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RESEARCH ARTICLE

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Study on the predictive value of laboratory inflammatory markers and blood count-derived inflammatory markers for disease severity and prognosis in COVID-19 patients: a study conducted at a university-affiliated infectious disease hospital

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ABSTRACT

Background: Since the outbreak of coronavirus disease 2019 (COVID-19), studies have found correlations between blood cell count-derived inflammatory markers (BCDIMs) and disease severity and prognosis in COVID-19 patients. However, there is currently a lack of systematic comparisons between procalcitonin (PCT), C-reactive protein (CRP), C-reactive protein-to-albumin ratio (CAR) and BCDIMs for assessing the severity and prognosis of COVID-19 patients.

Methods: A total of 1040 COVID-19 patients were included in the study. Demographics, comorbidities and laboratory results were analysed. BCDIMs refer to the following ratios: neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-C-reactive protein ratio (LCR), systemic inflammation response index (SIRI) and systemic inflammation index (SII). Disease severity and 28-day mortality are clinical outcomes of this study. Area under the curve (AUC) of receiver operating characteristic (ROC) curve was calculated for these markers, and DeLong's test compared their statistical differences. Cox regression analysis assessed their predictive value for the 28-day mortality rate.

Results: Among the 1040 patients, 35.3% were severe/critical, 49.6% were moderate and 15.1% were mild cases. Within 28 days, 15.1% died. The NLR had the highest predictive value for disease severity (AUC: 0.790, 95% CI: 0.762–0.818). NLR differed significantly from other markers, except LCR. LCR best predicted 28-day mortality (AUC: 0.798, 95% CI: 0.766–0.829). Some markers showed significant differences in AUC with LCR. Multivariable Cox regression identified BCDIMs, PCT, CRP and CAR as significant risk factors for 28-day mortality.

Conclusions: PCT, CRP, CAR and BCDIMs, easily obtained in clinical settings, are valuable predictors of disease severity and the 28-day mortality in COVID-19 patients. The NLR is particularly effective for disease severity, while the LCR is highly predictive of 28-day mortality. These markers provide guidance for stratified management of COVID-19 patients.

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Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and its emergence has had a profound impact on the world [1,2]. COVID-19 vaccination plays a crucial role in controlling the epidemic and protecting individual health [3,4]. Additionally, with the continuous mutation of virus strains, the currently predominant Omicron variant exhibits a reduced virulence compared to the original strain, leading to a decrease in the mortality rate among the population [5]. In May 2023, the World Health Organization (WHO) declared an end to the public health emergency related to COVID-19 [6]. However, the virus continues to be in a phase of ongoing transmission, with seasonal peaks occurring. Early identification of critically ill patients and the implementation of risk-stratified prognostic markers can help optimize the allocation of medical resources and improve the clinical prognosis of patients [7–9].

The emergence of COVID-19 has attracted great attention, and many clinical factors and laboratory indicators have been found to be associated with the severity of the disease and poor prognosis in patients. For example, factors such as patient age, diabetes, cardiovascular disease and pulmonary disease have been identified as relevant clinical factors [10,11]. Additionally, elevated levels of laboratory parameters such as lymphocyte levels, procalcitonin (PCT), C-reactive protein (CRP), D-dimer, ferritin, lactate dehydrogenase and IL-6 have been observed [12–15].

The combination of multiple laboratory indicators for the prediction of inflammation is receiving increasing attention, as it can provide a more comprehensive reflection of the patient's inflammatory status. Blood cell count-derived inflammatory markers (BCDIMs): NLR, MLR, PLR, LCR, SIRI and systemic inflammation index (SII) have been found to be significantly associated with systemic inflammation [16–19]. They have also been reported for predicting the prognosis of COVID-19 patients [20–24]. Furthermore, studies have indicated a correlation between C-reactive protein-to-albumin ratio (CAR) and clinical outcomes in COVID-19 patients [25–27]. However, there is currently a lack of research that provides a comprehensive comparison of these indicators for predicting the severity and prognosis of COVID-19 patients.

To address this question, we conducted a retrospective cohort study at an affiliated infectious disease hospital at a university. We analysed a large set of clinical and laboratory parameters from a group of patients infected with SARS-CoV-2 and compared the predictive efficacy of PCT, CRP, CAR and BCDIMs: NLR, MLR, PLR, LCR, SIRI and SII, for assessing the severity and prognosis of COVID-19 patients.

Patients and methods

Study design and participants

We conducted a retrospective study involving 1040 COVID-19 patients admitted to Beijing You'an Hospital Affiliated with Capital Medical University between 1 May 2022 and 31 May 2023. According to the diagnostic guidelines of the National Health Commission of China for COVID-19 patients (Provisional 9th Edition) [28], diagnosing COVID-19 patients relies on polymerase chain reaction (PCR) testing for viral nucleic acid. The patients were classified into categories of mild/moderate and severe/critical cases of COVID-19 based on the treatment guidelines for COVID-19 recommended by the National Institutes of Health (source: https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/).

The aim of this study was to evaluate the predictive value of inflammatory laboratory markers and BCDIMs at admission for disease severity and prognosis in COVID-19 patients. We analysed the data from the first laboratory tests within the first three days after admission. The primary outcome measure was mortality within 28 days. For disease severity, we categorized patients into two groups: severe/critical disease vs. mild/moderate disease. The study obtained approval from the Ethics Committee of Beijing Youan Hospital and adhered to the principles of the Helsinki Declaration (Approval No. LL-2023-092-K). Due to the retrospective nature of this study and the anonymization of the data used, the ethics committee approved a waiver of informed consent.

Inclusion and exclusion criteria

Inclusion criteria: (i) Patients who met the diagnostic criteria outlined in the National Health Commission's guidelines for COVID-19 patients (Provisional 9th Edition) [28].

Exclusion criteria: (i) Patients without complete blood routine examination results within three days of hospitalization. (ii) Patients under 18 years of age. (iii) Patients who died within 48 h of hospitalization. (iv) Pregnant women.

