The Egyptian Journal of Hospital Medicine (April 2022) Vol. 87, Page 2119-2124

Correlation between Platelet to Lymphocyte Ratio and the Severity of COVID-19 in Zagazig University Hospitals

Nariman Nabil Mohamed Hassan*, Neveen George Elantouny, George Emad Shaker, Heba Shafeak Abd El Khalik
Department of Internal Medicine, Faculty of Medicine, Zagazig University, Egypt
***Corresponding author:** Nariman Nabil Mohamed Hassan, **Email:** narimannabil.123@gmail.com

ABSTRACT

Background: It is possible to predict the severity of COVID-19 based on the platelet-to-lymphocyte ratio (PLR), which is a novel biomarker.

Objective: This study was aimed to evaluate the correlation between PLR levels and the severity of COVID-19 patients in Zagazig University Hospital.

Patients and Methods: At Zagazig University Hospitals' Isolation Hospital, a comparative cross-sectional study was conducted on 48 confirmed COVID-19 patients over the age of 18 of both sexes. Patients were categorized into two groups based on the severity of their symptoms (mild and severe) At least one of the following criteria was met by very ill patients: 1- Oxygen saturation is below 93% in the resting condition. 2- Breathing difficulty, RR equal or higher than 30 times/min. All patients underwent a laboratory investigations with assessment of PLR.

Results: A higher platelet count/lymphocyte ratio was not related with more severe disease since the median in severe cases (197.31) was somewhat higher than the median in mild cases (184.72) with non-statistically significant differences. Our study proved a strong correlation between a decrease in platelet count and the severity of illness. Because of its low AUC of 0.559, PLR was ruled out as a diagnostic biomarker that might be used to predict the severity of disease. The optimal cut-off value was ≥ 5.1464, sensitivity was 60%, specificity was 55.6%, positive predictive value (PPV) was 69.2%, negative predictive value (NPV) was 45.5% and its accuracy was 58.3% ($p>0.05$).

Conclusion: PLR could not be used as a potential diagnostic marker for COVID 19 disease severity.

Keywords: Platelet lymphocyte ratio, COVID-19.

INTRODUCTION

In Wuhan, China, a new type of pneumonia was discovered in December 2019 and later dubbed "novel corona virus pneumonia" (NCP) **(1).** At first, the infection was thought to have been spread from animal to human without any connection to any particular species of animal **(2).**

The majority of patients had minor symptoms. Acute respiratory distress syndrome (ARDS) or multiple organ failure (MOF) can occur in COVID-19 patients **(3).**

COVID-19 can be diagnosed using PCR, a chest CT scan that may show multiple, multi-lobar areas of ground-glass opacity, and laboratory tests **(4)**.

It is relatively simple and inexpensive to measure the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR), two novel biomarkers, in routine laboratory studies. Infectious disease patients who have elevated NLR and PLR are more likely to die and have a worse prognosis **(5).** Increased PLR during hospitalization could also be an indication of how the disease will progress **(6).**

The aim of the current work was to evaluate platelet to lymphocyte ratio as an effective prediction of severity of covid-19 among Zagazig university hospital COVID-19 patients.

PATIENTS AND METHODS

This comparative cross-sectional study included a total of 48 confirmed COVID-19 patients over the age of 18 of both sexes, attending at Zagazig University Hospitals' Isolation Hospital. Patients were categorized into two groups based on the severity of their symptoms (mild and severe).

***Ethical Consideration*:**

An approval of the study was obtained from Zagazig University Academic and Ethical Committee (ZU-IRB#6952). Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Inclusion Criteria: Confirmed cases of COVID-19 by PCR, and patients with age group older than 18 years of both sexes.

Exclusion criteria: Patients aged under 18 years, and COPD, hematological illnesses, liver disease, radiation, and chemotherapy. These conditions might alter blood cell count during the time of COVID-19.

Each participant was subjected to:

1. **Full history taking and thorough physical examination** with emphasis on demographic and clinical data.
2. Samples of blood were immediately taken and sent to a laboratory for analysis for **routine and specific investigations** with assessment of complete blood count (CBC) before any interventional measures and fluid administration.

Received: 24/11/2021
Accepted: 22/01/2022

3. **Laboratory Investigations included** CBC with calculation of blood indices (Hemoglobin, Hematocrit, MCV, MCH, MCHC), liver function tests (LFTs), kidney function tests (KFTs), arterial blood gases, LDH, D-dimer, serum ferritin, and C-Reactive Protein

Statistical analysis

Using SPSS software (USA) version 16. Numbers and percentages are used to represent data (percent) or mean ± SD. Different qualitative factors were examined using the Chi square (X^2) test. Fisher's Exact or Monte Carlo correction, Student t-test, as well as Mann Whitney test were used. If the significant probability was less than 0.05, the threshold for statistical significance, the results were considered statistically significant and highly significant. P value < 0.05 was considered significant.

