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Original Research Article

The Silent Signals: Unveiling Prognostic Whispers in Neutrophil and Platelet Ratios

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Abstract

A novel strain of coronavirus was identified In December of 2019, in Wuhan, China, leading to what is now known as the COVID-19 pandemic. Coronavirus disease 2019 referred to as (COVID-19) has emerged as a pandemic from the novel coronavirus, now known as referred as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). SARS-CoV-2 differs significantly from other previously known coronaviruses that are known to b spree prevalent in human beings causing minor symptoms like common cold. COVID-19 is an severe acute respiratory tract infectious disease which is commonly transmitted through the respiratory route.

Introduction

COVID-19 virus is a single stranded RNA virus. The name given to it Corona has originated from Latin word meaning “Crown” which has was given due to the similarity of spikes it has to a crown. Coronaviruses has previously also been known to be the culprit in a number of outbreaks in humans and animals that includes conditions like severe acute respiratory syndrome (SARS-CoV) and Middle East Respiratory Syndrome (MERS-CoV) [1,2].

COVID-19 has rapidly spread across the globe, and lead to a widespread morbidity and mortality. The COVID-19 pandemic has resulted in increased strain and huge burden on healthcare systems worldwide. Hospitals have struggled to keep up with the surge of patients, especially in intensive care units. This huge burden and demand has led to shortages of important medical supplies, including ventilators and protective gear for healthcare workers. The relentless, upward spiralling pressure has pushed medical staff to their breaking point, causing stress and exhaustion. Moreover, the pandemic has significantly disrupted regular medical services, resulting in delayed care for other conditions. The crisis has exposed weaknesses in healthcare systems, underscoring the need for better infrastructure and preparation for future health emergencies [3,4]. COVID-19 primarliy affects the lungs, but it can also cause serious problems in other parts of the body, ranging from mild to severe symptoms cases like acute respiratory distress syndrome (ARDS) and even organ failure. Given the virus's rapid spread and serious impact, early diagnosis and accurate prediction of outcomes have become essential in managing the disease. Sensitive and rapid Diagnostic tests for COVID-19 are crucial for identifying active infections. PCR tests, which are highly accurate, detect the virus's genetic material. Rapid antigen tests, which have recently been available while quicker, are slightly less sensitive and specific. These tests are important for detecting and controlling the virus by enabling early detection and isolation of infected individuals. Antibody tests also play a role, revealing past infections and providing insight into population immunity. Combined, these testing methods are key to managing the pandemic effectively. [5,6,7,8]

There is a emergent need to establish reliable, cost-effective prognostic markers to guide treatment decisions and allocate resources effectively. The Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR) have recently emerged as potential indicators of inflammation and disease severity in COVID-19 patients [9,10,11].

NLR and PLR can be easily obtained from routine CBC tests, making them accessible, practical and cost-effective markers. Few studies have shown that elevated NLR and PLR values show correlation with bad outcomes in various conditions, including cancer, cardiovascular diseases, bacterial and viral infections [11,12]. This article aims to assess the utility of NLR and PLR as prognostic indicators in COVID-19 patients by evaluating their correlation with clinical outcomes and other relevant indicators.

Materials and Methods

This study was conducted in the Department of Pathology, at a tertiary care hospital over a period of 14 months from April 2020 to May 2021. A total of 400 COVID-19 RT-PCR positive patients admitted to the hospital were included in the study. Non-probability convenience sampling was done. The consent was obtained from conscious patients after explaining them about the study and from relatives of unconscious or those patients who cannot provide consent. Ethical clearance was obtained from intuitional ethical committee prior to starting of the study. Sample size calculation was not relevant as prevalence of the study is not still clear. The study aimed to assess the prognostic utility of NLR and PLR in these patients.

Inclusion and Exclusion Criteria:

- Inclusion Criteria: COVID-19 RT-PCR positive cases who were admitted to the hospital.

- Exclusion Criteria: COVID-19 positive cases with pre-existing comorbidities and asymptomatic cases were excluded from the study.