Among the 1664 patients admitted to our hospital, 624 cases were excluded. The primary reason for exclusion was the absence of complete blood routine examination results within the first three days of hospitalization. Ultimately, 1040 patients met the

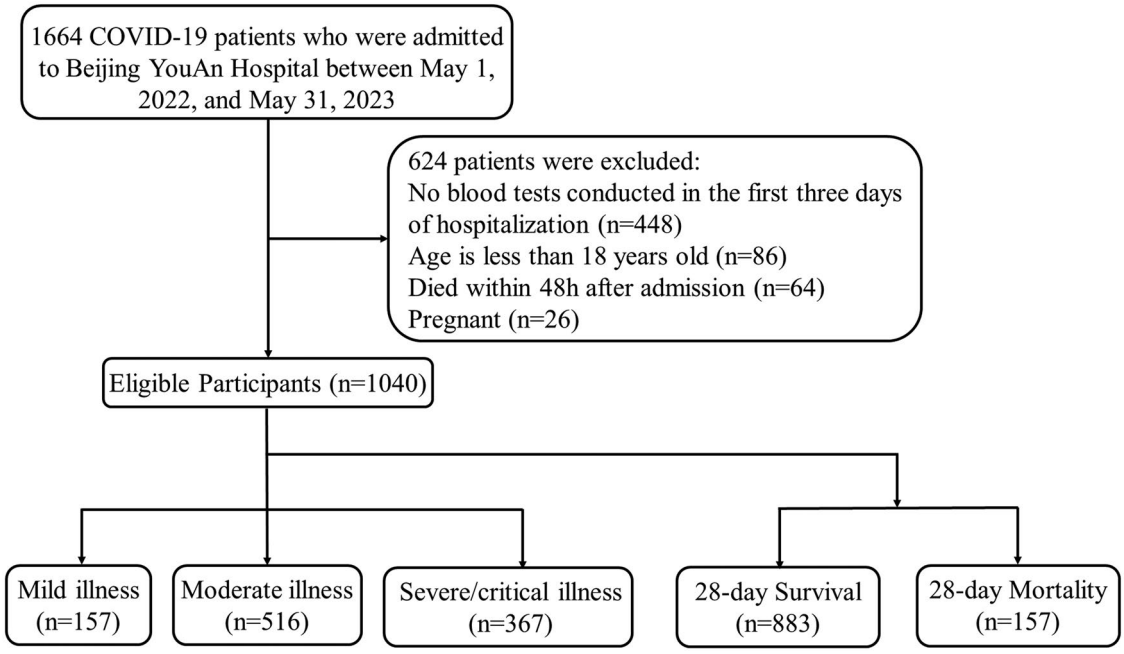

Figure 1. Flow diagram of patients enrolment.

criteria for further analysis and were included in the study, as shown in Figure 1.

Data collection

Demographic data, comorbidities, laboratory data and prognosis were extracted from electronic medical records. Disease severity classification was based on the guidelines of the 'Provisional 9th Edition' for the diagnosis and treatment of COVID-19 patients [28]. These classifications included asymptomatic infection, mild disease, moderate disease, severe disease and critical disease, with asymptomatic infections being excluded. The comorbidities considered in the study included hypertension, diabetes mellitus (DM), coronary artery disease, cerebrovascular disease, chronic obstructive pulmonary disease (COPD), liver disease and malignant tumours. Laboratory parameters include infection-related indicators, complete blood cell count (CBC), coagulation function, cardiac function and biochemical tests. Estimated glomerular filtration rate (eGFR) (mL/(min × 1.73 m^2]) = 175 × $(Scr)^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 for females). Refer to Table 1 for details.

The definition of blood count-derived inflammatory markers

BCDIMs are specific inflammatory markers that are derived from routine blood count tests. They provide valuable information about the presence and severity of inflammation in the body. These include: NLR (neutrophil-to-lymphocyte ratio), MLR (monocyte-to-lymphocyte ratio), PLR (platelet-to-lymphocyte ratio), LCR (lymphocyte-to-C-reactive protein ratio), SIRI (systemic inflammation response index) and SII (systemic immune-inflammation index). SIRI is calculated as (neutrophil count × monocyte count)/lymphocyte count, and SII is calculated as (neutrophil count × platelet count)/lymphocyte count.

Statistical analysis

The normality of continuous variables was assessed using the Shapiro–Wilk test. Normally distributed continuous variables were reported as mean ± standard deviation (SD) and compared using independent samples Student's *t*-test. Non-normally distributed continuous variables were reported as median and interquartile range (IQR) and compared using the Mann–Whitney *U*-test. Categorical variables were reported as counts and percentages and compared using Pearson's Chi-square test or Fisher's exact test. The Kruskal–Wallis test was used to compare multiple samples using non-parametric analysis. Variables with a *p* value less than .05 were considered statistically significant. The predictive performance of the 28-day mortality rate in COVID-19 patients was evaluated using receiver operating characteristic (ROC) curve analysis. The cut-off value, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy and Youden's index were also recorded. AUC values provide a measure of discriminatory power: an AUC of 0.5

Table 1. Baseline characteristics and clinical data after hospitalization of study population.

