17 days. 26 (9.8%) had a history of MI, 159 (60.0%) had CHF, 43 (16.2%) had PVD, 89 (33.5%) had CBVD, 3 (1.1%) had hemiplegia, 43 (16.2%) had dementia, 63 (23.7%) had COPD or asthma, 11 (4.1%) had CTD, 2 (0.7%) had UD, 199 (75.0%) had hypertension, 113 (42.7%) had diabetes, 121 (45.6%) had moderate to severe kidney disease, 23 (8.7%) had liver dysfunction, 43 (16.2%) had tumors, 1 (0.3%) had leukemia, 2 (0.7%) had lymphoma, and 1 (0.3%) had AIDS (Table 1). The essential indicators for diagnosing liver dysfunction and kidney disease, such as alanine aminotransferase, albumin, creatinine, and urea, have missing values, and the missing values all come from one patient with a missing rate of 0.03%. The filling completed by the EM method can be seen in Supplementary Table 1.

Receiver Operating Characteristic Curve Analysis

The ROC curve analysis showed that the AUC values for all-cause death during hospitalization were 0.686 (95% CI 0.592–0.781, P<0.001) for NLR, 0.749 (95% CI 0.667–0.832, P<0.001) for CAR, and 0.571 (95% CI 0.455–0.687, P=0.232) for PLR (Figure 1 and Supplementary Table 2). NLR and CAR had a higher AUC value compared to PLR (P=0.031 and P=0.012, respectively) (Supplementary Table 3).

Primary Outcome

In the multivariate Cox proportional hazard model, compared to the NLR (Q1) group, there was no statistically significant difference in the NLR (Q2), NLR (Q3), and NLR (Q4) groups (P=0.332, P=0.836, and P=0.458, respectively), and the trend of NLR did not affect the risk of all-cause death (P=0.096 for trend). Compared with the CAR (Q1) group, there was no statistical difference between the CAR (Q2) group [HR, 6.529 (95% CI, 0.777–54.859), P=0.084] and the CAR (Q3) group [HR, 6.669 (95% CI, 0.760–58.556), P=0.087], but the CAR (Q4) group had a higher risk [HR, 19.638 (95% CI, 2.574–149.846), P=0.004], and the higher the CAR level was, the greater the risk of all-cause death was (P<0.001 for trend). Compared with the PLR (Q1) group, there was no statistically significant difference among the PLR (Q2), PLR (Q3), and PLR (Q4) groups (P=0.992, P=0.593, and P=0.523, respectively), and the correlation between PLR trend and all-cause death risk was also not significant (P=0.544 for trend) (Table 2 and Figure 2).

Secondary Outcome

In the multivariate Cox proportional hazard model with cardiovascular death outcome, the NLR trend did not affect the risk of cardiovascular death (P=0.368 for trend). The higher the CAR level was, the greater the risk of cardiovascular death was(P=0.007 for trend). The PLR trend did not affect the risk of cardiovascular death (P=0.265 for trend) (Supplementary Table 4).

In a multivariate Cox proportional hazard model with respiratory failure death outcome, the NLR trend did not affect the risk of respiratory failure death (P=0.124 for trend). The higher the CAR level was, the greater the risk of respiratory failure death was (P=0.002 for trend). The PLR trend did not affect the risk of death from respiratory failure (P=0.817 for trend) (Supplementary Table 5).

