

Original Article

Neutrophil-Lymphocyte Ratio of Covid-19 Patients Admitted in Mariano Marcos Memorial Hospital and Medical Center, an Early Prognostic Marker

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Abstract: Neutrophil-Lymphocyte Ratio as an Early Prognostic Marker for COVID-19 Patients Admitted to Mariano Marcos Memorial Hospital and Medical Center. The emergence of COVID-19 as a global pandemic has prompted the need for reliable prognostic markers to assess disease severity and guide clinical management. While various biomarkers have been studied about COVID-19 prognosis, their accessibility and applicability in resource-constrained settings remain challenging. This study focused on the neutrophil Neutrophil-Lymphocyte Ratio (NLR), a routinely available parameter in complete blood counts, as a potential prognostic marker for COVID-19 patients in Mariano Marcos Memorial Hospital and Medical Center. This retrospective cross-sectional analytical study analyzed data from COVID-19 patients admitted. The study assessed the relationship between NLR and clinical outcomes, including discharge status, ICU admission, and mortality. The study also examined the correlation between NLR and C-reactive protein (CRP) levels, another inflammatory marker commonly associated with COVID-19 severity. The study included 702 COVID-19 patients with varying age groups and clinical classifications. The analysis revealed a statistically significant difference in NLR among different age groups ($p < 0.05$) and a moderate positive correlation between NLR and CRP (Pearson coefficient = 0.469, $p < 0.05$). Furthermore, NLR showed a statistically significant difference among clinical outcomes ($p < 0.05$), with higher NLR values associated with worse clinical outcomes, such as ICU admission and mortality. Logistic regression analysis supported NLR as a predictor of clinical outcomes ($p < 0.05$), while age, gender, and comorbidities showed no significant association. Neutrophil-lymphocyte ratio (NLR) emerged as a potential early prognostic marker for COVID-19 patients admitted to Mariano Marcos Memorial Hospital and Medical Center. Higher NLR values were associated with increased CRP levels, worse clinical outcomes, and a higher ICU admission or mortality likelihood. However, further research in more extensive and diverse populations is needed to validate these findings and consider other confounding factors. Integrating NLR with other clinical parameters could enhance its predictive power and clinical utility in assessing COVID-19 severity and prognosis.

Keywords: COVID-19, Neutrophil-Lymphocyte Ratio (NLR), C-reactive Protein (CRP), Prognostic Marker

1. INTRODUCTION

In December 2019, the coronavirus disease 2019 (COVID-19) emerged as the latest pandemic threatening the lives of the whole world. The disease mainly involves respiratory failure with associated flu-like symptoms, like myalgia, dyspnea, and fatigue, with some patients succumbing to multiple organ failure and death. The disease is classified based on these manifestations; patients are classified as mild,

