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Biochemistry Section

Association of Baseline Levels of C-Reactive Protein and Neutrophil to Lymphocyte Ratio in Assessing Severity and Mortality among COVID-19 Patients in Three Waves: A Cross-sectional Study

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ABSTRACT

Introduction: The Coronavirus Disease 2019 (COVID-19) infection has experienced three peaks in India, with possibilities of reinfections and future peaks. A comprehensive understanding of the disease, particularly in terms of inflammatory markers, is crucial. Neutrophil-to-Lymphocyte Ratio (NLR) and C-Reactive Protein (CRP) have been established as markers of disease severity in COVID-19 during the first wave, but limited data exists regarding these markers in the second and third waves.

Aim: This study aims to investigate the association between baseline levels of CRP and NLR with disease severity and mortality among COVID-19 patients in three waves.

Materials and Methods: A cross-sectional study was conducted at a tertiary care hospital in Bangalore from March 2020 to March 2022. The study included clinical data from 1485 patients with COVID-19. CRP and NLR levels were measured on the day of hospital visit, and their association with severity and mortality was assessed. Continuous variables were compared using independent t-test, one-way analysis of variance (ANOVA), or Kruskal-Wallis test as appropriate. Categorical variables were compared using the Chi-square test.

Results: Wave 1 demonstrated a significant increase in CRP and NLR values among patients with critical illness (mean±SD: 11.96±11.9, 12.41±13.7) compared to other categories. The values of these two parameters in other categories of wave 1 were as follows: asymptomatic (2.28±6.0, 3.17±2.0), mild (1.67±3.4, 2.41±2.7), moderate (1.07±1.7, 3.71±2.4), and severe (6.47±7.2, 4.39±4.3). In wave 2, critical illness (10.52±8.9 and 10.73±7.8) showed elevated values compared to other categories (0.957±1.1, 2.61±1.7), (4.90±5.9, 4.27±4.1), (4.84±4.8, 4.03±2.4), (7.35±6.7, 7.10±6.7). In wave 3, the two parameters in critical cases (15.0±17.3 and 16.47±7.6) were elevated compared to other categories (3.67±2.9, 16.44±10.3), (3.3 and 13.9), (3.7±5.9, 19.10±1.6).

Conclusion: CRP and NLR were found to be useful early markers for assessing disease severity and mortality in COVID-19 patients across all three waves.

Keywords: Acute-phase proteins, Complete blood counts, Inflammatory markers, Pandemic, Pneumonia

INTRODUCTION

The COVID-19 infection is a pandemic disease characterised by diffuse lung inflammation, caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus [1]. Genetic recombination and mutations of SARS-CoV-2 have led to different variants that have varying pathogenesis and transmissibility [2]. In an effort to reduce morbidity and mortality, age, gender, CRP levels, as well as NLR can be used as economical and practical clinical indicators to predict COVID-19 severity [2].

Feng X et al., found that inflammatory parameters such as white blood cells, lymphocytes, procalcitonin, CRP, and NLR can indicate the progression of COVID-19 [3]. NLR takes into account the levels of both neutrophils and lymphocytes for a comprehensive, accurate, and reliable examination. Monitoring CRP and NLR may help physicians recognise high-risk patients. It is beneficial for forecasting disease intensity to reduce clinical outcomes in pneumonia cases [3].

CRP is commonly used as a prognostic marker that indicates ongoing inflammation; it appears in the blood 6-10 hours after tissue inflammation begins and starts decreasing 18-20 hours after the inflammation reduces [4-6]. Furthermore, a complete blood count test, which includes the neutrophil count and lymphocyte count ratio, is an economical predictor of systemic inflammation.

Studies have been conducted to investigate the association between CRP and NLR ratio during the first wave period [7-10], but there are only a few studies [11,12] available regarding this association during the second or third wave periods. Ziuzia-Januszewska L et al., found that high NLR and CRP levels were predictors of poor outcomes of SARS-CoV-2 infection among the Polish population during the second and third waves of the pandemic [12].