Variables	Total (n = 1040)	28-day survival (n = 883)	28-day mortality (n = 157)	p Value
Demographic data				
Sex, male, n (%)	624 (60%)	517 (59%)	107 (68%)	.024*
Age, years	71 (62, 83)	70 (60, 81)	82 (71, 88)	<.001*
Co-morbidities				
Hypertension, n (%)	506 (49%)	413 (47%)	93 (59%)	.004*
Diabetes mellitus, n (%)	288 (28%)	234 (27%)	54 (34%)	.042*
Coronary heart disease, n (%)	220 (21%)	181 (20%)	39 (25%)	.220
Cerebrovascular disease, n (%)	115 (11%)	81 (9.2%)	34 (22%)	<.001*
COPD, n (%)	91 (8.8%)	76 (8.6%)	15 (9.6%)	.657
Liver disease, n (%)	89 (8.6%)	77 (8.7%)	12 (7.6%)	.237
Malignant tumour, n (%)	127 (12%)	107 (12%)	20 (13%)	.827
COVID-19 severity class, n (%)				<.001*
Mild illness	157 (15%)	151 (17%)	6 (4%)	
Moderate illness	517 (50%)	485 (55%)	32 (20%)	
Severe/critical illness	366 (35%)	247 (28%)	119 (76%)	
Laboratory parameters				
PCT, ng/mL	0.08 (0.04, 0.3)	0.06 (0.04, 0.170)	0.36 (0.13, 1.14)	<.001*
CRP, mg/L	36 (10, 76)	26 (7, 65)	77 (53, 105)	<.001*
HGB, g/L	123 (108, 136)	124 (108, 138)	123 (105, 135)	.366
WBC count, $\times 10^9$/L	5.78 (4.11, 8.54)	5.38 (3.88, 7.60)	8.45 (5.90, 11.27)	<.001*
Platelets count, $\times 10^9$/L	170 (123, 277)	169 (123, 223)	176 (120, 236)	.512
Neutrophils count, $\times 10^9$/L	4.23 (2.62, 6.83)	3.67 (2.39, 5.89)	7.02 (4.78, 9.97)	<.001*
Lymphocytes count, $\times 10^9$/L	0.87 (0.58, 1.22)	0.93 (0.63, 1.31)	0.65 (0.40, 0.96)	<.001*
ALT, U/L	23 (16, 36)	22 (15, 35)	26 (19, 39)	<.001*
AST, U/L	30 (20, 48)	27 (19, 41)	47 (31, 72)	<.001*
Albumin, g/L	32.7 (28.1, 36.1)	34.8 (30.8, 37.5)	27.9 (25.3, 31.9)	<.001*
TBIL, μmol/L	10.8 (7.9, 15.5)	10.4 (7.7, 15.2)	11.8 (8.5, 17.8)	.005*
DBIL, μmol/L	4.7 (3.1, 7.55)	4.3 (2.9, 6.8)	6.3 (4.2, 9.58)	<.001*
INR	1.09 (1.04, 1.19)	1.08 (1.03, 1.19)	1.14 (1.05, 1.23)	<.001*
D-dimer, mg/L	359 (165, 1018)	291 (136, 625)	1231 (481, 4256)	<.001*
Prothrombin time activity (%)	85 (74, 94)	87 (76, 95)	80 (70, 92)	<.001*
Blood urea nitrogen, mmol/L	5.7 (4.2, 8.9)	5.3 (3.9, 7.4)	8.9 (6.1, 14.1)	<.001*
Creatinine, μmol/L	72 (58, 94)	70 (57, 88)	82 (66, 134)	<.001*
eGFR, mL/min/1.73 m^2	82 (62, 95)	86 (69, 97)	67 (43, 84)	<.001*
BNP, pg/mL	391 (101, 1569)	227 (78, 717)	1646 (519, 4836)	<.001*
CAR	1.287 (0.328, 2.688)	0.852 (0.225, 2.158)	2.849 (1.736, 3.705)	<.001*
BCDIMs				
NLR	4.96 (2.56, 10.28)	3.90 (2.18, 7.78)	10.99 (6.62, 19.70)	<.001*
MLR	0.44 (0.29, 0.72)	0.42 (0.287, 0.67)	0.63 (0.36, 1.00)	<.001*
PLR	184 (120, 309)	175 (114, 272)	285 (150, 431)	<.001*
LCR	0.025 (0.009, 0.109)	0.036 (0.013, 0.157)	0.008 (0.005, 0.016)	<.001*
SIRI	1.72 (0.77, 4.01)	1.48 (0.70, 3.45)	4.05 (2.04, 7.74)	<.001*
SII	826 (348, 2127)	654 (296, 1441)	2386 (1015, 5489)	<.001*
Treatment-related information				
Hospital stay, days	11 (7, 15)	11 (7, 15)	8 (5, 14)	<.001*
Inhalation oxygen with facemask	219 (21%)	151 (17%)	68 (43%)	<.001*
Optiflow	116 (11%)	62 (7%)	54 (34%)	<.001*
Non-invasive ventilation	48 (5%)	18 (2%)	30 (19%)	<.001*
Invasive ventilation	210 (20%)	141 (16%)	69 (44%)	<.001*

COPD: chronic obstructive pulmonary disease; PCT: procalcitonin; CRP: C-reactive protein; HGB: haemoglobin; WBC: white blood cell; INR: international normalized ratio; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TBIL: total bilirubin; DBIL: direct bilirubin; INR: international normalized ratio; eGFR: estimated glomerular filtration rate; BNP: B-type natriuretic peptide; CAR: C-reactive protein-to-albumin ratio; BCDIMs: blood count-derived inflammatory markers; NLR: neutrophil-to-lymphocyte ratio; MLR: monocyte-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; LCR: lymphocyte-to-C-reactive protein ratio; SIRI: systemic inflammation response index; SII: systemic inflammation index.

SIRI = (neutrophil count × monocyte count)/lymphocyte count; SII = (neutrophil count × platelet count)/lymphocyte count; eGFR (mL/(min × 1.73 m^2)) = 175 × $(Scr)^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 for females).

Normally distributed continuous variables are displayed as mean ± standard deviation (SD) and were compared using the independent-samples Student's t-test. Non-normally distributed continuous variables are displayed as a median with interquartile range (IQR) and were compared using the Mann–Whitney U-test. Categorical variables are expressed as counts with percentages and were compared using Pearson's chi-square or Fisher's exact test.

*p Value <.05 was considered significant.

indicates no discriminatory power, 0.5–0.7 suggests poor to fair ability, 0.7–0.8 indicates reasonable ability, 0.8–0.9 suggests good ability, and an AUC greater than 0.9 indicates excellent discriminatory power. DeLong's test was used to compare whether there were statistically significant differences in the AUC for predicting the severity of the disease and 28-day mortality among different inflammatory markers. Spearman's rank correlation analysis was used to assess the correlation between age, laboratory inflammatory markers and BCDIMs.

When the absolute value of the correlation coefficient (r) is closer to 1, it indicates a stronger correlation between two indicators. Additionally, a p value less than .05 indicates a statistically significant correlation. Multivariable Cox regression analysis and

Table 2. AUC for predicting disease severity and prognosis in COVID-19 patients using laboratory inflammatory markers and BCDIMs.