moderate, severe, or critical [1]. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the virus that causes coronavirus disease 2019 (COVID-19). It spreads primarily via respiratory droplets during close face-to-face contact, with an average time from exposure to symptom onset of 5 to 11.5 days [2]. It is detected via reverse transcription polymerase chain reaction testing, but this depends on the testing quality and timing. Manifestations of COVID-19 include asymptomatic carriers and fulminant disease characterized by sepsis and acute respiratory failure. Due to the various clinical manifestations related to the disease and its erratic course, it is hard to anticipate how a particular person experience the condition, and because of this diversity, there is an urgent need for disease severity and prognostic biomarkers so that patients may be managed effectively and deadly consequences can be avoided [3,4]. A single factor unites severe COVID-19 and other serious illnesses: cytokine storm. This refers to a significant inflammatory reaction to an infection. This dysregulated immune response characterized by the activation of inflammatory cascades, complements, and pro-inflammatory cytokines plays a role in vasculitis damage leading to lung injury, cardiovascular damage, and cerebral injuries. The dysregulated inflammation in COVID-19 has similarities with patients infected with the Middle East respiratory syndrome (MERS) and is associated with poor clinical outcomes [5,6,7]. Several Biomarkers have already been studied; these include C-reactive protein (CRP), Interleukin (IL) -6, procalcitonin (PCT), White blood cell (WBC) count, neutrophil count, Lymphocyte count, neutrophil: lymphocyte ratio (NLR), D- Dimer, Prothrombin time (PT), and activated partial thromboplastin time (APTT). Other inflammatory markers belong to the enzyme family. These include Lactate dehydrogenase and transaminases, which indicate non-specific cellular damage or inflammation [8]. With the myriad of inflammatory biomarkers, it was found out the C-reactive protein confers the most significant prognostic capability in determining an increase in 28-day mortality for COVID-19 patients [9]. One of the most common tests clinicians request is the complete blood count. This includes the determination of hemoglobin, hematocrit, erythrocyte count, platelets, and leukocyte count with differential counts. These tests help diagnose patients with anemia, malignancies, immunosuppressive states, infections, and inflammatory states [10,11]. With constant improvements in the automation of hematology analyzers, the efficiency and clinical utilization of complete blood counts in various diseases are rising [12]. In general, the blood neutrophil count rises as the inflammatory illness progresses, but in specific situations, such as cachexia, the neutrophil count does not rise; thus, a false negative interpretation can ensue when assessing disease progression [13]. On the other hand, Lymphocyte count reflects a patient's immune status and generally decreases as inflammatory disease progresses; however, this decrease is relatively delayed and may not reflect disease progression well. Recently, studies have reported that the NLR is more reliable when predicting patient survival than neutrophil or lymphocyte counts alone [14]. The neutrophil to lymphocyte ratio, which is determined as a straightforward ratio between the counts of neutrophils and lymphocytes in peripheral blood, is a marker that combines the innate immune response, which is primarily supported by neutrophils, and adaptive immunity, which is supported by lymphocytes. Through various processes, including chemotaxis, phagocytosis, the release of reactive oxygen species (ROS), granular proteins, and the creation and release of cytokines, neutrophils represent the first line of defense for the immune system [15,16]. Neutrophils are the primary effector cells during the systemic inflammatory response and serve a crucial regulatory function in adaptive immunity. As gatekeepers of innate immunity, neutrophils coordinate other immune cells' recruitment, activation, and programming while secreting various cytokines that promote inflammation and immunomodulation. On the other hand, an antigen-specific response is provided by lymphocytes, and this is controlled by the MHC class I protein. The host's response to viruses, tumor cells, atopy, and SIRS is also influenced by lymphocyte activity[17,18]. Generally, the study aims to determine the relationship of neutrophil to lymphocyte ratio of patients with COVID-19 and compare it to their outcome. The study's findings determined the use of neutrophil to lymphocyte ratio as a biological marker in COVID-19. It enabled the laboratory to utilize the hematological analyzer effectively in routine examinations

and other emerging diseases. To provide data on the possible utilization of the neutrophil-lymphocyte ratio to prognosticate COVID-19 patients and monitor and manage various inflammatory and metabolic conditions. The data gathered on this research provided capabilities to other healthcare facilities without access to testing for inflammatory markers prognosticate and classify COVID-19 patients that need a higher level of care in a tertiary hospital.