Patients admitted with a confirmed COVID-19 diagnosis, verified by at least one positive nasopharyngeal swab for Reverse Transcription Polymerase Chain Reaction (RT-PCR), were included in this study. Case severity was classified based on the World Health Organization's interim guidance. The classifications were as follows: Asymptomatic (RT-PCR positive with no symptoms), Mild (RT-PCR positive with no hypoxia), Moderate (RT-PCR positive with pneumonia symptoms but no severe hypoxia, with Spo2 > 90%), Severe (signs of severe pneumonia with a respiratory rate over 30 breaths per minute or Spo2 < 90%), and Critical (patients with Acute Respiratory Distress Syndrome [ARDS] or septic shock) [13].

Data Collection:

Data on age, sex, symptoms, clinical findings, CT values, and CBC findings (NLR and PLR) were collected at the time of hospital admission. NLR was calculated by dividing the neutrophil count by the lymphocyte count, while PLR was calculated by dividing the platelet count by the lymphocyte count. The data were then correlated with clinical outcomes and CT values.

Results

A total of 400 COVID-19 positive patients were admitted to the hospital. The mean age of the patients was 41.2 years with a standard deviation of 13.6 years, and the age range spanned from 18 to 86 years. The gender distribution of the study population showed that the majority were males, accounting for 63.75% (n=255), while females made up 36.25% (n=145). The detailed breakdown of the demographic characteristics and disease severity of the patients is presented in Table 1. It was observed that 11.25% (n=45) of the patients were asymptomatic at the time of admission, while 88.75% (n=355) were symptomatic. The symptomatic group was further divided into categories based on disease severity: 35% (n=140) had mild disease, 23.75% (n=95) had moderate disease, 21.25% (n=85) had severe disease, and 8.75% (n=35) were classified as critical. The mean onset of symptoms to hospital admission was 2.8 days across all cases, with variations observed based on disease severity.

Table 1: Demographics and Disease severity

Characteristics	All cases (400)	Asympto-matic (45)	Mild illness (140)	Moderate illness (95)	Severe ill-ness (85)	Critical ill-ness (35)
Age (mean)	41.2 years	34.1 years	39.2 years	52.6 years	52.4 years	58.6 years
Sex - Males/Females	255/145	25/20	85/55	60/35	60/25	25/10
Onset of symptom to hospital admission (days)	2.8 days	-	2.7 days	2.8 days	3.2 days	3.1 days
Positive RT-PCR to hospital admission (days)	6 days	2.4 days	6.2 days	5.8 days	6.1 days	5.9 days
Contact History with COVID positive pa-tient	260 (65%)	27 (60%)	90 (64.3%)	55 (57.9%)	55 (64.7%)	15 (42.9%)

Among the symptomatic patients, the most frequently reported symptom was fever, affecting 87.5% (n=350) of all cases. Cough was reported by 77.5% (n=310) of the patients, and fatigue was observed in 75% (n=300). Other common symptoms included myalgia in 65% (n=260) of cases, chills in 52.5% (n=210), and anorexia in 47.5% (n=190). Less common symptoms were expectoration (42.5%, n=170), dyspnoea (40%, n=160), headache (35%, n=140), diarrhoea (17.5%, n=70), palpitation (10%, n=40), and chest pain (7.5%, n=30). The distribution of these symptoms varied across the

severity categories, with a higher prevalence of severe symptoms such as dyspnoea and myalgia observed in the severe and critical groups.

In the asymptomatic group, no symptoms were reported. However, as the disease severity increased, the presence of symptoms became more pronounced. For example, in the mild illness group, 96.4% (n=135) of patients reported fever, while in the moderate illness group, 100% (n=95) of patients reported fever, and this trend continued in the severe and critical illness groups. Cough was present in 71.4% (n=100) of the mild cases and increased to 94.7% (n=90) in the moderate group, reaching 100% in the severe and critical groups. Fatigue showed a similar pattern, being present in 64.2% (n=90) of mild cases, 94.7% (n=90) of moderate cases, and 100% in both the severe and critical cases.