Variables	AUC	Standard error	*p* Value	95% confidence interval	
				Lower limit	Upper limit
Predicting disease severity					
PCT, ng/mL	0.72	0.022	<.001*	0.69	0.75
CRP, mg/L	0.72	0.021	<.001*	0.69	0.76
NLR	0.79	0.019	<.001*	0.76	0.82
MLR	0.64	0.022	<.001*	0.60	0.68
PLR	0.67	0.022	<.001*	0.64	0.70
LCR	0.76	0.020	<.001*	0.73	0.79
CAR	0.72	0.020	<.001*	0.69	0.76
SIRI	0.71	0.022	<.001*	0.67	0.75
SII	0.75	0.021	<.001*	0.72	0.78
Predicting prognosis					
PCT, ng/mL	0.76	0.025	<.001*	0.73	0.80
CRP, mg/L	0.78	0.023	<.001*	0.75	0.81
NLR	0.79	0.025	<.001*	0.76	0.82
MLR	0.64	0.030	<.001*	0.58	0.70
PLR	0.66	0.031	<.001*	0.61	0.70
LCR	0.80	0.023	<.001*	0.77	0.83
CAR	0.78	0.023	<.001*	0.75	0.82
SIRI	0.71	0.028	<.001*	0.66	0.77
SII	0.75	0.028	<.001*	0.72	0.79

AUC: area under the receiver operating characteristic curve; BCDIMs: blood count-derived inflammatory markers; PCT: procalcitonin; CRP: C-reactive protein; NLR: neutrophil-to-lymphocyte ratio; MLR: monocyte-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; LCR: lymphocyte-to-C-reactive protein ratio; CAR: C-reactive protein-to-albumin ratio; SIRI: systemic inflammation response index; SII: systemic inflammation index.
SIRI = (neutrophil count × monocyte count)/lymphocyte count; SII = (neutrophil count × platelet count)/lymphocyte count.
*p Value <.05 was considered significant.

Kaplan–Meier's curves were used to evaluate the parameter risk prediction for the 28-day mortality rate in COVID-19 patients. In the Cox regression analysis, PCT, CRP, CAR and BCDIMs were divided into two groups based on cut-off values determined by ROC analysis. Data analysis was performed using SPSS software (version 22.0; IBM Corp., Armonk, NY) and R language (version 4.2.1; R Foundation for Statistical Computing, Vienna, Austria), and visualization was done using GraphPad Prism 9 (GraphPad Software Inc., La Jolla, CA).

Results

Clinical parameters upon admission and treatment-related information of the patients

Among the included 1040 patients, 367 cases (35.3%) were classified as severe or critical, 516 cases (49.6%) as moderate and 157 cases (15.1%) as mild. Furthermore, 157 cases (15.1%) of patients ultimately died within 28 days after admission.

Table 1 describes the baseline characteristics and clinical parameters of the patients. Among them, 624 cases (60%) were male, with a median age of 71 years. As shown in Table 1, there were significant statistical differences in demographic data, co-morbidities, disease severity, laboratory indicators, BCDIMs and treatment-related parameters between patients who died within 28 days and those who survived.

Blood count-derived inflammatory markers have demonstrated good predictive value for disease severity and prognosis in COVID-19 patients

We analysed the predictive performance of BCDIMs, PCT, CRP and CAR for disease severity and 28-day mortality in COVID-19 patients, as illustrated in ROC curves (Figure S1) and Table 2. For disease severity (Figure S1A and Table 2), NLR demonstrated the best predictive value with an AUC of 0.79 (95% CI: 0.76–0.82). For disease prognosis (Figure S1B and Table 2), the LCR exhibited the best predictive performance with an AUC of 0.80 (95% CI: 0.77–0.83).

We also compared the value of different indicators for predicting disease severity and patient prognosis using statistical methods (DeLong's test), as shown in Table 3. The NLR and PCT, CRP, MLR, PLR, CAR, SIRI and SII all showed statistically significant differences in predicting disease severity (AUC) ($p < .05$), except for LCR ($p = .1275$). For patient prognosis prediction, LCR demonstrated statistical differences in AUC compared to CRP, MLR, PLR and SIRI ($p < .05$), while there were no statistical differences in AUC between LCR and PCT, NLR, CAR and SII ($p = .1764$, .7628, .5711 and .0818, respectively). Table 4 presents specific information regarding the predictive value of different indicators, such as optimal cut-off values and Youden's index.

Correlation between age, inflammatory laboratory markers and BCDIMs

The correlations and corresponding p values among age, inflammatory laboratory markers and BCDIMs, totalling 26 indicators, are displayed in the heatmap shown in Figure 2(A,B). For example, age has significant correlations with PCT ($r = 0.09$, $p = .003$), NLR ($r = 0.12$, $p < .001$) and PLR ($r = 0.11$, $p < .001$). However, there is no significant correlation between age and CRP ($r = -0.04$, $p = .590$) or MLR ($r = 0.05$, $p = .117$).

Inflammatory laboratory markers and BCDIMs are predictive factors for the risk of 28-day mortality in hospitalized COVID-19 patients

We evaluated the predictive value of PCT, CRP, CAR and BCDIMs for patient survival at 28 days using both

Table 3. Comparing the AUC for different clinical parameters for disease severity and prognosis in COVID-19 patients.

Variables	PCT	CRP	NLR	MLR	PLR	LCR	CAR	SIRI	SII
Predicting disease severity									
PCT	**AUC = 0.718**								
CRP	$p = .8789$	**AUC = 0.722**							
NLR	$p = .0015$	$p = .0020$	**AUC = 0.790**						
MLR	$p = .0043$	$p = .0023$	$p < .0001$	**AUC = 0.641**					
PLR	$p = .0483$	$p = .0303$	$p < .0001$	$p = .2956$	**AUC = 0.669**				
LCR	$p = .0943$	$p < .0001$	$p = .1275$	$p < .0001$	$p = .0002$	**AUC = 0.758**			
CAR	$p = .8434$	$p = .9619$	$p = .0026$	$p = .0022$	$p = .0285$	$p = .1371$	**AUC = 0.723**		
SIRI	$p = .6225$	$p = .5211$	$p = .0006$	$p < .0001$	$p = .1791$	$p = .0406$	$p = .4970$	**AUC = 0.705**	
SII	$p = .1765$	$p = .2206$	$p < .0001$	$p < .0001$	$p < .0001$	$p = .7477$	$p = .2448$	$p = .0801$	**AUC = 0.750**
Predicting prognosis									
PCT	**AUC = 0.764**								
CRP	$p = .5965$	**AUC = 0.778**							
NLR	$p = .2941$	$p = .5828$	**AUC = 0.791**						
MLR	$p = .0003$	$p < .0001$	$p < .0001$	**AUC = 0.639**					
PLR	$p = .0002$	$p < .0001$	$p < .0001$	$p = .6568$	**AUC = 0.655**				
LCR	$p = .1764$	$p = .0372$	$p = .7628$	$p < .0001$	$p < .0001$	**AUC = 0.798**			
CAR	$p = .4246$	$p = .7747$	$p = .7941$	$p < .0001$	$p < .0001$	$p = .5711$	**AUC = 0.784**		
SIRI	$p = .1206$	$p = .0438$	$p = .0154$	$p < .0001$	$p = .0921$	$p = .0076$	$p = .0261$	**AUC = 0.714**	
SII	$p = .6956$	$p = .3529$	$p = .0004$	$p = .0010$	$p < .0001$	$p = .0818$	$p = .2335$	$p = .2227$	**AUC = 0.754**