Table 1 Clinical Characteristics of NLR, CAR, and PLR Stratification

	NLR				P	CAR				P	PLR				P
	Q1 (<2.65) (N=66)	Q2 (2.65–4.49) (N=66)	Q3 (4.49–8.74) (N=67)	Q4 (≥8.74) (N=66)		Q1 (<0.11) (N=68)	Q2 (0.11–0.38) (N=66)	Q3 (0.38–1.44) (N=64)	Q4 (≥1.44) (N=67)		Q1 (<132.41) (N=66)	Q2 (132.41–195.83) (N=66)	Q3 (195.83–323.69)N= (67)	Q4 (≥323.69) (N=66)	
Age, years	86.0 (73.00–89.00)	86.0 (75.75–90.00)	88.0 (77.00–92.00)	88.0 (81.75–91.00)	0.037	87.0 (75.75–91.25)	87.0 (75.00–90.00)	87.0 (76.00–91.00)	87.5 (78.00–91.00)	0.070	82.5 (75.00–90.00)	88.0 (79.75–94.00)	85.0 (75.25–91.00)	87.0 (82.00–91.00)	0.851
Female sex, no. (%)	30 (45.5)	26 (39.4)	26 (38.8)	22 (33.3)	0.564	34 (50)	32 (48.5)	22 (34.4)	16 (23.9)	0.005	15 (22.7)	28 (42.4)	32 (47.8)	29 (43.9)	0.015
Previous MI, no. (%)	4 (6.1)	11 (16.7)	4 (6.0)	7 (10.6)	0.126	7 (10.3)	7 (10.6)	3 (4.7)	9 (13.4)	0.398	8 (12.1)	5 (7.6)	5 (7.5)	8 (12.1)	0.662
CHF, no. (%)	32 (48.5)	38 (57.6)	39 (58.2)	50 (75.8)	0.013	27 (39.7)	40 (60.6)	43 (67.2)	49 (73.1)	<0.001	39 (59.1)	38 (57.6)	36 (53.7)	46 (69.7)	0.276
PVD, no. (%)	8 (12.1)	11 (16.7)	12 (17.9)	12 (18.2)	0.764	12 (17.6)	8 (12.1)	12 (18.8)	11 (16.4)	0.748	8 (12.1)	13 (19.7)	11 (16.4)	11 (16.7)	0.702
CBVD, no. (%)	20 (30.3)	23 (34.8)	24 (35.8)	22 (33.3)	0.915	23 (33.8)	23 (34.8)	20 (31.3)	23 (34.3)	0.974	23 (34.8)	23 (34.8)	21 (31.3)	22 (33.3)	0.970
Hemiplegia, no. (%)	1 (1.5)	1 (1.5)	0 (0)	1 (1.5)	0.795	1 (1.5)	0 (0)	2 (3.1)	0 (0)	0.277	1 (1.5)	1 (1.5)	0 (0)	1 (1.5)	0.795
Dementia, no. (%)	13 (19.7)	8 (12.1)	9 (13.4)	13 (19.7)	0.499	8 (11.8)	12 (18.2)	12 (18.8)	11 (16.4)	0.686	11 (16.7)	7 (10.6)	13 (19.4)	12 (18.2)	0.527
COPD/asthma, no. (%)	16 (24.2)	19 (28.8)	12 (17.9)	16 (24.2)	0.531	14 (20.6)	21 (31.8)	16 (25)	12 (17.9)	0.255	17 (25.8)	17 (25.8)	12 (17.9)	17 (25.8)	0.637
CTD, no. (%)	2 (3)	2 (3)	4 (6)	3 (4.5)	0.801	1 (1.5)	4 (6.1)	1 (1.6)	5 (7.5)	0.190	1 (1.5)	4 (6.1)	0 (0)	6 (9.1)	0.033
UD, no. (%)	1 (1.5)	0 (0)	1 (1.5)	0 (0)	0.572	1 (1.5)	0 (0)	1 (1.6)	0 (0)	0.565	1 (1.5)	0 (0)	0 (0)	1 (1.5)	0.566
Hypertension, no. (%)	50 (75.8)	49 (74.2)	52 (77.6)	48 (72.7)	0.926	53 (77.9)	48 (72.7)	49 (76.6)	49 (73.1)	0.872	48 (72.7)	48 (72.7)	55 (82.1)	48 (72.7)	0.504
Diabetes, no. (%)															
Without complication	18 (27.3)	17 (25.8)	17 (25.4)	9 (13.6)	0.218	13 (19.1)	15 (22.7)	20 (31.3)	13 (19.4)	0.317	20 (30.3)	14 (21.2)	17 (25.4)	10 (15.2)	0.202
With complications	9 (13.6)	11 (16.7)	18 (26.9)	15 (22.7)	0.221	18 (26.5)	15 (22.7)	9 (14.1)	11 (16.4)	0.258	16 (24.2)	12 (18.2)	11 (16.4)	14 (21.2)	0.688

(*Continued*)

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Table 1 (Continued).