In an effort to identify severe patients irrespective of the variant of SARS-CoV-2 in an early stage to reduce morbidity and mortality, parameters such as age, gender, CRP levels, as well as NLR can be used as economical and practical clinical indicators to predict COVID-19 severity in three different waves of the disease.

Hence, the present study was conducted to evaluate the association of baseline levels of CRP and NLR with disease severity and mortality among COVID-19 patients in three waves.

MATERIALS AND METHODS

A cross-sectional, retrospective study was conducted at a tertiary care hospital, which is a state government-approved centre for the care of COVID-19 patients and an Indian Council of Medical Research (ICMR) approved COVID-19 testing centre in Bangalore. Comparative data analysis was performed between COVID-19 patients during March 2020 to February 2021, considered as the first

wave of the COVID-19 disease, with the second wave patients from April 2021 to September 2021 and the third wave from November 2021 to March 2022. Waves were determined based on the number of daily new cases recorded in India from internet data sources. The study was approved by the Institutional Ethics Committee (IEC:VIEC/2021/APP/016), and a waiver for permission was granted.

Inclusive criteria: Patients aged ≥18 years, who tested positive for SARS-CoV-2 by Reverse Transcription Polymerase Chain Reaction (RT-PCR) method using nasal and oropharyngeal swabs, within the study duration, were included.

Exclusion criteria: Patients with comorbid conditions such as heart attacks, trauma, infections, burns, chronic inflammatory diseases like lupus, vasculitis, rheumatoid arthritis, and inflammatory bowel diseases were excluded.

Sample size estimation: In this study, the data were collected from the medical record section. The total data of 1485 patients were retrieved and investigated for CRP and NLR levels. Out of that, data of 1027 patients during the first wave period, 419 patients during the second wave, and 39 patients during the third wave were collected.

Study Procedure

Data regarding demographic variables (age, gender), serum CRP, NLR levels within 24 hours after hospitalisation, clinical status, and the need for oxygen and ventilator support were retrieved. The data on epidemiological, clinical, laboratory, radiological findings, and outcomes were collected using a data collection checklist from electronic medical records.

After collecting the data, patients were categorised based on disease severity at the time of hospitalisation. Classification was done based on the new guidelines for COVID-19 disease severity by the National Institute of Health (NIH) issued by the Government of India, as described below [13]:

- **Asymptomatic or presymptomatic infection:** Individuals who tested positive for SARS-CoV-2 using a virological test (i.e., nucleic acid amplification test or antigen test), but have no symptoms.
- **Mild illness:** Individuals with symptoms such as fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell, but without any respiratory symptoms such as shortness of breath, dyspnea, or abnormal chest imaging.
- **Moderate illness:** Individuals with a saturation level of oxygen (SpO_2) ≥94% on room air at sea level.
- **Severe illness:** Individuals with SpO_2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mmHg, respiratory frequency >30 breaths per minute, or lung infiltrates >50% [13].
- **Critical illness**: Individuals with respiratory failure, septic shock, and/or multiple organ dysfunctions.

Serum CRP was estimated by the Nephelometry method, using the Immage-800 Beckman Coulter fully automatic instrument. The coefficient of variation for the assay was 6.5%. The normal serum CRP levels in adult males and females were <0.8 mg/dL [14,15]. Blood NLR was estimated by the calculation method from neutrophil and lymphocyte counts, which were collected from the complete blood count test. Neutrophil and lymphocyte counts were estimated by the volume conductivity light scatter method in the DXH 900 Beckman Coulter instrument. The normal blood NLR levels in adult males and females were 2-2.33 [15].

STATISTICAL ANALYSIS

The collected data was entered into Microsoft Excel. Continuous variables were presented as mean±standard deviation. Qualitative variables were presented as frequency and percentage. The continuous variables were compared using an independent t-test, one-way ANOVA, or Kruskal-Wallis test as appropriate, whereas the qualitative variables were compared using the Chi-square test. A two-tailed p-value <0.05 was considered statistically significant.