PCT: procalcitonin; CRP: C-reactive protein; NLR: neutrophil-to-lymphocyte ratio; MLR: monocyte-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; LCR: lymphocyte-to-C-reactive protein ratio; CAR: C-reactive protein-to-albumin ratio; SIRI: systemic inflammation response index; SII: systemic inflammation index.
SIRI = (neutrophil count × monocyte count)/lymphocyte count; SII = (neutrophil count × platelet count)/lymphocyte count.
The table displays the *p* values (DeLong's test) for each comparison. A *p* value less than .05 indicates a statistically significant difference in the area under the curve (AUC) between the two parameters. The diagonal contains the AUC values, which are highlighted in bold.

univariate and multivariate Cox regression analyses. The survival curves are shown in Figure 3(A–I), and specific details can be found in Table 5. PCT, CRP, CAR and BCDIMs all emerged as significant predictive factors for 28-day mortality in COVID-19 patients. Even after adjusting for covariates such as sex, age, hypertension, DM and cerebrovascular disease, these results still exhibited statistically significant differences.

Discussion

Our study included 1040 cases of COVID-19 patients for analysis, of which 157 patients died within 28 days after admission. There were significant differences in clinical parameters between the 28-day survival group and the death group. We compared the predictive efficacy of different inflammatory markers for the severity and prognosis of COVID-19 and found that the NLR showed the best predictive value for disease severity, while the LCR exhibited the best predictive performance for disease prognosis. We also analysed the correlation between age, laboratory inflammatory markers and BCDIMs. We found a low correlation between CRP and BCDIMs, while there was a high correlation between CAR and BCDIMs. Finally, our multivariate Cox regression analysis identified PCT, CRP, CAR and BCDIMs levels as risk factors for 28-day mortality in patients.

The NLR is a valuable inflammatory response marker that is clinically accessible. Previous studies have suggested its significant predictive value in various diseases, including cardiovascular diseases, COPD, pancreatitis and malignant tumours, regarding disease progression and clinical outcomes [29–34]. The release of a large number of inflammatory factors in COVID-19 patients may stimulate an increase in neutrophil count, while critically ill patients may experience lymphocyte depletion and reduction, leading to an elevated NLR

Table 4. Predicted value information of laboratory inflammatory markers and BCDIMs for disease severity and prognosis in COVID-19 patients.

Variables	Cut off value	Sensitivity	Specificity	PPV	NPV	Accuracy	Youden index
Predicting disease severity							
PCT, ng/mL	0.135	0.75	0.62	0.77	0.59	0.70	0.37
CRP, mg/L	34.8	0.62	0.74	0.80	0.53	0.66	0.36
NLR	3.97	0.58	0.85	0.87	0.54	0.68	0.43
MLR	0.45	0.59	0.62	0.79	0.385	0.62	0.21
PLR	231	0.68	0.60	0.76	0.51	0.60	0.27
LCR	0.0269	0.64	0.78	0.84	0.57	0.78	0.43
CAR	1.31	0.65	0.72	0.78	0.56	0.72	0.36
SIRI	2.56	0.72	0.61	0.82	0.47	0.61	0.33
SII	1022	0.71	0.69	0.82	0.57	0.69	0.40
Predicting prognosis							
PCT, ng/mL	0.175	0.76	0.69	0.90	0.42	0.74	0.44
CRP, mg/L	46.0	0.66	0.80	0.93	0.38	0.69	0.46
NLR	5.64	0.65	0.83	0.94	0.38	0.69	0.48
MLR	0.70	0.77	0.48	0.90	0.25	0.73	0.25
PLR	268	0.74	0.55	0.86	0.35	0.70	0.29
LCR	0.0232	0.61	0.88	0.95	0.38	0.67	0.49
CAR	1.44	0.64	0.83	0.93	0.40	0.69	0.47
SIRI	2.62	0.68	0.69	0.93	0.26	0.69	0.38
SII	1003	0.64	0.76	0.91	0.35	0.67	0.40

BCDIMs: blood count-derived inflammatory markers; PPV: positive predictive value; NPV: negative predictive value; PCT: procalcitonin; CRP: C-reactive protein; NLR: neutrophil-to-lymphocyte ratio; MLR: monocyte-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; LCR: lymphocyte-to-C-reactive protein ratio; CAR: C-reactive protein-to-albumin ratio; SIRI: systemic inflammation response index; SII: systemic inflammation index.
SIRI = (neutrophil count × monocyte count)/lymphocyte count; SII = (neutrophil count × platelet count)/lymphocyte count.

[35]. Since the emergence of COVID-19, it has been widely recognized, and numerous studies have compared the predictive value of NLR for disease severity and prognosis [34,36–38].