	NLR				P	CAR				P	PLR				P
	Q1 (<2.65) (N=66)	Q2 (2.65–4.49) (N=66)	Q3 (4.49–8.74) (N=67)	Q4 (≥8.74) (N=66)		Q1 (<0.11) (N=68)	Q2 (0.11–0.38) (N=66)	Q3 (0.38–1.44) (N=64)	Q4 (≥1.44) (N=67)		Q1 (<132.41) (N=66)	Q2 (132.41–195.83) (N=66)	Q3 (195.83–323.69)N= (67)	Q4 (≥323.69) (N=66)	
Moderate/ severe nephropathy, no. (%)	24 (36.4)	23 (34.8)	35 (52.2)	39 (59.1)	0.01	28 (41.2)	32 (48.5)	18 (28.1)	43 (64.2)	<0.001	30 (45.5)	27 (40.9)	29 (43.3)	35 (53)	0.532
Liver dysfunction, no. (%)															
Mild	3 (4.5)	7 (10.6)	3 (4.5)	7 (10.6)	0.317	1 (1.5)	3 (4.5)	5 (7.8)	11 (16.4)	0.007	6 (9.1)	7 (10.6)	3 (4.5)	4 (6.1)	0.527
Moderate/ severe	1 (1.5)	1 (1.5)	0 (0)	1 (1.5)	0.795	2 (2.9)	0 (0)	0 (0)	1 (1.5)	0.314	1 (1.5)	0 (0)	0 (0)	2 (3)	0.292
Tumor, no. (%)															
No metastasis	5 (7.6)	10 (15.2)	7 (10.4)	7 (10.6)	0.574	13 (19.1)	6 (9.1)	6 (9.4)	4 (6)	0.08	6 (9.1)	7 (10.6)	12 (17.9)	4 (6.1)	0.158
Metastasis	4 (6.1)	3 (4.5)	5 (7.5)	2 (3)	0.692	4 (5.9)	3 (4.5)	5 (7.8)	2 (3)	0.649	2 (3)	3 (4.5)	7 (10.4)	2 (3)	0.173
Leukemia, no. (%)	0 (0)	1 (1.5)	0 (0)	0 (0)	0.388	0 (0)	1 (1.5)	0 (0)	0 (0)	0.388	0 (0)	0 (0)	1 (1.5)	0 (0)	0.397
Lymphoma, no. (%)	1 (1.5)	0 (0)	0 (0)	1 (1.5)	0.566	0 (0)	1 (1.5)	1 (1.6)	0 (0)	0.553	1 (1.5)	0 (0)	0 (0)	1 (1.5)	0.566
AIDS, no. (%)	0 (0)	0 (0)	0 (0)	1 (1.5)	0.388	0 (0)	1 (1.5)	0 (0)	0 (0)	0.388	0 (0)	1 (1.5)	0 (0)	0 (0)	0.388

Note: Values are numbers (%) or medians (interquartile ranges).

Abbreviations: AIDS, acquired immune deficiency syndrome; CAR, C-reactive protein-to-albumin ratio; CBVD, cerebral vascular disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CTD, connective tissue disease; MI, myocardial infarction; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PVD, peripheral vascular disease; UD, ulcer disease.