RESULTS

In the present study, out of a total of 1485 COVID-19 positive cases, most of them (752, 73.2%) had mild illness during the first wave period, 221 (52.74%) during the second wave period, but in the third wave, most of them (23, 58.97%) were critically ill cases. In the third wave, there were no asymptomatic cases, and only 1 (2.56%) subject with moderate illness visited the hospital [Table/Fig-1].

Waves	N	Asymptomatic cases (n, %)	Mild illness (n, %)	Moderate illness (n, %)	Severe illness (n, %)	Critically ill (n, %)
Wave 1	1027	43 (4.18%)	752 (73.22%)	20 (1.94%)	173 (16.84%)	39 (3.79%)
Wave 2	419	11 (2.62%)	221 (52.74%)	44(10.5%)	94 (22.43%)	49 (11.69%)
Wave 3	39	0	6 (15.38%)	1 (2.56%)	9 (23.07%)	23 (58.97%)

[Table/Fig-1]: Distribution of subjects among three waves in different clinical categories of COVID-19 disease.

The mean age of patients significantly increased as the disease progressed in all three waves of the COVID-19 disease [Table/Fig-2]. In all categories, the number of male patients was significantly higher than females in the first and second waves of the COVID-19 disease. In the third wave, males outnumbered females in all categories, but the difference was not found to be significant [Table/Fig-3].

The results indicate that the mean CRP and NLR levels were elevated in asymptomatic cases, followed by lower mean values in mild cases and moderate cases. They were again markedly elevated in severe and critically ill categories during the first wave. Mean CRP and NLR values increased with disease severity and positively correlated with each other in asymptomatic cases, mild cases, moderate cases, and severe cases in the second wave. The mean CRP levels maintained the same levels in mild, moderate, and severe cases and were markedly elevated only in critically ill cases. Mean NLR values were elevated in mild cases, further elevation was found in severe cases, and they maintained the same levels as mild cases in critically ill cases. Mean CRP and NLR values were positively correlated with each other in mild cases, severe cases, and critically ill cases [Table/Fig-4].

In all three waves, the number of deaths in asymptomatic cases was nil. In mild cases during the first wave period, 6 deaths occurred, and during the second wave period, 13 deaths occurred. Among moderate cases during the second wave period, 2 deaths occurred. In severe cases during the first wave period, 6 deaths occurred, and during the second wave period, 19 deaths occurred. Markedly more deaths were found in critically ill cases during the first wave period (11 deaths) and the second wave period (23 deaths). In the third wave, there were no deaths in any category of the disease [Table/Fig-5]. In the first and second waves, mean CRP and NLR values were significantly higher in deceased patients compared to survivors [Table/Fig-6].

Age (Mean±SD) (years)	Asymptomatic cases	Mild illness	Moderate illness	Severe illness	Critically ill	p-value
Wave 1	38±16.39	40±15.41	52±15.42	52±15.11	56±12.49	<0.0001
Wave 2	30±11.05	45±14.87	53±15.08	52±14.28	59±14.64	<0.0001
Wave 3	0	49±11.18	40	66±19.66	58±12.96	0.0089

[Table/Fig-2]: Comparison of mean age among three waves in different clinical categories of COVID-19 disease.