RESULTS

Table (1) shows that about 64.6% of the 48 studied patients were males. Distribution of the studied patients according to associated comorbidities. Out of them, 45.8%, 37.5% and 16.7% had comorbid diabetes, hypertension and heart diseases respectively. Twelve patients had no comorbidities

Table (1): Distribution of the studied patients according to demographic data and comorbidities:

	N=48	**%**
Sex:		
Female	**17**	**35.4%**
Male	**31**	**64.6%**
	N=48	**%**
Comorbidities		
Diabetes	**22**	**45.8%**
Hypertension	**18**	**37.5%**
Heart disease	**8**	**16.7%**
No	**12**	**25%**

Table (2) shows that disease severity did not differ significantly with sex, presence of comorbid diabetes, hypertension or heart disease (about 73% of those with severe disease versus 50% of mild form were males). Diabetes, hypertension and heart diseases prevailed in 53.3%, 40% and 16.7% respectively within severe disease versus 33.3%, 33.3% and 16.7% respectively within mild form.

Table (2): Relation between disease severity and both demographic data and comorbidities:

Parameter	**Disease severity**		**Test**	
	Mild	**Severe**	**χ^2**	**P**
	N=18 (%)	**N=30 (%)**		
Sex:				
Female	9 (50%)	8 (26.7%)		
Male	9 (50%)	22 (73.3%)	2.678	0.102
Comorbidities				
Diabetes	6 (33.3%)	16 (53.3%)	1.813	0.718
Hypertension	6 (33.3%)	12 (40%)	0.213	0.644
Heart disease	3 (16.7%)	5 (16.7%)	0	>0.999
No	5 (27.8%)	7 (23.3%)	0.077	0.781

Table (3) shows that disease severity differ significantly with each of neutrophil, lymphocyte, platelet count, AST, creatinine, BUN, serum albumin, and total bilirubin. Severe disease was associated was higher neutrophil, lower lymphocytes, lower platelet count and serum albumin, higher AST, creatinine, BUN, and total bilirubin. There is non-significant relation between disease severity and ALT or direct bilirubin.

Table (3): Relation between disease severity and routine laboratory data

Parameter	Disease severity		Test	
	Mild	Severe	Z	p
	Median (range)	Median(range)		
Neutrophil (mcL)	4.47 ± 0.91	9.1 ± 1.56	-5.092	<0.001**
Lymphocyte (mcL)	1.4 ± 0.17	0.8 ± 0.13	-3.144	0.002*
Platelet count (mcL)	211 ± 48.31	187.5 ± 40.1	-2.833	0.005*
ALT (U/L)	25.2 ± 5.71	31.2 ± 7.12	-1.672	0.095
AST (U/L)	25.75 ± 6.12	43 ± 8.32	-4.932	<0.001**
Creatinine (mg/dl)	0.78 ± 0.11	1.52 ± 0.23	-4.101	<0.001**
BUN (mg/dl)	64.8 ± 12.35	130.2 ± 28.64	-4.686	<0.001**
T. bilirubin (µmol/L)	0.44 ± 0.11	0.7 ± 0.10	-2.844	0.004*
D. bilirubin (µmol/L)	0.23 ±0.031	0.27± 0.1	-0.32	0.749
Serum albumin (g/dl)	3.29 ± 0.27	2.97 ± 0.25	4.708	<0.001**

Table (4) shows that disease severity did not differ significantly with platelet count/lymphocyte ratio. Severe disease was associated was higher platelet count/ lymphocyte ratio.

Table (4): Relation between disease severity and platelet count/lymphocyte ratio among the studied patients

Parameter	Disease severity		Test	
	Mild	Severe	Z	p
	Median (range)	Median (range)		
Platelet/lymphocyte ratio	184.72 ± 41.23	197.31 ± 44.32	-0.596	0.551

Table (5) shows that there was statistically significant negative correlation between platelet/lymphocyte ratio and lymphocyte. There was statistically non-significant positive correlation between platelet/lymphocyte ratio and either neutrophil, AST, creatinine, BUN., ALT, direct and total bilirubin

Table (5): Correlation between platelet count/lymphocyte ratio and the studied routine laboratory data:

	R	p
Neutrophil (mcL)	0.075	0.613
Lymphocyte (mcL)	-0.579	<0.001**
Platelet count (mcL)	0.37	0.01*
ALT (U/L)	-0.109	0.463
AST (U/L)	-0.018	0.902
Creatinine (mg/dl)	0.098	0.507
BUN (mg/dL)	-0.118	0.425
T. bilirubin (µmol/L)	-0.081	0.586
D. bilirubin (µmol/L)	-0.103	0.487
Serum albumin (g/dl)	0.112	0.45

Table (6) shows that there was statistically non-significant correlation between platelet/lymphocyte ratio and either CRP, LDH, d dimer or serum ferritin.