2. MATERIALS & METHOD

A retrospective cross-sectional analytical study was conducted to determine the neutrophil-lymphocyte ratio and its correlation with clinical outcomes of COVID-19 patients. The study was conducted at Mariano Marcos Memorial Hospital and Medical Center, a tertiary government hospital in Batac City, Ilocos Norte. This study included COVID-19 patients admitted to Mariano Marcos Memorial Hospital and Medical Center. Neutrophil to lymphocyte ratio - This is computed by dividing the absolute neutrophil count by the total lymphocyte count of COVID-19 patients. Clinical classification pertains to the classification of COVID-19 patients as clinical symptoms. Patients can be classified as mild, moderate, severe, or critical. Clinical Outcomes – The patient's disposition after treatment and management. Discharged <1 month: The patient was discharged less than a month ago with no history of ICU admission after completing treatment and management. Discharged >1 month: The patient was discharged more than a month ago with no history of ICU admission after completing treatment and management. ICU admission: Any patient admitted to the Intensive care during their treatment for the disease but was later discharged. Died: The patient expired despite a complete course of treatment and management. A total enumeration of subjects that satisfy the eligibility criteria done. Independent variables for this study included the patient's age, gender, and neutrophil-to-lymphocyte ratio. The dependent variable was outcome of the patient. A data abstraction tool was developed based on the objectives of the study and review of related literature. This included information on the subject's demographic profile, such as age and gender [19]. The neutrophil-lymphocyte ratio of the subject's complete blood count result was also included. The patient's diagnosis was considered together with the presence of comorbidities. COVID-19 Patients were further profiled as to demographic (age and gender) clinical classification (Mild, Moderate, Severe, Critical), and diagnostic test done (CRP). We asked for approval from the Ethics and Review Board of Mariano Marcos Memorial Hospital and Medical Center before we conducted the study. All patients diagnosed with COVID-19 who satisfy the inclusion criteria were profiled. In profiling patients with COVID-19, approval from the head of the Medical Records Section was obtained asking permission to review the charts of patients diagnosed with COVID-19 [20]. The COVID-19 patients were classified based on their clinical classification and outcome. A patient who was admitted to an ICU at any time during their hospital stay was classified as ICU admission. Records of complete blood count reports of COVID-19 patients were checked. Only the initial complete blood count report was included should a subject have multiple complete blood count reports. Pregnant patients and patients admitted for surgery were included. Data was encoded using Microsoft Excel and was analyzed using IBM SPSS Statistics. Qualitative data included gender. Quantitative data included the age group, CRP, and NLR results. These were summarized using measures of central tendencies. Means (Standard Deviation) and Frequency (percentages) statistics used to describe the study population characteristics; we classified the patients based on their clinical classification (Mild, Moderate, Severe, Critical) [21]. The primary endpoint of this study is the clinical outcome of the patients. Pearson correlation used to determine the association of NLR to CRP [22]. Spearman correlation used to determine the association between NLR and clinical outcomes. Logistics regression was also employed to estimate the probability of a particular outcome or event happening, given a set of predictor variables. Descriptive analysis was employed in analyzing the profile of patients with COVID-19. Subjects, records and information treated with the utmost privacy and confidentiality. Patient names anonymized using codes. The data abstraction tool used placed safely in a locked cabinet

inside the Department of Pathology of MMMH and MC and kept for five years. Disposal of records through shredding. No vulnerability issue is being foreseen by the investigator as to patients who involved in the study. Recruitment of patients based on the eligibility criteria set in this study. A waiver of informed consent is requested from the Ethical Review Board since the research procedure entails only a review of medical records in which data anonymized. Also, the Data set is considered nonsensitive. Neither the investigator nor the subjects compensated for participating in this study.

3. RESULTS & DISCUSSIONS

Table 01: Admitted COVID-19 patients' Demographics

Age Group	N	Percentage
<1 year Old	22	3.13%
1-17 years old	24	3.41%
18-65 years old	367	52.27%
>65 Years Old	298	41.16%
TOTAL	702	100%

The study included a total of 24 participants in the age range of 1-17 years, indicating a relatively smaller proportion of the sample falling within this age group; most participants (367) were between the ages of 18 and 65, suggesting that the majority are adults. Furthermore, 298 participants were above the age of 65, indicating a significant representation of older adults in the sample. Additionally, there were 22 participants below the age of 1 year, suggesting a small but notable presence of infants in the study.

Table 02: Gender distribution

Gender	N	Percentage
Male	224	41.88%
Female	326	58.12%

In terms of gender distribution, the study comprised 224 male participants and 326 female participants. This indicates a relatively higher representation of females in the sample.

Table 03: Clinical classifications based on the severity of condition.