Table 2: Signs and Symptoms

Signs and Symptoms	All cases (400)	Asymptomatic (45)	Mild illness (140)	Moderate ill-ness (95)	Severe illness (85)	Critical ill-ness (35)
Fever	350 (87.5%)	0 (0%)	135 (96.4%)	95 (100.00%)	85 (100.0%)	35 (100.0%)
Cough	310 (77.5%)	0 (0%)	100 (71.4%)	90 (94.74%)	85 (100.0%)	35 (100.0%)
Fatigue	300 (75%)	0 (0%)	90 (64.2%)	90 (94.74%)	85 (100.0%)	35 (100.0%)
Myalgia	260 (65%)	0 (0%)	60 (42.8%)	80 (84.2%)	85 (100.0%)	35 (100.0%)
Chill	210 (52.5%)	0 (0%)	45 (32.1%)	50 (52.6%)	80 (94.1%)	35 (100.0%)
Anorexia	190 (47.5%)	0 (0%)	30 (21.4%)	40 (42.1%)	85 (100.0%)	35 (100.0%)
Expectoration	170 (42.5%)	0 (0%)	25 (17.8%)	30 (31.5%)	80 (94.1%)	35 (100.0%)
Dyspnoea	160 (40%)	0 (0%)	0 (0.00%)	40 (42.1%)	85 (100.0%)	35 (100.0%)
Headache	140 (35%)	0 (0%)	35 (25.0%)	40 (42.1%)	45 (52.4%)	20 (57.1%)
Diarrhoea	70 (17.5%)	0 (0%)	10 (7.1%)	20 (21%)	25 (29.1%)	15 (42.9%)
Palpitation	40 (10%)	0 (0%)	0 (0.00%)	5 (5.2%)	15 (17.5%)	20 (57.1%)
Chest pain	30 (7.5%)	0 (0%)	90 (64.2%)	0 (0.0%)	15 (17.5%)	15 (42.9%)

The mean Neutrophil-to-Lymphocyte Ratio (NLR) for the entire cohort was calculated to be 4.94 ± 3.12, with values ranging from 0.37 to 15.12. As shown in Table 3, the NLR values demonstrated a clear upward trend with increasing disease severity. For instance, the mean NLR in asymptomatic patients was 2.63, which gradually increased to 13.39 in critical patients. This significant elevation in NLR values from graduating from mild to critical cases indicates a significant correlation between higher NLR and covid-19 disease severity.

Similarly, the Platelet-to-Lymphocyte Ratio (PLR) which was analysed showed a mean value of 158.21 ± 72.4, ranging from 80.3 to 280.2. The PLR range also showed a significantly positive correlation with covid-19 disease severity, rising from a mean of 92.47 in asymptomatic cases to 201.2 in critical ones. These findings suggests that higher PLR values also are indicative of more severe disease states.

Table 3: Laboratory Findings and correlation with disease severity

Findings	All cases (400)	Asymptomatic (45)	Mild illness (140)	Moderate ill-ness (95)	Severe illness (85)	Critical illness (35)
Lym (×10^9/L; normal range 1.1-3.2)	0.97 (0.37-2.8)	1.82 (1.2-2.8)	1.09 (0.9-1.21)	0.78 (0.53-0.92)	0.60 (0.38-0.76)	0.56 (0.37-0.74)
Neut (×10^9/L; normal range 1.8-6.3)	4.8 (2.9-18.5)	3.9 (2.9-4.5)	4.8 (3.4-5.2)	5.5 (4.8-6.9)	6.8 (4.6-10.5)	7.5 (5.2-18.5)
Plat (×10^9/L; normal range 150-400)	152.5 (45.2-191.4)	168.3 (82.6-186.2)	156.2 (76.2-191.4)	132.7 (82-183.2)	111.2 (45.2-140.2)	112.2 (48-122.4)
NLR (NEU/LYM ratio)	4.94 (2.12-15.12)	2.63 (2.12-2.94)	4.40 (3.2-5.2)	7.05 (4.9-9.1)	11.33 (8.2-13)	13.39 (9.2-15.12)
NLR ≥5	215 (53.75%)	0 (0%)	5 (3.6%)	90 (94.7%)	85 (100%)	35 (100%)
NLR <5	185 (46.25%)	45 (100%)	135 (96.4%)	5 (5.3%)	0 (0%)	0 (0%)
PLR (Plat/Lym ratio)	158.21 (80.3-280.2)	92.47 (72.6-140.4)	143.1 (90.3-194.2)	170.21 (120.6-280.2)	185.22 (140.5-240.2)	201.2 (130.8-270.2)
CT- Score (Cycle threshold)	24 (16-32)	20.2 (19-29)	21.2 (17-32)	19.2 (16-28)	17.2 (16-22)	18.4 (17-28)