Waves		Asymptomatic cases	Mild illness	Moderate illness	Severe illness	Critically ill	p- value
Wave 1	N	43	752	20	173	39	<0.0001
	Female	8 (18.6%)	236 (31.4%)	7 (35%)	54 (31.2%)	15 (38.5%)	
	Male	35 (81.3%)	516 (68.6%)	13 (65%)	119 (68.8%)	24 (61.5%)	
Wave 2	N	11	221	44	94	49	<0.0001
	Female	3 (27.3%)	69 (31.2%)	16 (36.4%)	33 (35.1%)	16 (32.7%)	
	Male	8 (72.7%)	152 (68.8%)	28 (63.6%)	61 (64.9%)	33 (67.3%)	
Wave 3	N	0	6	1	9	23	0.06
	Female	0	2 (33.3%)	0	2 (22.2%)	10 (43.5%)	
	Male	0	4 (66.6%)	1 (100%)	7 (77.8%)	13 (56.5%)	

[Table/Fig-3]: Comparison of gender among three waves in different clinical categories of COVID-19 disease.
A p-value <0.05 was considered statistically significant

	Wave 1					Wave 2					Wave 3				
Category	N	CRP Mean±SD	NLR Mean±SD	R value	p-value	N	CRP Mean±SD	NLR Mean±SD	R value	p-value	N	CRP Mean±SD	NLR Mean±SD	R value	p-Value
Asymptomatic cases	43	2.28±6.0	3.17±2.0	0.65	<0.001	11	0.957±1.1	2.61±1.7	0.318	0. 340	0	....	....	.....	.....
Mild illness	752	1.67±3.4	2.41±2.7	0.324	<0.001	221	4.90±5.9	4.28±4.1	0.392	<0.001	6	3.67±2.9	16.44±10.3	0.504	0.248
Moderate illness	20	1.07±1.7	3.71±2.4	0.558	0.011	44	4.84±4.8	4.03±3.4	0.532	<0.001	1	3.3	13.9	.....	.....
Severe illness	173	6.47±7.2	4.39±4.3	0.358	<0.001	94	7.35±6.7	7.10±6.7	0.391	<0.001	9	3.70±5.9	19.10±1.6	0.516	0.154
Critically ill	39	11.96±11.9	12.41±13.7	0.002	0.99	49	10.52±8.9	10.73±7.8	0.376	0.008	23	15.0±17.3	16.47±7.6	0.073	0.74
Total		2.86±5.4	3.18±4.5	-	-		6±6.6	5.59± 5.6	-	-		10.45±14.7	16.71±7.7	-	-
p-value		<0.0001	<0.0001	-	-		<0.0001	<0.0001	-	-		<0.0001	<0.0001	-	-

[Table/Fig-4]: CRP, NLR values in different clinical categories among three waves of COVID-19 disease.
A p-value <0.05 was considered statistically significant

Waves		Asymptomatic cases	Mild illness	Moderate illness	Severe illness	Critically ill	p-value
Wave 1	N	43	752	20	173	39	<0.0001
	Deaths	0	6 (0.8%)	0	6 (3.4%)	11 (28%)	
	Survivors	43 (100%)	746 (99.2%)	20 (100%)	167 (96.5%)	28 (71.8%)	
Wave 2	N	11	221	44	94	49	<0.0001
	Deaths	0	13 (5.8%)	2 (4.5%)	19 (20.2%)	23 (47%)	
	Survivors	11 (100%)	208 (94.5%)	42 (95.5%)	75 (79.8%)	26 (53.1%)	
Wave 3	N	0	6	1	9	23	0.016
	Deaths	0	0	0	0	0	
	Survivors	0	6 (100%)	1 (100%)	9 (100%)	23 (100%)	

[Table/Fig-5]: Comparison of deaths and survivors among three waves in different clinical categories of COVID-19 disease.
A p-value <0.05 was considered statistically significant

	Wave 1			Wave 2			Wave 3		
Category	N	CRP (Mean±SD)	NLR (Mean±SD)	N	CRP (Mean±SD)	NLR (Mean±SD)	N	CRP (Mean±SD)	NLR (Mean±SD)
Dead	23	12.9±9.6	12.76±13.7	57	13.3±9.9	11.9±9	0	0	0
Survived	1004	2.63±5.1	2.96±3.7	362	4.84±5.1	4.6±4.1	39	10.45±14.7	16.71±7.7
p-value		<0.0001	<0.0001		<0.0001	<0.0001		<0.0001	<0.0001

[Table/Fig-6]: Comparison of deaths and survivors among three waves in terms of CRP and NLR.