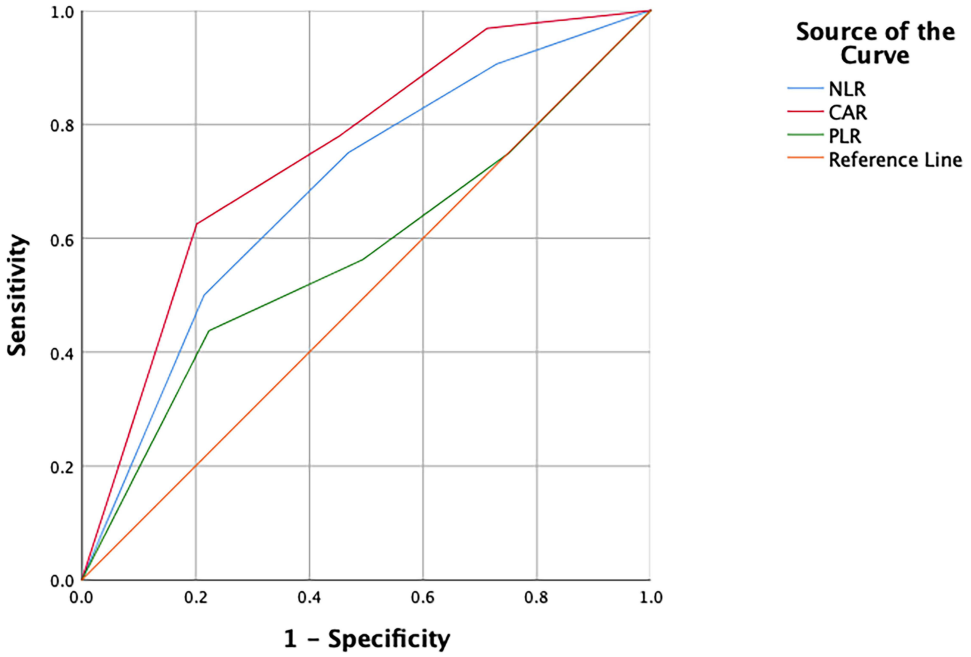

Figure 1 ROC Curves of NLR, CAR, and PLR for the all-cause death during hospitalization.
Abbreviations: CAR, c-reactive protein-to-albumin ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; ROC, receiver operating characteristic.

Subgroup Analyses

CAD was divided into ACS and CCS. In the ACS cohort, the trends of NLR and PLR did not affect the risk of all cause death (P=0.240 and 0.216 for trend, respectively), while the higher the CAR level was, the greater the risk of all cause death was (P=0.048 for trend). In the CCS cohort, the higher the levels of NLR and CAR were, the higher the risk of all cause death were (P=0.047 and 0.010 for trend, respectively), while the trend of PLR did not affect the risk of all cause death (P=0.185 for trend). Further interaction tests showed that there were no differences in the effects of NLR, CAR, and PLR on all cause death (P=0.691, 0.369, and 0.242 for interaction, respectively) (Supplementary Table 6).

Table 2 Cox Regression Analysis of All-Cause Death During Hospitalization

Vairable	HR	Univariate Analysis for 95% CI	*P*	HR	Multivariate Analysis* for 95% CI	*P*
NLR						
Q2 vs Q1	1.702	0.407–7.125	0.467	–	–	0.836
Q3 vs Q1	2.217	0.588–8.362	0.240	–	–	0.458
Q4 vs Q1	5.020	1.460–17.262	0.01	–	–	0.096
P for trend	–	–	0.003	–	–	0.096
CAR						
Q2 vs Q1	7.685	0.922–64.067	0.059	6.529	0.777–54.859	0.084
Q3 vs Q1	6.861	0.799–58.887	0.079	6.669	0.760–58.556	0.087
Q4 vs Q1	27.314	3.651–204.359	0.001	19.638	2.574–149.846	0.004
P for trend	–	–	<0.001	–	–	<0.001

(*Continued*)

Table 2 (Continued).

Vairable	HR	Univariate Analysis for 95% CI	*P*	HR	Multivariate Analysis* for 95% CI	*P*
PLR						
Q2 vs Q1	0.713	0.247–2.057	0.532	–	–	0.593
Q3 vs Q1	0.480	0.144–1.596	0.231	–	–	0.523
Q4 vs Q1	1.726	0.722–4.126	0.219	–	–	0.332
P for trend	–	–	0.217	–	–	0.544
Age	1.034	0.984–1.088	0.188	–	–	0.777
Sex	2.144	0.962–4.780	0.062	–	–	0.268
Previous MI	0.623	0.189–2.053	0.436	–	–	0.141
CHF	5.404	1.645–17.757	0.005	3.2	0.958–10.691	0.059
PVD	1.135	0.487–2.643	0.769	–	–	0.814
CBVD	0.479	0.219–1.045	0.064	–	–	0.054
Hemiplegia	0.048	0.000–9157.171	0.625	–	–	0.663
Dementia	0.722	0.295–1.766	0.475	–	–	0.686
COPD/asthma	0.908	0.407–2.026	0.813	–	–	0.819
CTD	0.047	0.000–110.985	0.440	–	–	0.124
UD	0.049	0.000–180,025.715	0.695	–	–	0.761
Hypertension	0.654	0.315–1.358	0.255	–	–	0.539
Diabetes	1.135	0.763–1.689	0.533	–	–	0.142
Moderate/severe nephropathy	4.355	1.785–10.626	0.001	3.306	1.320–8.285	0.011
Liver dysfunction	2.331	1.352–4.020	0.002	–	–	0.129
Tumor	0.609	0.252–1.472	0.271	–	–	0.616
Leukemia	0.049	$0.000–1.747*10^{20}$	0.905	–	–	0.948
Lymphoma	0.045	0.000–14,540.542	0.631	–	–	0.562
AIDS	0.049	$0.000–2.672*10^{11}$	0.841	–	–	0.721

Notes: *Adjusting NLR (categorical covariates), CAR (categorical covariates), PLR (categorical covariates), age, sex, previous MI, CHF, PVD, CBVD, hemiplegia, dementia, COPD/asthma, CTD, UD, hypertension, diabetes, moderate/severe nephropathy, liver dysfunction, tumor, leukemia, lymphoma, and AIDS through forward likelihood ratio method.

