



THE ROLE OF HEMATOLOGICAL INFLAMMATORY BIOMARKERS: NEUTROPHIL LYMPHOCYTE RATIO (NLR), PLATELET LYMPHOCYTE RATIO (PLR) AND RDW IN COVID-19 PATIENTS.

Pathology

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ABSTRACT

Background : The novel coronavirus SARS-CoV-2, causing the new infectious disease COVID-19, has spread widely around the world. On March 11th World Health Organization (WHO) declared it as a global pandemic. There are various hematological and biochemical parameters alteration has been documented in SARS-Cov-2 infection. In addition, combined ratios of these parameters are also used as inflammation indexes and have been proposed as biomarkers to assist with the diagnosis, progress, and risk stratification. **Objectives of the study:** To investigate the role of Platelet-to-lymphocyte ratio [PLR], Neutrophil lymphocyte ratio (NLR) and Red cell distribution width [RDW] in COVID-19 disease and to study the prognostic impact of COVID-19 infection with the potential use of hematological diagnostic biomarkers. **Materials and Methods:** Neutrophil Lymphocyte Ratio (NLR), Platelet Lymphocyte Ratio (PLR) and RDW data available of 500 COVID 19 positive patients were collected from the pathology Laboratory RRMCH from April 2021 to September 2021, Data about age and gender of each patient are obtained from Laboratory Information system. **Results:** Elevated NLR (>3.5) is observed in severe COVID-19 cases, moderate NLR ($2.0-3.5$) seen in moderate cases, indicating ongoing inflammation and Normal NLR (<2.0) found in mild or asymptomatic cases. Platelet to Lymphocyte Ratio (PLR) has been found to be significantly elevated in COVID-19 patients compared to healthy individuals or non-COVID-19 controls, notably higher PLR in COVID-19 patients (314.95 ± 213.04) compared to controls (260.66 ± 203.57). This difference was statistically significant ($p = 0.0066$), suggesting that PLR may serve as a potential biomarker for identifying and assessing COVID-19 patients. **Conclusion:** the neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and RDW have been shown to be useful for the diagnosis and severity assessment of COVID-19 patients. NLR may serve as a surrogate marker of early risk identification in COVID 19 infection.

KEYWORDS

INTRODUCTION

The novel coronavirus SARS-CoV-2, causing the new infectious disease COVID-19, has spread widely around the world. On March 11th World Health Organization (WHO) declared it as a global pandemic. There are various hematological and biochemical parameters alteration has been documented in the literature in SARS-Cov-2 infection.

Clinical laboratory investigations are essential to confirm COVID-19 infection and also to follow up patient's health status. It has been found that coronaviruses can infect bone marrow cells leading to abnormal blood production (haematopoiesis). Thus, several changes have been reported in haematological parameters among COVID-19 patients.

Routine blood tests for the assessment of inflammatory processes are often useful in the early diagnosis of several diseases. In particular, the complete blood count is easy to perform, inexpensive, and provides information regarding various cell types and morphological parameters, i.e., white blood count, lymphocytes, neutrophils and platelet count (PLT) In addition, combined ratios of these parameters are also used as inflammation indexes and have been proposed as biomarkers to assist with the diagnosis, progress, and risk stratification of inflammatory diseases. Recently, the neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and RDW have been shown to be useful for the diagnosis and severity assessment of COVID-19 patients

Objectives of the study

1. To investigate the role of Platelet-to-lymphocyte ratio [PLR], Neutrophil lymphocyte ratio (NLR) and Red cell distribution width [RDW] in COVID-19 disease.
2. To study the prognostic impact of COVID-19 infection with the potential use of hematological diagnostic biomarkers PLR, NLR and RDW values.
3. To analyze the results and compare with the available literature.

MATERIALS AND METHODS:

Neutrophil Lymphocyte Ratio (NLR), Platelet Lymphocyte Ratio (PLR) and RDW data available of 500 COVID 19 positive patients were collected from the pathology Laboratory RRMCH. Data about age and gender of each patient are obtained from Laboratory Information system.

Inclusion Criteria

The patients who were confirmed to have SARS-CoV-2 infection by RT-PCR and the hematological parameters data available are included in the study. There are no restrictions on gender, age, race, or any comorbidities.

Exclusion Criteria

The patients with confirmed COVID – 19 positives but without the hematological parameters data are excluded from the study.

RESULTS

Table 1: Age Wise Distribution Of Covid-19 Patients

SNO.	AGE DISTRIBUTION	NO. OF PATIENTS (%)
1	< 1 Year	1 (0.2%)
2	1 to 16 Years	0 (0%)
3	16 – 20 Years	10 (2%)
4	21 – 40 Years	159 (31.8%)
5	40 – 60 Years	189 (37.8%)
6	60 – 80 Years	138 (27.6%)
7	> 80 Years	3 (0.6%)
Total		500 (100%)

The most common age group affected were between 40 and 60 years.