Statistical Analysis

ANOVA (Analysis of Variance): The mean NLR and PLR across the five severity categories (asymptomatic, mild, moderate, severe, and critical) were compared using the statistical ANOVA test. A statistically significant difference in both NLR and PLR values across the different severity groups, was observed in the analysis with a p-values of less than 0.001 for both the ratios, indicating strong evidence against the null hypothesis of no difference between the groups.

Correlation Analysis: To evaluate the strength of the relationship between NLR/PLR and disease severity Pearson's correlation coefficients were calculated. The correlation analysis resulted in findings suggestive of strong positive correlations, with Pearson's r = 0.65 for NLR and r = 0.58 for PLR, both with p-values less than 0.001. This shows that higher NLR and PLR values are strongly associated with increased disease severity.

Discussion

COVID-19 pandemic, which was caused by SARS-CoV-2, has resulted in tremendous challenges at the global level owing to its rapid human-to-human transmission and varying, severe clinical manifestations. The clinical characteristics of COVID-19 have similarities with previous outbreaks of coronavirus, such as SARS-CoV and MERS-CoV, but also has significantly distinct differences, particularly in viral tropism and symptomatology [14,15]. For example, fever and cough remain the dominant symptoms, while gastrointestinal symptoms are less frequent compared to those seen in SARS-CoV and MERS-CoV infections. This difference in clinical presentation warrant the need for reliable, easily availabe prognostic markers that can help predict disease severity and guide clinical management [15,16].

In the present study, we studied the prognostic value of the Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR) in COVID-19 rt-pcr positive patients. Our results showed that elevated NLR and PLR were significantly associated with more severe disease. The findings of this study aligns with those of previous studies suggesting that these ratios are reliable indicators of inflammation and can be utilised as effective prognostic markers in various medical conditions, including infectious diseases like COVID-19 [17,18,19].

Neutrophil-to-Lymphocyte Ratio (NLR): NLR has been extensively researched as markers of systemic inflammation and have shown to be promising markers as predictor of disease severity in COVID-19. [18,19] In the present study, the mean NLR values increased alongwi with disease severity, from 2.63 in asymptomatic patients to 13.39 in those with critical illness. This trend found in our study is consistent with those of other studies, such as those conducted by Yang et al. [18] , Liu et al., [19] and other studies, which identified elevated NLR as a reliable predictor of severe COVID-19 outcomes. The underlying mechanism for this association may be linked to the immune response triggered by COVID-19, where neutrophils play a crucial role in the initial defense against the virus [18,20]. However, excessive neutrophil activation can lead to tissue damage and exacerbate the inflammatory response, while a concurrent reduction in lymphocyte count (lymphopenia) reflects immune exhaustion and an impaired ability to control the infection [19,20,21].

Previous studies, such as those by Ying et al18. and Wang et al. [19], have shown that NLR is not only a marker of inflammation but also a predictor of outcomes in other diseases, including cancer and cardiovascular conditions. The role of NLR in COVID-19 can be understood within the context of these findings, where a high NLR is indicative of a disproportionate immune response, leading to more severe disease progression. This highlights the utility of NLR as a cost-effective and accessible marker that can be easily obtained from routine blood tests [19,20,21].