Table (6): **Correlation between platelet count/lymphocyte ratio and the studied acute phase reactants:**

	R	p
CRP (mg/L)	0.092	0.533
LDH (U/L)	-0.11	0.457
D dimer (mg/L)	-0.032	0.827
Ferritin (µg/L)	-0.076	0.608

Table (7) and figure (1) shows that the best cutoff of platelet count/lymphocyte ratio in prediction of severe disease is ≥5.1464 with area under curve 0.559, sensitivity60%, specificity55.6%, positive predictive value (PPV) 69.2%, negative predictive value (NPV) 45.5%, accuracy 58.3% (p>0.05).

Table (7): Performance of platelet count/lymphocyte ratio in prediction of severe disease:

Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy	p
≥186.06	0.559	60%	55.6%	69.2%	45.5%	58.3%	0.498

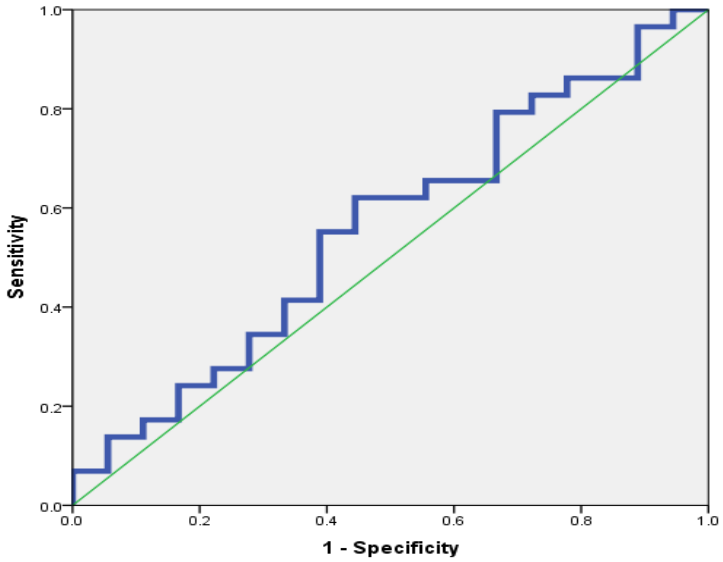

Figure (1): ROC curve showing performance of platelet count/lymphocyte ratio in prediction of severe disease

DISCUSSION

With a median incubation period of three days and a low death rate, COVID-19 has caused an outbreak that has moved rapidly from person to person [(7)].

COVID-19 shares several clinical features with SARS-CoV. Compared to SARS-CoV, MERS-CoV, and influenza, the predominant symptoms were fever and cough, with gastrointestinal symptoms being infrequent [(8)].

The mildest type of the illness was found in the majority of COVID-19 cases. Death is common in individuals with delayed innate immune responses that suddenly intensify during the second week of admission, resulting in a deadly over-inflammation. As a result, it is imperative to accurately forecast COVID-19 refractoriness and critical disease as soon as possible [(9)].

Inflammatory and hematological biomarkers including C-Reactive protein, d-dimer, Ferritin, and coagulation profile might play an important role in predicting disease severity and providing better guidance for rapid care of patients, therefore, reducing disease mortality as well as morbidity [(10)].

For patients with viral pneumonia, many studies have looked at the inflammatory markers peripheral white blood cell count, NLR ratio, platelet to lymphocyte ratio, and lymphocyte to monocyte ratio as indicators of prognosis [(11)].

New biomarkers such as neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio are easy to obtain from normal laboratory investigations and provide vital information about the systemic inflammatory status. Patients with infectious disorders have a higher mortality rate when their NLR and PLR are raised [(12)].

Study participants in the Isolation Hospital in Zagazig University Hospitals who have been verified to have COVID-19 include 48 patients who are at least 18 years of age, both sexes. The majority of patients were males (n=31, 64.6%) and the females (n=17, 35.4%) unlike **Sebo *et al.*** [(13)] who first reported this information (63 percent of patients were female). Patients were divided into two categories based on the severity of their COVID: severe and mild. 62.5 percent of the cases were severe, including critical illness, and 37.5 percent were mild.