Abbreviations: AIDS, acquired immune deficiency syndrome; CAR, c-reactive protein-to-albumin ratio; CBVD, cerebral vascular disease; CHF, congestive heart failure; CI; confidence interval; COPD, chronic obstructive pulmonary disease; CTD, connective tissue disease; HR, hazard ratio; MI, myocardial infarction; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PVD, peripheral vascular disease; UD, ulcer disease.

Patient Characteristics After Propensity Score Matching

When the binary grouping with NLR as the main study variable, the PSM model performed well, with a C-statistic of 0.863 for all-cause death. According to the 1:1 matching requirement, 102 patients in the low-risk group and 102 patients in the high-risk group completed the matching, with a matching rate of 76.7%. Except that the matching of diabetes and kidney disease reached a general balance, the matching of other variables reached a high balance (Supplementary Table 7).

When the binary grouping with CAR as the main study variable, the PSM model performed well, with a C-statistic of 0.870 for all-cause mortality. According to the 1:1 matching requirement, 93 patients in the low-risk group and 93

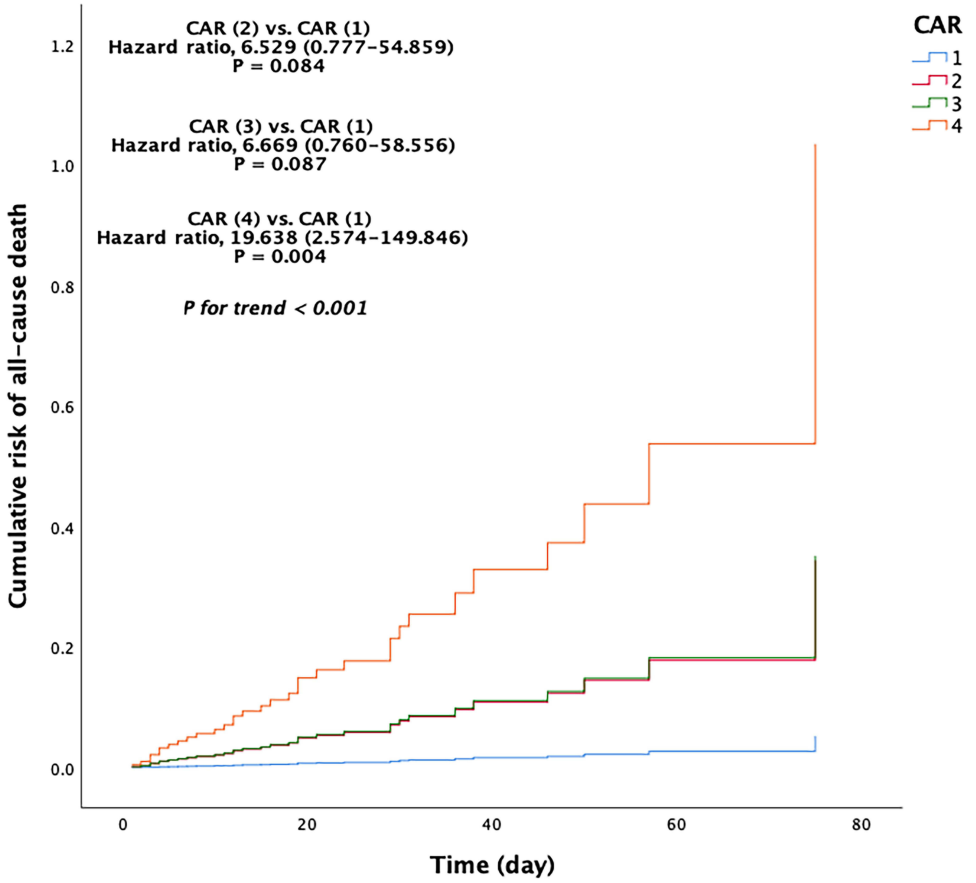

Figure 2 Cumulative incidence of the all-cause death among four CAR level groups in the multivariate COX proportional risk model with forward likelihood ratio.
Abbreviation: CAR, c-reactive protein-to-albumin ratio.

patients in the high-risk group completed the matching, with a matching rate of 71.0%. Except that the matching of lymphoma reached a general balance, the matching of other variables reached a high balance (Supplementary Table 8).