DISCUSSION

In the present retrospective study, more than 1000 subjects were involved [16-34].

Naess A et al., found that viral infections lead to lymphocytosis, contrary to the present study where SARS-CoV-2 led to lymphopenia [16]. Wang D et al., Huang C et al., Guan W-J et al., Yang X et al., and Chan PKS et al., observed that COVID-19 infection presents with lymphopenia [17-21]. The cause of this could be attributed to either viral particles attacking and damaging the cytoplasmic components of lymphocytes or intense cytokine storms inducing apoptosis of the lymphocytes. Similarly, the present study also observed lymphopenia across all categories of COVID-19 infection in all three waves.

Similarly, studies by Ali N, Sharifpour M et al., Clyne B and Olshaker JS, and Gabay C and Kushner I found elevated CRP levels in severe and critical illness across all three waves [22-25]. Alkhatip AAAMM et al., in their study found high NLR levels in all cases of COVID-19 across all three waves [26]. Marked elevation of NLR values was seen as the severity progressed, as in studies by Liu J et al., Yang A-P et al., and Erdogan A et al., [27-29]. Significant higher values were found among wave 3 cases compared to waves 1 and 2. These findings are consistent with the findings in the present study.

As found in studies by Shang W et al., Yufei Y et al., and Liu YP et al., an association was found between CRP and NLR values in the present study as well [30-32]. For wave three, due to the omicron variant of the COVID-19 disease, where most people had been vaccinated and the virus was not proving to be as fatal anymore, CRP and NLR still had positive correlations but not significant.

Similar to Peckham H et al., a higher number of males compared to females were infected across all three waves [33]. Like in Bonanad C et al., and Yan X et al., this study also supports that for waves 1 and 2, age is an independent predictor of mortality, however not in wave 3 because people with no vaccine presented with more serious symptoms [34]. It was also noted that CRP and NLR levels positively correlated with the mortality rate in waves 1 and 2, but no deaths were observed in wave 3.

A comparison of the findings in the present study with contrasting studies is shown in [Table/Fig-7] [16-35].