There was non-statistically significant relation between disease severity and sex, (about 73% of those with severe disease versus 50% of mild form were males). These results were in line with **Yang *et al.*** [(4)] who reported in terms of gender, there was no noticeable difference.

A quarter (n=12) of the patients had no pre-morbidity, while the remainder (n=48) had underlying chronic health issues. There were 45.8% (n=22) with diabetes, 37.5% (n=18) with hypertension, and 16.7% (n=8) with heart disease who also had one of the other premorbid disorders.

Diabetes was a common incidence among the most severely ill people (53.3%), hypertension (40%) and heart diseases (16.7%) versus mild case patients which exhibited 33.3%, 33.3% and 16.7% respectively. There was non-statistically significant relation between disease severity, presence of comorbid diabetes, hypertension or heart disease, may be due to population heterogeneity. Unlike **Yang *et al.*** [(4)] study which showed Diabetes, hypertension, and renal failure were all found to be present in a significant number of severe case patients (p lower than 0.01).

According to PLR, we could identify that, severe disease was not associated with higher platelet count /lymphocyte ratio, as the median in severe cases was (197.31) tended to be slightly higher than the median in mild cases (184.72) with non-statistically significant difference. Unlike our results, **Mousavi *et al.*** [(14)] have discovered a direct link between a high PLR (>233) and an increased risk of death in individuals with the cancer Covid-19. A higher PLR is related with more severe

sickness in COVID-19 patients compared to those with moderate disease, according to a recent systematic review by **Simadibrata *et al.* [15].** Patients with COVID-19 had a linear correlation between the severity of their illness and their length of hospitalization, according to their study.

Our study revealed significant association of platelet count with the severity of disease. These results were in agreement with **Liao *et al.* [16]** they found that patients with critical and severe illness had a much lower platelet count, while **Fan [17]** only 20% of the patients in his research had moderate thrombocytopenia. Patients with COVID-19 have been reported to have thrombocytopenia, which has been linked to an increased risk of in-hospital mortality in research by **Szklanna *et al.* [18]**.

Hospitalized patients with a low lymphocyte count and increased CRP, D-dimers, ferritin, cardiac troponin, and IL-6 levels may be at greater risk of developing severe and fatal COVID-19 if clinicians take these factors into consideration [19].

In the present study, severe disease was associated was higher levels of each of CRP, LDH, D dimer and serum ferritin. These results were consistent with **Chen *et al.* [20], Ruan *et al.* [21] and Sun *et al.*[22]** who confirms that the inflammatory indicators such as CRP and ESR, serum ferritin LDH and D dimer were higher in the severely and critically ill participants.

According to our results, PLR could not be used as a potential diagnostic biomarker for predicting disease severity because its AUC was weak 0.559. The optimal cut-off value was ≥ 5.1464, sensitivity 60%, specificity 55.6%, positive predictive value (PPV) 69.2%, negative predictive value (NPV) 45.5%, accuracy 58.3% (p>0.05). Our results were comparable with **Qu *et al.* [6] and Sun *et al.* [22]**.

Our finding disagreed with **Asghar *et al.* [23] and Zhao *et al.* [5]** as **Asghar *et al.* [23]** showed that Pre-admission higher PLR levels have been linked to disease severity (95% CI: 0.576–0.816, AUC: 0.696). **Zhao *et al.* [5]** found high PLR to be 274 (AUC: 0.69 had sensitivity: 57% as well as specificity: 79%. A PLR difference of 126.7 is the cut-off point had 81.5% specificity, as well as 100% sensitivity and ($p = 0.014$) proven by **Qu *et al.* [6].**

CONCLUSION

Patients with COVID-19 have a wide range of hematological and coagulation abnormalities, including elevated inflammatory markers induced by different cytokines and liver enzymes. For patients with COVID-19, ICU admission is mostly dependent on their clinical condition and concurrent conditions, however various laboratory measures can aid in the evaluation of disease severity and reasonable triaging.

For COVID 19 severity, our study found that PLR could not be employed as a potential diagnostic marker.

Financial support and sponsorship: Nil.

Conflict of interest: Nil.