Clinical Classification on Admission	N	Percentage
Mild	26	3.72%
Moderate	434	61.82%
Severe	181	25.78%
Critical	61	8.68%

The study participants were categorized into different clinical classifications based on the severity of their condition. Most participants (434) were classified as moderate, suggesting a significant proportion of individuals with moderate illness severity. There were 181 participants categorized as severe, indicating a smaller but still substantial group experiencing more severe symptoms. Additionally, 61 participants were classified as critical, suggesting a subset of participants with the most severe presentation of the condition. Furthermore, there were 26 participants categorized as mild, representing the smallest group in terms of clinical classification. Overall, these findings provide insights into the distribution of participants across age groups, gender, and clinical classification. The results indicate a focus on adults, with a higher representation of females in the sample. Many participants had a moderate clinical classification, while a smaller proportion experienced severe or critical symptoms.

Table 04: Neutrophil to Lymphocyte Ratio and CRP of COVID-19 patients admitted in Mariano Marcos Memorial Hospital and Medical Center.

Age Group	Gender	NLR			CRP		
		Mean	Standard Deviation	P Value	Mean	Standard Deviation	P-Value
<1 year old	Male	1.99	1.892	0.287	24.385	38.02	0.028
	Female	N/a					
1-18 years old	Male	5.53	8.14	0.945	34.55	51.31	0.2286
	Female	7.37	3.74		110.21	83.154	
18-65 years old	Male	11.69	9.93	0.887	109.93	110.6771	0.3412
	Female	11.54	9.26		128.2213	113.0976	
>65 years old	Male	9.17	8.61	0.887	130.991	172.428	0.3412
	Female	9.42	8.75		119.542	110.5	

In this study, the T-test revealed no statistical difference in the mean neutrophil-lymphocyte ratio between males and females by age group. In terms of CRP, there is a statistically significant difference between males and females within the group of 1-18 years old, while the rest of the group has no statistical significance. The NLR rises with illness progression, particularly in inflammatory diseases. It was also stated in several studies that a high NLR could be an independent predictor of prognosis in a variety of clinical circumstances, including malignancies, cardiovascular disease, lung injury, and fibrotic liver diseases. Additionally, NLR was able to forecast mortality in the general populace. An early increase, less than 6 hours in NLR following acute physiological stress, could confer on NLR the role of a marker of acute stress earlier than other laboratory parameters. Neutrophil to lymphocyte ratio (NLR)

has proven its prognostic value in cardiovascular diseases, infections, inflammatory diseases, and several cancers. However, no cut-off has been proposed based on reference values from healthy populations. Some studies have identified the normal NLR values in adults, non-geriatric, and healthy populations. These values, however, are derived from foreign populations and cannot be accurately used for Asians. This is evident with the different articles using different values of NLR with different methods and in different populations. Lower NLR is often mirrored by positive prognostic variables in every application area, reflecting a conserved immunological balance.

Table 05: Neutrophil to Lymphocyte Ratio of COVID-19 Patients by Age Group

DATA SUMMARY				
Groups	N	Mean	Standard Deviation	Standard Error
<1 year old	11	3.0204	2.9775	0.8978
1-17 years old	12	4.9518	4.0457	1.1679
18-65 years old	189	7.8449	7.8812	0.5733
> 65 years old	123	10.0835	10.9395	0.9864

Table 06: ANOVA Summary

ANOVA SUMMARY					
Source	Degree of Freedom	Sum of Squares	Mean Square	F-Stat	p-value
Between Groups	3	867.8553	289.2851	3.6071	0.0137
Within Groups	331	26546.0671	80.19960		
Total	334	27413.9924			

F-statistics of 3.60 and a p-value of 0.013 suggest that there is evidence of a statistically significant difference between the means of neutrophil to lymphocyte ratio of the different age groups of COVID-19 patients admitted at Mariano Marcos Memorial Hospital and Medical Center.

Table 07: Pearson Correlation of Neutrophil to Lymphocyte ratio and C-reactive protein among COVID-19 patients admitted at Mariano Marcos Memorial Hospital and Medical Center

	N	Mean	Standard Deviation	Degree Of Freedom	T-value	p-value
NLR	335	8.40	9.059	333	10.45016	<0.05
CRP	335	104.98	115.15	333		

In this study, the Pearson correlation coefficient shows a value of 0.469, a t-value of 10.45, and a p-value of <0.05. The coefficient of 0.4969 suggests a moderate positive correlation between the variables. The t-value of 10.45 indicates a strong deviation from the null hypothesis and suggests that the correlation is unlikely to have occurred by chance. The p-value also indicates strong evidence against the null hypothesis.