When the binary grouping with PLR as the main study variable, the propensity score model performed well, with a C-statistic of 0.889 for all-cause mortality. According to the 1:1 matching requirement, 109 patients in the low-risk group and 109 patients in the high-risk group completed the matching, with a matching rate of 82.0%. Except that the matching of gender and dementia reached a general balance, the matching of other variables reached a high balance (Supplementary Table 9).

Outcomes After Propensity Score Matching

After the PSM pair, there was no statistically significant difference in the all-cause death risk of the high-risk group compared to the low-risk group in the binary grouping with NLR as the main study variable [HR, 1.949 (95% CI, 0.791–4.801), P=0.147] (Table 3).

When the binary grouping with CAR as the main study variable, the high-risk group had a higher risk of all-cause death compared to the low-risk group [HR, 3.217 (95% CI, 1.142–9.064), P=0.027].

When the binary grouping with PLR as the main study variable, there was no statistically significant difference in the all-cause mortality risk between the high-risk group and the low-risk group [HR, 11.060 (95% CI, 0.483–2325), P=0.885].

Post Hoc Analysis

The baseline data of confounding variables included in the post hoc analysis model could be found in Supplementary Table 10. 68 (25.6%) of whom had a history of PCI, 55 (20.7%) took aspirin, 101 (38.1%) took P2Y12 receptor inhibitor,

Table 3 All-cause death among propensity score matched patient pairs

	NLR		HR (95% CI)	*P*
	< Median (n=102)	**≥ Median (n=102)**		
All-cause death, no. (%)	57 (6.8)	15 (14.7)	1.949 (0.791–4.801)	0.147
	CAR		HR (95% CI)	*P*
	< Median (n=93)	≥ Median (n=93)		
All-cause death, no. (%)	5 (5.3)	13 (13.9)	3.217 (1.142–9.064)	0.027
	PLR		HR (95% CI)	*P*
	< Median (n=109)	≥ Median (n=109)		
All-cause death, no. (%)	11(12)	13 (11.9)	1.060 (0.483–2.325)	0.885

Abbreviations: CAR, c-reactive protein-to-albumin ratio; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; HR, hazard ratio; PLR, platelet-to-lymphocyte ratio.

96 (36.2%) took ACEI or ARB, 123 (46.4%) took beta blocker, 115 (44.3%) took calcium channel blocker, and 149 (56.2%) took lipid lowering agent. The post hoc analysis model showed no statistically significant difference in NLR and PLR levels and all-cause death (P=0.562 and P=0.647 for trend, respectively). But a higher CAR level corresponded to a higher risk of all-cause death (P<0.001 for trend) (Supplementary Table 11).

Discussion

Patients with CAD complicated with COVID-19 generally exhibit varying degrees of expression of inflammation in their bodies. The NLR and CAR effectively predicted the risk of all-cause death, while the PLR failed to predict it. In the multivariate Cox proportional hazard model with all-cause mortality as the outcome, only the CAR was included in the final model. The fourth level of the CAR was 19.638 times the risk of the first level, and the higher the CAR level was, the greater the risk of all-cause death was. In a multifactorial Cox proportional hazard model with the outcomes of cardiovascular death and respiratory failure death, the higher the CAR level was, the greater the risk of cardiovascular death and respiratory failure death were. However, changes in NLR and PLR levels did not affect the risk of all-cause death, cardiovascular death, and respiratory failure death. The outcome of all-cause death after PSM was consistent with the total cohort.

There have been several studies evaluating the efficacy of the NLR, CAR, and PLR in patients with CAD or COVID-19, and showed that these inflammatory scores have good clinical utility in predicting all-cause mortality in CAD or COVID-19.[4–8,12–17] However, few studies evaluated whether these inflammatory scores could effectively predict the prognosis for patients with CAD complicated with COVID-19.