REFERENCES

1. **Zhu N, Zhang D, Wang W *et al.* (2020):** A Novel Coronavirus from Patients with Pneumonia in China, 2019. The New England Journal of Medicine, 382(8): 727–733.
2. **Oliveira B, Oliveira L, Sabino E *et al.* (2020):** SARS-CoV-2 and the COVID-19 disease: a mini review on diagnostic methods. Revista do Instituto de Medicina Tropical de Sao Paulo, 62: 44-48.
3. **Rothan H, Byrareddy S (2020):** The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. Journal of Autoimmunity, 109: 433-38.
4. **Yang A, Liu J, Tao W *et al.* (2020):** The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. International Immunopharmacology, 84: 504-8.
5. **Zhao Y, Yu C, Ni W *et al.* (2021):** Peripheral blood inflammatory markers in predicting prognosis in patients with COVID-19. Some differences with influenza A. Journal of Clinical Laboratory Analysis, 35(1): 657-62.
6. **Qu R, Ling Y, Zhang Y *et al.* (2020):** Platelet-to-lymphocyte ratio is associated with prognosis in patients with coronavirus disease-19. Journal of Medical Virology, 92(9): 1533–1541.
7. **Li Z, Yi Y, Luo X *et al.* (2020):** Development and clinical application of a rapid IgM-IgG combined antibody test for SARS-CoV-2 infection diagnosis. Journal of Medical Virology, 92(9): 1518–1524.
8. **Guo L, Ren L, Yang S *et al.* (2020):** Profiling early humoral response to diagnose novel coronavirus disease (COVID-19): Clin Infect Dis., 71: 778-785.
9. **Kerboua K (2021):** NLR: A Cost-effective Nomogram to Guide Therapeutic Interventions in COVID-19. Immunological Investigations, 50(1): 92-100.
10. **Taj S, Kashif A, Arzinda Fatima S *et al.* (2021):** Role of hematological parameters in the stratification of COVID-19 disease severity. Annals of Medicine and Surgery, 62: 68-72.
11. **Aly M, Meshref T, Abdelhameid M *et al.* (2021)**: Can Hematological Ratios Predict Outcome of COVID-19 Patients? A Multicentric Study. J Blood Med., 12: 505-515.
12. **Wang X, Li X, Shang Y *et al.* (2020):** Ratios of neutrophil-to-lymphocyte and platelet-to-lymphocyte predict all-cause mortality in inpatients with coronavirus disease 2019 (COVID-19): a retrospective cohort study in a single medical centre. Epidemiology and Infection, 148: 211-214.
13. **Sebo P, Tudrej B, Lourdaux J *et al.* (2021):** Cross sectional study of the clinical characteristics of French primary care patients with COVID-19. Scientific Reports, 11(1): 492-96.
14. **Mousavi S, Rad S, Rostami T *et al.* (2020):** Hematologic predictors of mortality in hospitalized patients with COVID-19: a comparative study. Hematology, 25(1): 383-388.
15. **Simadibrata D, Pandhita B, Ananta M *et al.* (2020):** Platelet-to-lymphocyte ratio, a novel biomarker to predict the severity of COVID-19 patients: A systematic review and meta-analysis. Journal of the Intensive Care Society, 20: 587-91.

16. **Liao D, Zhou F, Luo L *et al.* (2020):** Haematological characteristics and risk factors in the classification and prognosis evaluation of COVID-19: a retrospective cohort study. The Lancet Haematology, 7(9): 671-678.
17. **Fan B (2020):** Hematologic parameters in patients with COVID-19 infection: a reply. American journal of hematology, 95(8): 223-228.
18. **Szklanna P, Altaie H, Comer S *et al.* (2021):** Routine Hematological Parameters May Be Predictors of COVID-19 Severity. https://www.frontiersin.org/articles/10.3389/fmed.2021.682843
19. **Velavan T, Meyer C (2020):** Mild versus severe COVID-19: Laboratory markers. International Journal of Infectious Diseases, 95: 304-307.
20. **Chen L, Li X, Chen M *et al.* (2020):** The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. Cardiovasc Res., 116: 1097-1100.
21. **Ruan Q, Yang K, Wang W *et al.* (2020):** Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Medicine, 46(5): 846-848.
22. **Sun S, Cai X, Wang H *et al.* (2020):** Abnormalities of peripheral blood system in patients with COVID-19 in Wenzhou, China. Clinica Chimica Acta; International Journal of Clinical Chemistry, 507: 174–180.
23. **Asghar M, Khan N, Haider Kazmi S *et al.* (2020):** Hematological parameters predicting severity and mortality in COVID-19 patients of Pakistan: a retrospective comparative analysis. J Community Hosp Intern Med Perspect., 10(6): 514-520.

.