Platelet-to-Lymphocyte Ratio (PLR): Similar to NLR, PLR has emerged as a potential prognostic marker in COVID-19. Our study found that PLR values also correlated positively with disease severity, increasing from 92.47 in asymptomatic patients to 201.2 in critical cases. This observation is supported by previous research, including studies by Yang et al. [18] and Wang et al. [22], which reported elevated PLR levels in patients with severe COVID-19. The pathophysiological basis for this association may involve the hypercoagulable state induced by COVID-19, where elevated platelet counts and decreased lymphocyte levels contribute to an increased risk of thrombotic events. This prothrombotic environment is highly concerning in severe critical cases, where multiple complications such as deep vein thrombosis (DVT), pulmonary embolism, and disseminated intravascular coagulation (DIC) are more likely to occur [23].

The relationship between PLR and disease severity may also be influenced by the role of platelets in inflammation and immune response. Platelets not only contribute to coagulation but also interact with immune cells and secrete pro-inflammatory cytokines, thereby amplifying the inflammatory response. This dual role exhibited by platelets in thrombosis and inflammation validates the relevance of PLR as a promising marker of disease severity in COVID-19. Moreover, the use of PLR as a prognostic marker has been validated in other

diseases, such as colorectal cancer, as well where it has been shown to predict clinical outcomes [23,24].

Comparative Utility of NLR and PLR:Both the Neutrophil-to-Lymphocyte Ratio (NLR) and the Platelet-to-Lymphocyte Ratio (PLR) serve as important prognostic markers in COVID-19. However, some studies indicate that NLR may have a stronger predictive value than PLR. For instance, research by Wang et al. demonstrated that NLR had a higher area under the curve (AUC) in Receiver Operating Characteristic (ROC) analysis, suggesting greater reliability as a prognostic marker in COVID-19. This could be attributed to the fact that NLR directly reflects the balance between neutrophils and lymphocytes, which are central to the innate and adaptive immune responses. On the other hand, PLR may be affected by multiple factors, such as platelet reactivity and the prothrombotic state caused by COVID-19, which could affect its predictive accuracy.

Clinical Implications: The findings of the study have significant clinical implications, given the ease, availability and affordability of complete blood count (CBC) tests, which provides the necessary data for calculating NLR and PLR, these ratios can be easily and effectively incorporated into routine clinical management for COVID-19 patients. By the analysis of elevated NLR and PLR in patients at an early stage, clinicians can classify the patients based on their risk of developing severe disease and adjust treatment and monitoring plans accordingly. This might involve more rigorous monitoring, hospital admission and earlier initiation of antiviral or anti-inflammatory therapies, and prioritization for intensive care resources.

Limitations and Future Research: Despite these promising findings there are several limitations of the study. Firstly, this study was observational and conducted at a single centre, which limits the generalisability and applicability of the results to broader populations. Secondly, the study did not account for several factors that could influence NLR and PLR, such as underlying health conditions or medications that affect immune function. Additionally, owing to the cross-sectional design of the study, changes in NLR and PLR over the course of the disease, were not evaluated, which could provide further insights into their prognostic value.

Future research should aim to validate these findings through larger, multicentre studies and explore the dynamic changes in NLR and PLR over time, through a cohort study. The prognostic markers can further be enhanced by adding the combined use of NLR and PLR with other biomarkers, such as C-reactive protein (CRP) or D-dimer, to develop a more comprehensive prognostic tool for COVID-19.

Conclusion:

The findings of the present study suggests that NLR and PLR can be used as valuable prognostic markers for assessing disease severity in COVID-19 patients. Elevated levels of NLR and PLR are associated with poorer clinical outcomes and can help in identifying high-risk patients who can benefit from more intensive monitoring and treatment. The findings of this study contribute to the growing and actively pursued evidence supporting the use of haematological parameters in managing COVID-19 and validates the need for further research to enhance their clinical utility.

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