Table 2: Gender Wise Distribution Of Covid-19 Patients

1	Male	291 (58.2%)	MEAN AGE OF MALES	49.57 $\pm$ 15.82
2	Female	209 (41.8%)	MEAN AGE OF FEMALES	49.91 $\pm$ 14.49

500 RT-PCR positive for COVID-19 patients were included in the study, 58.8% of them were males and 41.2% of them were females their mean age was 49.57 $\pm$ 15.82 and 49.91 $\pm$ 14.49

Table 3: Laboratory Parameters In Covid-19 Positive Patients

SNO.	LABORATORY PARAMETERS	MEAN $\pm$ SD
1	Neutrophil Count	11.34 $\pm$ 11.59
2	Lymphocyte Count	1.22 $\pm$ 0.78
3	Platelet Count	249.37 $\pm$ 117.44
4	Red Cell Distribution Width	14.48 $\pm$ 2.68
5	Neutrophil to Lymphocyte Ratio	13.44 $\pm$ 13.93
6	Platelet to Lymphocyte Ratio	277.74 $\pm$ 207.92

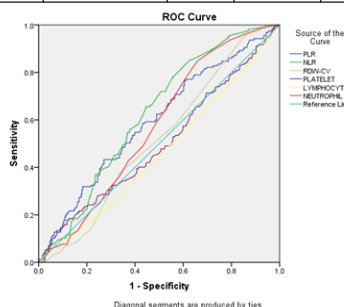
Patients with confirmed COVID-19 infection has low percentage of lymphocyte, Current study shows that those patients with confirmed RT-PCR positive for COVID-19 infection had low total count of white blood cells with lymphopenia with significant correlation.

Table 4: Laboratory Parameters In Covid-19 Patients And Covid-19 Patients In Icu

S NO.	LABORATORY PARAMETERS	PATIENTS ADMITTED IN ICU	PATIENTS NOT ADMITTED IN ICU	T VALUE	P VALUE
1	Neutrophil Count	11.61 $\pm$ 5.61	11.21 $\pm$ 13.49	0.3575	0.7209
2	Lymphocyte Count	1.08 $\pm$ 0.73	1.28 $\pm$ 0.80	2.6642	0.0080
3	Platelet Count	257.54 $\pm$ 151.76	245.62 $\pm$ 97.78	1.0530	0.2929
4	Red Cell Distribution Width	14.28 $\pm$ 1.93	14.57 $\pm$ 2.97	1.1194	0.2635
5	Neutrophil to Lymphocyte Ratio	15.08 $\pm$ 11.83	12.69 $\pm$ 14.75	1.7836	0.0751
6	Platelet to Lymphocyte Ratio	314.95 $\pm$ 213.04	260.66 $\pm$ 203.57	2.7260	0.0066

Table 4: Roc Analysis For Predicting The Requirement Of Icu Admission

LABORATORY PARAMETERS	AUC (95% CI)	CUT OFF	SENSITIVITY %	SPECIFICITY %	P VALUE
Neutrophil Count	0.570 (0.520-0.621)	2.50	99%	94%	0.0120
Lymphocyte Count	0.460 (0.406-0.514)	0.50	81%	85%	0.1520
Platelet Count	0.498 (0.442-0.553)	92.50	95%	96%	0.9350
Red Cell Distribution Width	0.517 (0.465-0.569)	10	99%	99%	0.5360
Neutrophil to Lymphocyte Ratio	0.623 (0.573-0.673)	1.90	99%	96%	0.0001
Platelet to Lymphocyte Ratio	0.592 (0.538-0.646)	102.76	89%	85%	0.0010



Elevated NLR (>3.5) is observed in severe COVID-19 cases, moderate NLR (2.0-3.5) seen in moderate cases, indicating ongoing inflammation and Normal NLR (<2.0) found in mild or asymptomatic cases.

Platelet to Lymphocyte Ratio (PLR) has been found to be significantly elevated in COVID-19 patients compared to healthy individuals or non-COVID-19 controls. The results (mean $\pm$ standard deviation) indicate a notably higher PLR in COVID-19 patients (314.95 $\pm$ 213.04) compared to controls (260.66 $\pm$ 203.57). This difference was

statistically significant ($p = 0.0066$), suggesting that PLR may serve as a potential biomarker for identifying and assessing COVID-19 patients.

Statistical analysis showed a p-value of 0.2635, indicating that there was no statistically significant difference in RDW

Therefore, based on these results, RDW does not appear to be significantly altered in COVID-19 patients compared to the control group studied.

DISCUSSION

The 2019 Coronavirus Disease (COVID-19) pandemic has threatened millions of people worldwide. Since the first outbreak of COVID-19 in Wuhan, China, researchers have extensively analysed the characteristics, clinical presentation and risk factors of individuals with SARS-CoV-2 infection.