A meta-analysis conducted in 2020, which included 13 studies involving 1579 patients, found that the NLR had a predictive value for the severity of COVID-19, with an AUC of 0.85 (95% CI 0.81–0.88). Additionally, 10 studies involving 2967 patients assessed the predictive value of NLR on mortality, and the AUC was found to be 0.90 (95% CI 0.87–0.92) [34]. In 2022, a meta-analysis involving 90 studies also indicated that the summary receiver operating curve analysis demonstrated a significant predictive value for both mortality (AUC = 0.87; 95% CI: 0.86–0.87) and severity (AUC = 0.82; 95% CI: 0.80–0.84) [36]. In our study, the NLR showed an AUC of 0.790 (95% CI: 0.762–0.818) for predicting disease severity, and an AUC of 0.791 (95% CI: 0.758–0.823) for predicting 28-day mortality. The predictive value of NLR in our study is lower compared to the meta-analysis. A recent study has reported a similar AUC of 0.787 for predicting patient mortality, which is consistent with our research findings [39]. It is important to note that there is significant heterogeneity among the studies included in the meta-analysis, with an I^2 value greater than 80% [36]. Additionally, the optimal cut-off values for NLR vary considerably among the studies. These findings suggest that NLR is a useful indicator, but its predictive value may differ among different patient populations. Clinicians should consider its clinical significance on a case-by-case basis.

Some studies have also indicated a correlation between elevated MLR and PLR and the prognosis of COVID-19 patients [40–44]. In our study, these two indicators showed relatively lower AUC values compared to other markers, which is consistent with the findings of these studies. This further reinforces the reliability of our research. One possible reason for this difference could be the significant decrease in lymphocyte count observed in the deceased group, while the differences in monocyte and platelet counts contributed minimally. This indicates notable differences in MLR and PLR between the group of patients who survived and those who did not, but with a lower predictive value [45,46].

In our study, the LCR demonstrated a higher predictive value, which can be attributed to the decrease in lymphocyte count and the increase in CRP levels. Currently, there is limited research on the association between LCR and the prognosis of COVID-19 patients. A study conducted in 2020, which is relatively early, reported results similar to ours. In our study, the AUC for predicting 28-day mortality was 0.798 (95% CI: 0.766–0.829), while the mentioned study found an AUC of 0.817 (95% CI: 0.747–0.886) for predicting in-hospital mortality in COVID-19 patients [47]. However, a study conducted in 2023 in the emergency department found that LCR is not accurate in predicting severity and mortality [48]. The specific value of LCR requires further research [49].

SIRI includes three peripheral blood parameters: neutrophil count, monocyte count and lymphocyte