Authors	Place and year of the study	Sample size	Findings
Wang D et al., [17]	Wuhan, China, 2020	138	Hospital-related transmission of 2019-nCoV was suspected in 41% of patients, 26% of patients received ICU care, and mortality was 4.3%.
Huang C et al., [18]	Wuhan, China 2020	41	The 2019-nCoV infection caused clusters of severe respiratory illness similar to severe acute respiratory syndrome coronavirus and was associated with ICU admission and high mortality.
Guan WJ et al., [19]	China 2020	1099	Lymphocytopenia was present in 83.2% of COVID-19 patients on admission.
Yang X et al., [20]	Wuhan, China 2020	52	The mortality of critically ill patients with SARS-CoV-2 pneumonia is considerable. The survival time of the non survivors is likely to be within 1-2 weeks after ICU admission. Older patients (>65 years) with co-morbidities and ARDS are at increased risk of death.
Ali N [22]	Letter to editor	12 studies	Elevated level of CRP may be a valuable early marker in predicting the possibility of disease progression in non severe COVID-19 patients.
Sharifpour M et al., [23]	Atlanta, GA 2020	268	Utility of daily CRP values in hospitalised COVID-19 patients and provide early thresholds during hospitalisation that may facilitate risk stratification and prognostication.
Clyne B and Olshaker JS [24]	Systematic review	84 studies	Elevated CRP seen with complications or treatment failures in patients with pneumonia, pancreatitis, Pelvic Inflammatory Disease (PID), and urinary tract infections.
Gabay C and Kushner I [25]	Systematic review	64 studies	Determination of serum C-Reactive Protein (CRP) has advantages over the traditional strategy of measuring the erythrocyte sedimentation rate.
Alkhatip AAAMM et al., [26]	Systematic review and meta-analysis	8120	Patients with COVID-19 had significantly higher levels of NLR compared to negative individuals. Advanced COVID-19 stages had significantly higher levels of NLR than earlier stages.
Liu J et al., [27]	China, 2020	61	NLR is a predictive factor for early stage prediction of patients infected with COVID-19 who are likely to develop critical illness. Patients aged ≥50 and having an NLR ≥3.13 are predicted to develop critical illness.
Yanga AP et al., [28]	Wuhan, China 2020	93	Elevated age and NLR can be considered independent biomarkers for indicating poor clinical outcomes.
Erdogan A et al., [29]	Turkey 2020	304	NLR, PLR, and LCR ratios can be used as more significant biomarkers than other values in predicting the prognosis of COVID-19 patients.
Shang et al., [30]	China 2020	443	NLR, CRP and platelets can effectively assess the severity of COVID-19, among which NLR is the best predictor of severe COVID-19, and the combination of three clinical indicators can further predict severe COVID-19.
Yufei Y et al., [31]	Wuhan, China 2020	241	NLR and CRP were independent risk factors for COVID-19, and the combined detection of the NLR and CRP showed improved diagnostic performance for COVID-19.
Liu YP et al., [32]	China 2020	84	Our results demonstrated that the nomogram and combined index calculated from the NLR and CRP are potential and reliable predictors of COVID-19 prognosis and can triage patients at the time of admission.
Peckha M et al., [33]	World wide 2020 Meta-analysis	107 reports	Large-scale data demonstrate that although there is no sex difference in the proportion of people infected with SARS-CoV-2, males are at a significantly higher risk of severe disease and death than females.
Bonanad C et al., [34]	Meta-analysis 2020	17 studies	A determinant effect of age in mortality of COVID-19 patients with a relevant threshold on age >50 and especially >60.
Yan X et al., [35]	Wuhan, China 2020	1004	NLR appears to be a significant prognostic biomarker of outcomes in critically ill patients with COVID-19.
Present study	India, 2023	1485	An association was observed between CRP and NLR levels in each wave, regardless of the variant of SARS-CoV-2 virus.

[Table/Fig-7]: Comparison of findings in present study with contrast studies [16-35].
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; COVID-19: Coronavirus disease 2019; ARDS: Acute respiratory distress syndrome; NLR: Neutrophil lymphocyte ratio; MLR: Monocyte lymphocyte ratio; CRP: C-reactive protein; ICU: Intensive care unit; nCov: Novel coronavirus

Limitation(s)

This study has certain limitations. First, only one-time measured NLR and CRP levels within 24 hours of hospitalisation were used for analysis. Serial measurements throughout hospitalisation would have been more helpful. Secondly, there was only one moderate case in wave three. Thus, comparison between waves was limited due to a lack of data. Third, there was a huge difference in sample size among the three waves of different clinical categories of COVID infection. Fourth, genetic sequencing was not done among the three waves of COVID infection to confirm the different variants of the SARS-CoV-2 virus.

CONCLUSION(S)

The study findings revealed that CRP levels did not differ much between the three different waves, but NLR levels greatly increased in wave 3 cases. An association was observed between CRP and NLR levels in each wave, regardless of the variant of the SARS-CoV-2 virus. This research confirms that a combination of older age and male sex, as well as elevated CRP and NLR levels, are independent predictors of disease severity and mortality among Asian Indian patients with COVID-19 in all three waves. As part of future studies, positive cases of COVID-19 will be sent for gene sequencing studies. Collecting specific variant data from gene sequencing and comparing it with the vaccine status of individuals can provide a clearer picture for understanding CRP and NLR variations.

Author contributions: SA supervised the acquisition of the data, analysed and interpreted the data. SD assisted in collecting clinical information about the patients and helped interpret the data. The manuscript was established by UA and JAN. The manuscript was critically reviewed by MNS. All authors edited and approved the final version of this manuscript.

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