Reliable laboratory diagnosis represents one of the main tools for the promotion, prevention, and control of infectious diseases. Other laboratory parameters have been used as an aid in the clinical monitoring of patients with COVID-19 [1,2]

The Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR) in COVID-19 infection underscores their potential as biomarkers for assessing disease severity and prognosis. Both ratios are derived from routine complete blood count (CBC) tests, making them easily accessible and cost-effective tools in clinical practice.

Inflammatory Response and Immune Dysregulation: COVID-19 triggers a complex interplay between the inflammatory response and immune dysregulation. Elevated NLR and PLR are often observed in severe cases, reflecting increased neutrophil counts and decreased lymphocyte counts relative to platelets. This imbalance suggests a heightened inflammatory state and impaired immune response, which are characteristic of severe COVID-19 disease.

Numerous studies have demonstrated the prognostic value of NLR and PLR in COVID-19 patients. Higher NLR and PLR values at admission have been associated with worse outcomes, including increased risk of ICU admission, mechanical ventilation, and mortality. Conversely, lower ratios have been correlated with milder disease courses and better recovery.

Lippi G et al carried out a systematic literature review and highlighted that the most important hematological parameter abnormalities observed in COVID-19 patients, which may predict the progression toward severe or critical forms of COVID-19, include leukocytosis, neutrophilia, and lymphopenia. Each of these prognostic parameters retains a specific clinical and biological significance, which, altogether, can contribute to reflect the evolution toward more unfavourable clinical pictures. [3]

From a study conducted in Huizhou, China of the 30 COVID 19 cases with increased platelets and prolonged hospital stay is due to cytokine storm which means The Platelet Lymphocyte Ratio (PLR) provide a novel biomarker for monitoring the patients with COVID-19. [4]

The Neutrophil-to-Lymphocyte ratio (NLR) is a biomarker for the assessment of the severity of bacterial infections and the prognosis of patients with pneumonia and tumor.

NLR may serve as a surrogate marker of early risk identification in COVID 19 infection

Clinically, NLR and PLR can aid in risk stratification and early identification of patients at higher risk of developing severe complications. This allows for timely allocation of resources and implementation of appropriate therapeutic strategies, such as early administration of anti-inflammatory agents or immunomodulators. [5] Despite their potential, several factors influence the interpretation of NLR and PLR in COVID-19. Variations in patient demographics, comorbidities, and stages of infection can affect these ratios. Additionally, while elevated ratios generally indicate inflammation and severity, they do not provide specific mechanistic insights into disease progression or response to treatment. [6]

Future Directions: Ongoing research is essential to validate the consistency and reliability of NLR and PLR as prognostic markers across diverse patient populations and healthcare settings. Further investigation into the underlying mechanisms driving these ratios in COVID-19 could enhance their clinical utility and inform personalized treatment approaches. [7,8]

While NLR and PLR offer valuable insights into the inflammatory and immune responses in COVID-19 infection, their clinical application requires careful consideration of context and additional validation. Integrating these biomarkers into comprehensive patient management protocols has the potential to improve outcomes by facilitating early intervention and optimized care strategies. [9,10, 11]

Lymphocytes play a crucial role in inflammation, including during conditions like COVID-19, primarily through their adaptive immune responses. Once activated by antigen recognition, lymphocytes initiate and coordinate the immune response. This includes the production of cytokines and chemokines that recruit other immune cells to the site of infection, enhancing inflammation to combat the virus. The circulating leukocytes respond to stress by elevating the neutrophils and decreased lymphocytes and the ratio of these two parameters serves as an inflammatory biomarker in many diseases including COVID 19 [12,13]

Considering previous research, the use of circulating biomarkers representing inflammation and the immune system have been considered as a prognostic indicator in COVID-19-positive patients. Neutrophil lymphocyte ratio (NLR) = Absolute neutrophil count/Absolute lymphocyte count. Platelet lymphocyte ratio = absolute. PLT/absolute lymphocyte count. act as surrogates to assess the extent of systemic inflammation. [14,15]

CONCLUSION:

The Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR) have emerged as valuable indicators in assessing the severity and prognosis of COVID-19 infections.

These ratios reflect the dynamic interplay between inflammatory response and immune regulation in affected individuals. Studies consistently demonstrate their potential as cost-effective and accessible biomarkers that aid in early identification of high-risk patients, guiding timely interventions and improving clinical outcomes in various other diseases like diabetes mellitus and autoimmune disorders.

Despite variations in findings across populations and stages of infection, the trend supports their utility in risk stratification and therapeutic decision-making. Continued research is crucial to further elucidate their mechanistic relevance and optimize their clinical application amidst evolving epidemiological trends and treatment protocols.

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