This present study found that the NLR and CAR had predictive values for all-cause death, with the AUC value of CAR greater than 0.7 indicating acceptable accuracy. However, there was no significant statistical difference in predictive value between the two, and the PLR did not effectively predict all-cause death. In the univariate Cox proportional hazard model with all-cause death as the outcome, the higher the NLR level was, the greater the risk of all-cause death was. However, in the multivariate Cox proportional hazard model using forward likelihood ratio method, NLR was excluded from the final model. Similarly, the level of NLR was not correlated with the risk of respiratory failure and cardiovascular death, indicating that when patients with the co-presentation of CAD and COVID-19, the NLR's assessment of the risk of all-cause death, including cardiovascular death and respiratory failure death, was not as strong as when CAD or COVID-19 exist alone. Part of the explanation may be attributed to the decreasing trend in lymphocyte count in COVID-19 infected patients,[22,23] and the recent high attention to the neutrophil extracellular traps hypothesis also suggested that high expression of neutrophils was a common phenomenon in COVID-19 infection,[24–26] where the NLR is elevated in all COVID-19 patients. Therefore, the generalization of high inflammatory status in these patients masks the risk of low-grade inflammatory changes brought about by coronary artery disease. Another possible explanation is that previous

studies[4,27,28] evaluated NLR levels and the long-term prognosis of all-cause mortality and cardiovascular events, but this study evaluated the outcome events for patients with CAD during hospitalization. It is worth noting that the rupture of acute coronary plaques or imbalanced blood oxygen supply may lead to drastic changes in the level of inflammation in the body.[12] However, only 25 cases in the population included in this study belong to ACS, leading to a decrease in the evaluation effectiveness of NLR. Interestingly, after manually removing CAR from the multivariate Cox proportional hazard model for all-cause death, The NLR was included in the final model (Supplementary Table 12), indicating a correlation between NLR and all-cause death, but not as strong as CAR.

CAR is composed of the CRP and albumin, with CRP widely recognized as one of the strongest risk indicators for predicting cardiovascular disease. Although elevated CRP titer is not common in viral infections, it has been proven to be a reliable marker of COVID-19 infection and death. A study found that in patients with COVID-19, for every 50 units increased in CRP, the probability of death increased by nearly 42%, and for every 100 units increased in CRP, the mortality rate doubled.[29] Albumin is the main component of plasma viscosity, negatively correlated with red blood cell aggregation, and inhibits platelet activation and aggregation. It is also considered to be an antioxidant that can prevent damage to vascular endothelium by oxygen free radicals, and has good predictive value for cardiovascular risk.[30] At the same time, it could bind and inactivate many inflammatory promoters, such as pathogen-related molecular patterns, bioactive lipid metabolites, reactive oxygen species, and nitric oxide. A recent meta-analysis[31] also further confirmed that CAR was a good predictor of mortality risk in patients with COVID-19. The good adaptability of CAR to changes in these two diseases may explain its best performance in the present study.

The value of PLR in evaluating patient prognosis in this study was disappointing. Earlier, we evaluated the risk of major cardiovascular adverse events during hospitalization in patients with acute myocardial infarction and found that the predictive value of PLR was not as good as the combined indicator of the CRP and albumin.[10] Therefore, this may also be partly attributed to the fewer ACS and shorter observation times among the included patients in this study.

This study included a CAD cohort that included ACS and CCS, but in the subgroup analyses, there were no statistical differences between the groups. We also used the propensity score matching method to fully balance the baseline data between groups. In addition, we further included more confounding variables for a post hoc analysis. These results were consistent with the multivariate Cox hazard proportion model, indicating that our results were robust. There are some limitations in this clinical study. Firstly, the baseline data included had biases between groups, but after multivariate Cox regression analyses, subgroup analyses, and propensity score matching, similar results were still obtained. In addition, we only observed the risk of death during hospitalization, and long-term follow-up will provide a more comprehensive assessment.

Conclusions

In patients with CAD complicated with COVID-19, higher levels of CAR were associated with a higher risk of all-cause death, cardiovascular death, and respiratory failure death during hospitalization, while trends in NLR and PLR did not affect these mortality risks. Large-scale and prospective clinical trials still need to be conducted to determine the clinical utility of these inflammatory scores in patients with the co-presentation of CAD and COVID-19.

Ethical Approval and Consent to Participate

All procedures performed in studies involving human participants were following the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for Publication

This study was a retrospective cohort study, and an exemption from the informed consent requirement was approved by the ethics committee of Hangzhou Red Cross Hospital (Ethical Application Ref: 2023YS112).

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Disclosure

The authors declare that they have no conflicts of interest for this work.

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