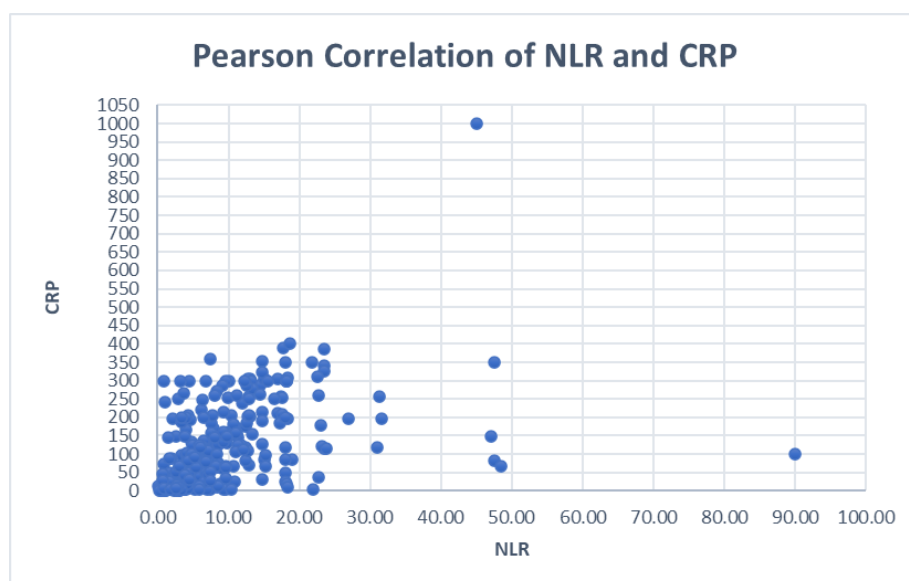


Figure 01. Scattergram between NLR and CRP

Table 08: ANOVA analysis between neutrophil to lymphocyte ratio and different clinical outcomes.

DATA SUMMARY				
Groups	N	Mean	Standard Deviation	Standard Error
Discharged<1 month	211	4.379	3.2198	0.2217
Discharged > 1 month	4	8.74	4.9231	2.4616
ICU admission	55	14.5804	8.756	1.1809
Died	65	16.3286	13.3288	1.6532

Table 09: ANOVA Summary

ANOVA Summary						
Source	Degree of Freedom	Sum of Squares	Mean Square	F-Stat	p-value	
Between Groups	3	9651.9011	3217.3004	59.9573	<0.05	
Within Groups	331	17761.4066	53.6598			
Total	334	27413.3077				

The F statistic (59.9573) suggests a substantial difference among the groups. The p-value (<0.05) indicates the probability of obtaining the observed F statistic under the null hypothesis. Based on this, we can conclude that there is a statistically significant difference among the group means.

Table 10: ANOVA analysis between neutrophil to lymphocyte ratio and clinical classification on admission

Data Summary				
Groups	N	Mean	Standard Deviation	Standard Error
Mild	11	9.0509	6.3879	1.926
Moderate	188	7.291	7.6249	0.5561
Severe	105	9.067	10.3903	1.014
Critical	31	12.689	11.6227	2.0875

Table 11: ANOVA Summary

ANOVA Summary					
Source	Degree of Freedoms	Sum of Squares	Mean Square	F-Stat	P-value
Between Groups	3	852.8443	284.2814	3.5428	0.0149
Within groups	331	26560.3458	80.2427		
Total	334	27413.19			

The F-statistic value of 3.54277 suggests that there is some evidence of a difference between the group means. Based on the given p-value of 0.01492, we can conclude that the observed differences between the group means are statistically significant.

Table 12: Spearman Correlation of Neutrophil to lymphocyte ratio and Clinical outcomes

Variable	Value
Sample Size (n)	335
Spearman Coefficient	0.375
T- value	7.39
Degree of Freedom	333
p-value	1.188E-12

A Spearman coefficient of 0.375 indicates a moderate positive correlation between NLR and clinical outcome, and the p-value of <0.05 suggests the Spearman coefficient is statistically significant. This indicates that the higher NLR values may be associated with worse clinical outcomes.