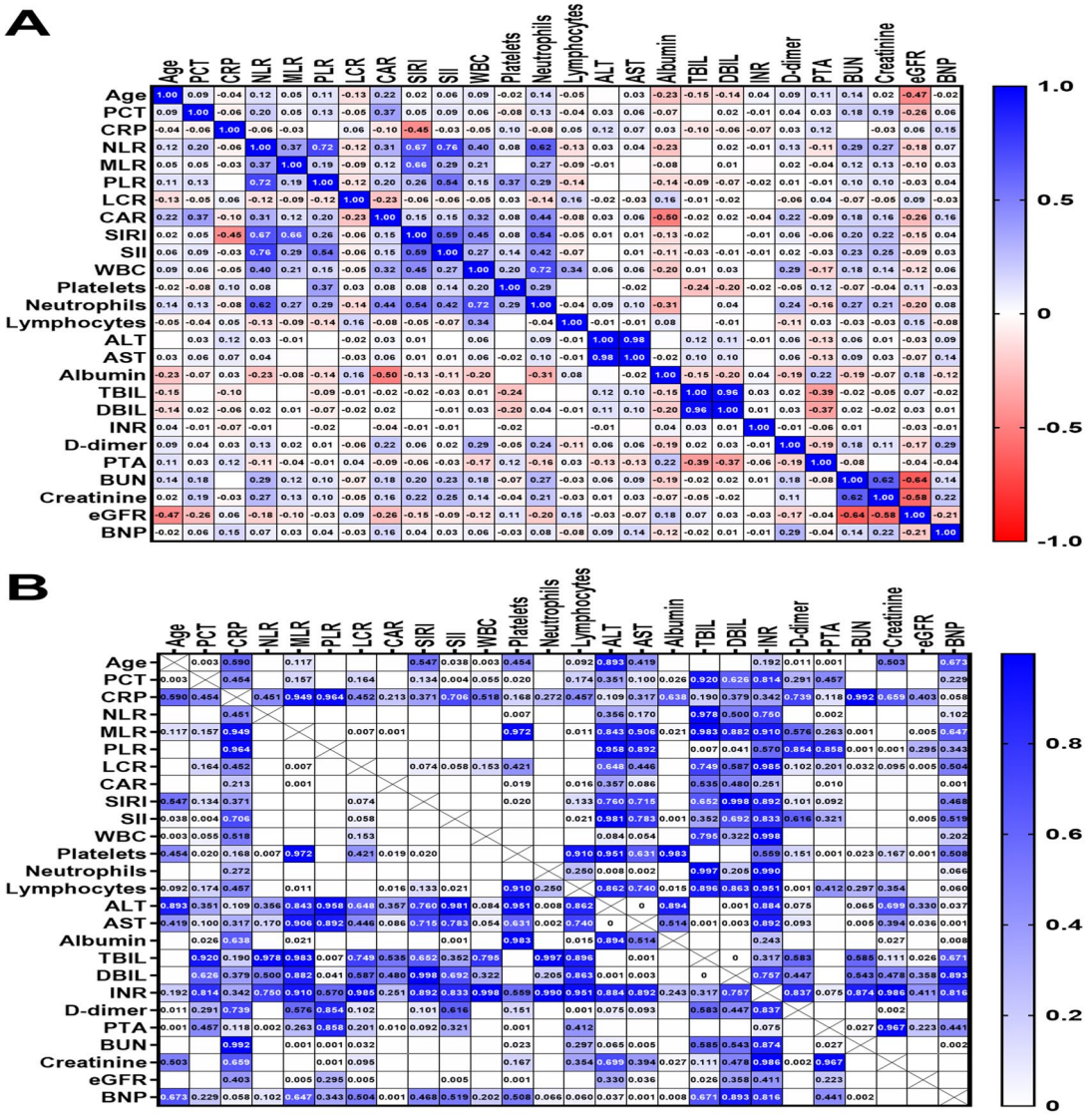

Figure 2. Heatmap depicting the correlation between age, laboratory inflammatory markers and BCDIMs. (A) The values are presented as Spearman's correlation coefficient (*r*) for a sample of 1040 runners. The colormap ranges from 1 to −1, with blue indicating the highest value and red indicating the lowest value. (B) The heatmap of corresponding *p* values. The colormap ranges from 0 to 1, with blue representing the largest value and white representing the smallest value. White cells without numerical values indicate that the *p* value is smaller than .001, indicating a highly significant correlation. PCT: procalcitonin; CRP: C-reactive protein; WBC: white blood cell; INR: international normalized ratio; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TBIL: total bilirubin; DBIL: direct bilirubin; INR: international normalized ratio; eGFR: estimated glomerular filtration rate; BNP: B-type natriuretic peptide; BCDIMs: blood count-derived inflammatory markers; NLR: neutrophil-to-lymphocyte ratio; MLR: monocyte-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; LCR: lymphocyte-to-C-reactive protein ratio; CAR: C-reactive protein-to-albumin ratio; SIRI: systemic inflammation response index; SII: systemic inflammation index. SIRI = (neutrophil count × monocyte count)/lymphocyte count; SII = (neutrophil count × platelet count)/lymphocyte count.

count. SII includes three peripheral blood parameters: neutrophil count, platelet count and lymphocyte count. Both of these indices are important in assessing the severity and predicting outcomes of sepsis [50,51]. SII has also been shown to be associated with poor survival rates in various solid tumours and adverse prognosis in cardiovascular-related diseases [52–54]. Since the emergence of COVID-19, studies have also found correlations between these two indices and disease severity and prognosis in COVID-19 patients [6,55–63]. In our study, we found that SII and SIRI, although incorporating three parameters, had lower predictive value compared to NLR and LCR. Similar conclusions have been drawn by other studies [6,56]. However, overall, SII and SIRI show good predictive value for disease severity and prognosis in COVID-19 patients.

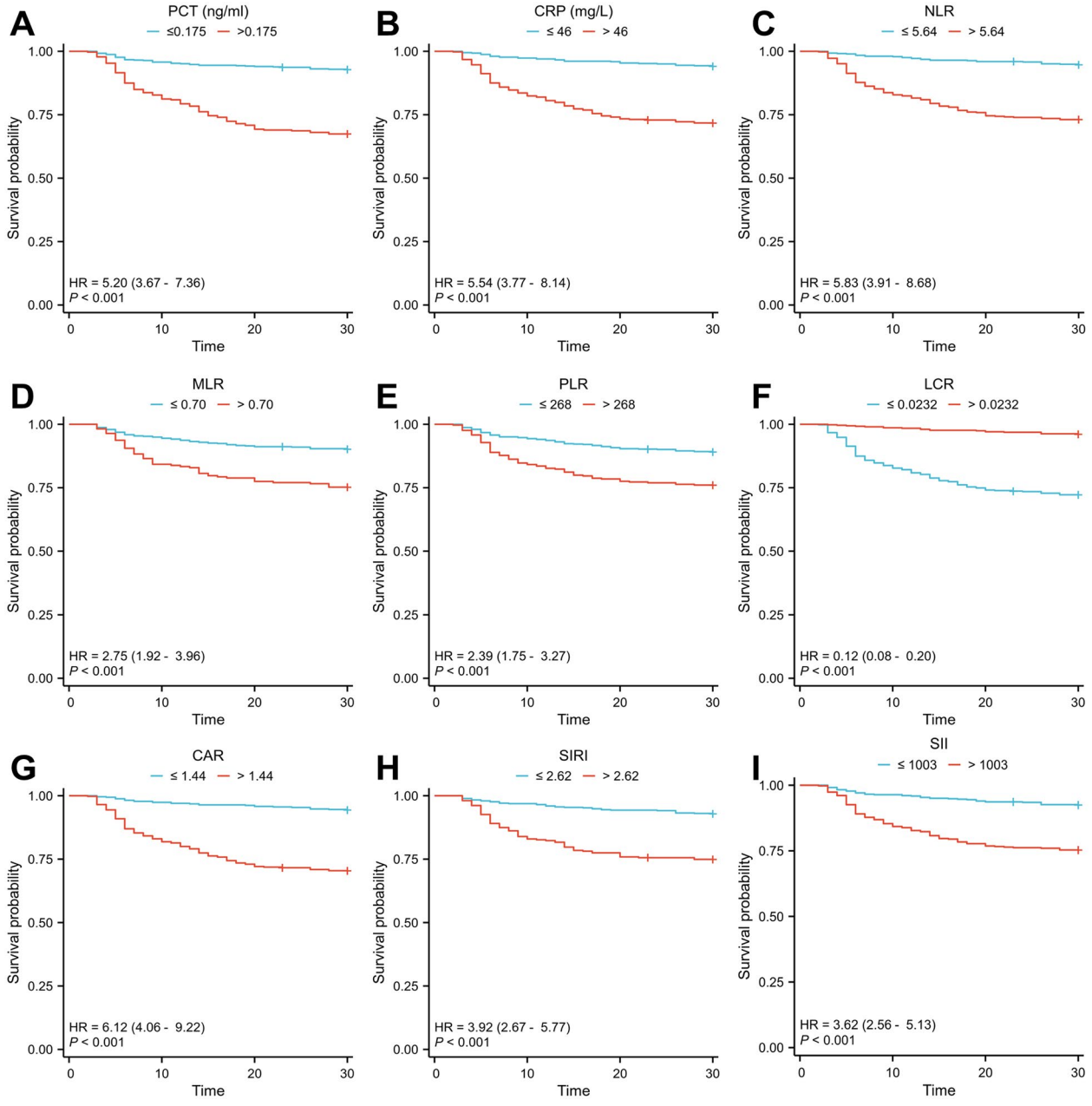

Figure 3. Kaplan–Meier's curves for 28-day survival categorized by laboratory inflammatory markers and BCDIMs. The grouping is based on the optimal cut-off value. PCT (A), CRP (B), NLR (C), MLR (D), PLR (E), LCR (F), CAR (G), SIRI (H) and SII (I). BCDIMs: blood count-derived inflammatory markers; PCT: procalcitonin; CRP: C-reactive protein; NLR: neutrophil-to-lymphocyte ratio; MLR: monocyte-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; LCR: lymphocyte-to-C-reactive protein ratio; CAR: C-reactive protein-to-albumin ratio; SIRI: systemic inflammation response index; SII: systemic inflammation index. SIRI = (neutrophil count × monocyte count)/lymphocyte count; SII = (neutrophil count × platelet count)/lymphocyte count.