Table 13: Logistics Regression Analysis of NLR, Age, Gender, and Presence of Comorbidities to Clinical Outcome , donors must be protected.

Discharged < 1 month						
	B	S. E	Wald	Df	Sig	Exp(B)
NLR	-.120	0.21	31.211	1	.000	.887
Age			0.86	3	.994	
Age (1)	.155	1.126	.019	1	.890	1.168
Age (2)	.002	.404	.000	1	.995	1.002
Age (3)	.306	1.147	.071	1	.789	1.359
Gender (1)	.204	.346	.348	1	.555	1.226
ComorbiditiesComorbidities (1)	.185	.453	.167	1	.683	1.203
Constant	2.837	.398	50.748	1	.000	17.068
Discharged > 1 month						
	B	S. E	Wald	Df	Sig	Exp(B)
NLR	.008	.048	.028	1	.867	1.008
Age			.254	3	.968	
Age (1)	18.796	4297.751	.000	1	.997	145547048.1
Age (2)	.624	1.237	.254	1	.614	.1866
Age (3)	-14.870	10448.316	.000	1	.999	.000
Gender (1)	.066	1.033	.000	1	.996	1.006
ComorbiditiesComorbidities (1)	-16.360	4297.751	.000	1	.997	.000
Constant	-4.796	1.206	15.806	1	.000	.008
ICU Admission						
	B	S. E	Wald	Df	Sig	Exp(B)
NLR	.076	.017	19.1015	1	.000	1.079
Age			.468	3	.926	
Age (1)	-19.1482	11988.019	.000	1	.999	.000

Age (2)	-.150	.367	.167	1	.682	.861
Age (3)	-.618	1.094	.319	1	.572	.539
Gender (1)	-.015	.314	.002	1	.962	.985
ComorbiditiesComorbidities (1)	-.031	.397	.006	1	.937	.969
Constant	-2.243	.344	42.547	1	.000	.106
Died						
	B	S. E	Wald	Df	Sig	Exp(B)
NLR	.138	.022	38.382	1	.000	1.147
Age			.989	3	.804	
Age (1)	-.048	.864	.003	1	.855	.953
Age (2)	.174	.387	.203	1	.652	1.1191
Age (3)	.711	.786	.818	1	.366	2.036
Gender (1)	-.198	.314	.398	1	.528	.820
ComorbiditiesComorbidities (1)	.453	.399	1.289	1	.256	.1573
Constant	-2.901	.392	54.718	1	.000	.055

The logistic regression analysis indicates a statistical significance between the NLR and the clinical outcomes Discharged <1 month, ICU Admission, and Died, while no statistical significance was seen between NLR and Discharged >1 month. This table also shows that age, gender, and the presence of comorbidities have no statistical significance to the clinical outcomes.

4. CONCLUSIONS

The study focused on the predictive utilization of the neutrophil-lymphocyte ratio in COVID-19 patients. It uses a retrospective approach for data gathering. It will be limited to complete blood count results to compute neutrophil-lymphocyte ratio, CRP values, and chart review in profiling COVID-19 patients. In conclusion, the findings suggest that NLR may serve as a valuable biomarker in predicting outcomes and severity levels among COVID-19 patients. Higher NLR values were associated with increased levels of CRP, worse clinical outcomes, and a higher likelihood of ICU admission. However, further research and validation are necessary to confirm and generalize these findings, considering confounding factors and limitations of the study. It is essential to continue exploring the relationship between NLR and clinical outcomes in larger and more diverse populations. Additionally, investigating the influence of other confounding factors and comorbidities on the NLR-outcome relationship would strengthen the understanding of its clinical significance. To enhance outcome assessment's predictive power and accuracy, consider integrating NLR with other relevant clinical, laboratory, and imaging parameters. A multidimensional approach could provide a more comprehensive understanding of disease progression and prognosis.

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