The CAR is an available biomarker that possesses the clinical advantage of being easily obtainable due to the widespread use of CRP and albumin in most healthcare centres. However, a consensus on the normal range for CAR has not been reached thus far [64]. Previous studies have found associations between CAR and prognosis in cardiovascular diseases, sepsis and various malignant tumours [65–67]. It is now being used as a novel predictive marker for COVID-19 patients [68–70]. A recent meta-analysis also concluded that the CAR values upon admission were higher in critically ill COVID-19 patients compared to non-critically ill COVID-19 patients (MD: 1.69; 95% CI: 1.35–2.03; $p < .001$; $I^2 = 89\%$); the CAR values in non-surviving COVID-19 patients were higher than those in surviving patients (MD: 2.59; 95% CI: 1.95–3.23; $p < .001$; $I^2 = 92\%$) [25].

In summary, our study included over 1000 COVID-19 patients and systematically compared multiple BCDIMs

Table 5. Risk factors for 28-day mortality in COVID-19 patients.

	UV		MV	
Variables	HR (95% CI)	*p*-Value	Adjusted HR (95% CI)	*p*-Value
PCT, ng/mL				
≤ 0.175				
> 0.175	5.2 (3.7–7.4)	<0.001*	4.4 (3.1–6.3)	<0.001*
CRP, mg/L				
≤ 46				
> 46	5.5 (3.8–8.1)	<0.001*	4.5 (3.05–6.6)	<0.001*
NLR				
≤ 5.64				
> 5.64	5.8 (3.9–8.7)	<0.001*	5.0 (3.4–7.5)	<0.001*
MLR				
≤ 0.70				
> 0.70	2.8 (1.9–4.0)	<0.001*	2.4 (1.7–3.5)	<0.001*
PLR				
≤ 268				
> 268	2.4 (1.7–3.3)	<0.001*	2.2 (1. 6–3.0)	<0.001*
LCR				
≤ 0.0232				
> 0.0232	0.12 (0.08–0.20)	<0.001*	0.15 (0.09–0.25)	<0.001*
CAR				
≤ 1.44				
> 1.44	6.1 (4.1- 9.2)	<0.001*	5.1 (3.4–7.8)	<0.001*
SIRI				
≤ 2.62				
> 2.62	3.9 (2.7–5.8)	<0.001*	3.4 (2.3–5.1)	<0.001*
SII				
≤ 1003				
> 1003	3.6 (2.6–5.1)	<0.001*	3.1 (2.2–4.4)	<0.001*

Performed with Sex, Age, Hypertension, Diabetes mellitus and Cerebrovascular disease as covariates. Cox regression analyses was performed on 1040 COVID-19 patients. Abbreviations: UV, Univariate Analysis; MV, Multivariate Analysis; HR, Hazard Ratio; PCT, Procalcitonin; CRP, C-reactive protein; NLR, Neutrophil-to-lymphocyte ratio; MLR, Monocyte-to-lymphocyte ratio; PLR, Platelet-to-lymphocyte ratio; LCR, Lymphocyte-to-C-reactive protein ratio; CAR, C-reactive protein-to-albumin ratio; SIRI, Systemic inflammation response index; SII: Systemic inflammation index. SIRI = (Neutrophil count × Monocyte count) / Lymphocyte count; SII = (Neutrophil count × Platelet count) / Lymphocyte count. **p*-Value <0.05 was considered significant.

with CAR, PCT and CRP for predicting disease severity and prognosis in COVID-19 patients. We provided detailed information on the comparative results and further conducted multivariate Cox analysis to validate the predictive risk of these values for 28-day mortality in COVID-19 patients. This study contributes to the research on predicting disease severity and prognosis in COVID-19 patients by providing valuable insights.

The clinical presentation of patients plays a crucial role in predicting disease clinical outcomes. Clinical prediction scoring systems that combine clinical presentation and laboratory indicators have been continuously developed [71,72]. These clinical scores demonstrate clinical utility and reliability. The included parameters in our study can become part of clinical scoring models, further improving the predictive value for disease prognosis in COVID-19 patients. Clinical prediction scores, such as The International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) 4C mortality score, COVID-GREM score, CURB-65 score, etc., are used to assess the prognosis of COVID-19 patients [71–73]. The combination of laboratory inflammatory markers with clinical prediction scores is a future research trend. It has the potential to further enhance the predictive value for disease clinical outcomes [74].

Certainly, our study has some limitations as well. It is a single-centre retrospective study, and like other retrospective studies, it cannot completely eliminate the influence of selection bias. Second, our study did not include information on the vaccination status of patients, which could introduce some confounding bias. Third, in this study, we did not monitor the predictive effect of dynamic changes in these laboratory indicators on patient outcomes. Dynamic monitoring of these indicators may hold more significance. Finally, we did not validate the results of this study using external data. In the future, multicentre studies or further prospective research are needed to confirm our findings.

Conclusions

This study demonstrates that laboratory inflammatory markers, including PCT, CRP, CAR and BCDIMs, are effective predictors of disease severity and the 28-day mortality rate in COVID-19 patients. These markers also serve as significant risk factors for 28-day mortality. Specifically, the NLR exhibits the highest predictive value for disease severity, while the LCR shows the highest predictive value for 28-day mortality. BCDIMs, easily obtained in clinical settings, offer valuable guidance for the stratified management of COVID-19 patients.

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Author contributions

All authors contributed to the manuscript. Conceptualization: YM, BL, ZW, YC and ZL; data collection: NG, WP and YZ; formal analysis: ZW, ZL and YC; funding acquisition: YM, BL, HS and QS; investigation: NG, WP and YZ; methodology: ZW, YC and ZL; supervision and validation: YM, BL, HS and QS; visualization: ZW, YC and ZL; writing – original draft: ZW and YC; manuscript revising: YM and BL. All authors read and approved the final manuscript.

Ethics approval

This study was approved by the Ethical Committee of Beijing Youan Hospital (Approval No. LL-2023-092-K).

Consent form

Due to the retrospective nature of this study and the anonymization of the data used, the ethics committee approved a waiver of informed consent.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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