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Original Research Article

A Comprehensive Analysis of CRP, D-Dimer, and CBC as Inflammatory Markers in Adult Patients with COVID-19

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Abstract

Background and Objectives: Given the highly contagious nature of COVID-19, numerous healthcare systems worldwide are strained to their limits. It is imperative to establish straightforward and expeditious risk stratification methods for the identification of severe cases. This study endeavors to underscore the utility of readily accessible laboratory biomarkers with robust predictive value for assessing the severity of COVID-19.

Methodology: A retrospective collection of data involved 118 individuals who tested positive for COVID-19. All fundamental laboratory biomarkers such as anemia, leukocytosis, lymphopenia, Neutrophil-to-Lymphocyte Ratio (NLR), in conjunction with C - reactive protein (CRP), and D-dimer at the time of admission were meticulously documented.

Results: Parameters such as anemia, leukocytosis, lymphopenia, Neutrophil-to-Lymphocyte Ratio (NLR), in conjunction with C - reactive protein (CRP), and D-dimer were notably elevated. Nevertheless, through the application of multivariate logistic regression, solely anemia, elevated NLR, elevated PLR, and heightened D-dimer levels demonstrated a significant association with the risk of ICU admission.

Conclusion: At the time of admission, anemia, a Neutrophil-to-Lymphocyte Ratio exceeding 8.5, a Platelet-to-Lymphocyte Ratio surpassing 193, and a D-dimer level exceeding 1 mg/L emerge as accessible and straightforward predictors for identifying severe COVID-19 cases necessitating ICU admission.

Keywords: COVID-19, Neutrophil-to-lymphocyte ratio, Anemia, D-dimer, CRP.

Introduction

Since the World Health Organization (WHO) declared COVID-19 a pandemic in March 2020, this infection has emerged as a significant threat to human health, exerting substantial strain on the resources of efficient healthcare systems. Globally, many hospitals are grappling with a shortage of Intensive Care Unit (ICU) beds for critically ill COVID-19 patients. Establishing a hazard stratification based on clinical, radiological, and laboratory factors becomes imperative to effectively categorize patients requiring hospitalization or ICU admission. Although several laboratory biomarkers are initially employed for predicting or diagnosing COVID-19 infection, their accuracy in assessing infection severity and prognosis, along with the critical threshold levels for concern, remains to be thoroughly evaluated [1].

Lymphopenia, leukocyte counts, and elevated neutrophil levels are proposed as straightforward initial parameters for distinguishing between severe and non-severe COVID-19 cases. T cells, crucial for antiviral immunity, experience a decline in count in COVID-19 cases, but the factors causing this decline and the activation status of T cells remain largely unclear. Increased prothrombin time and elevated D-dimer values may serve as indicators of a worsened prognosis, attributed to dysregulated coagulopathy in severe COVID-19 cases. Inflammation-related proteins, such as elevated procalcitonin, C-reactive protein (CRP) levels, and serum ferritin, are discriminators between mild and severe COVID-19 cases [2-7]. Additional inflammatory cytokines like Interleukin-2R (IL-2R) and Interleukin-6 (IL-6), along with biochemical factors including liver enzymes, kidney function tests, and lactic dehydrogenase

(LDH), may also exhibit marked alterations in severe COVID-19 patients [8–11].

The objective of this study is to underscore accessible laboratory biomarkers with robust predictive value for COVID-19 severity and identify precise cut-off points for these markers.

Material and Methods

In a retrospective observational cohort study conducted on COVID-19 patients admitted to a tertiary hospital in India, all participants received a diagnosis of COVID-19 in accordance with the definitions provided by the World Health Organization (WHO) and the Egyptian Ministry of Health and Population (MOHP) [12,13]. Confirmation of cases was achieved through RT-PCR detection, employing a total coverage sample that included all patients admitted during the study period in the designated hospitals. The inclusion criteria encompassed all adult hospitalized COVID-19 patients, irrespective of gender or disease severity level. Upon reviewing records, individuals younger than 18 years or those lacking laboratory data or primary outcome status were excluded from the study.

Clinical records and laboratory data underwent thorough examination, with the extraction of the following information for analysis: demographic and clinical data, including age, gender, presenting symptoms, comorbidities, and outcomes; laboratory investigations encompassing a complete blood count, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and D-dimer; additionally, C-reactive protein (CRP) levels were assessed.

Results

A total of 118 participants were included in the study, comprising 40 (33.90%) females and 78 (66.10%) males. The mean age of the participants was 54.85 years, with a standard deviation of 16.55. The majority of participants presented with fever (66.95%), followed by constitutional symptoms (27.97%), cough (62.71%), dyspnea (33.90%), and gastrointestinal (GIT) symptoms (22.88%). 105 participants (88.98%) reported no history of Diabetes Mellitus, while 13 participants (11.02%) had a history of this condition. Regarding hypertension, 107 participants (90.68%) had no history, whereas 11 participants (9.32%) reported a history of hypertension. A total of 112 participants (94.92%) reported not being vaccinated for COVID-19, while 6 participants (5.08%) had received the COVID-19 vaccine (Table 1).

Table 1: Clinico-demographic parameters of study participants

Variable	n	%
Gender		
Female	40	33.90
Male	78	66.10
Age (Mean ± SD)	54.85 ± 16.55	
Presenting symptoms		
Fever	79	66.95
Constitutional symptoms	33	27.97
Cough	74	62.71
Dyspnea	40	33.90
GIT symptoms	27	22.88
History of Diabetes Mellitus		
No	105	88.98
Yes	13	11.02
History of Hypertension		
No	107	90.68
Yes	11	9.32
Vaccinated for COVID-19		
No	112	94.92
Yes	6	5.08

The platelet count in COVID-19 patients averaged 211,438.94 ± 103,690.20, and the hemoglobin level was 11.48 ± 1.92 g/dL. Total leukocyte count (TLC) was measured at 11,478.95 ± 4,757.94 cells/μL. Neutrophil count and lymphocyte count exhibited mean values of 82.43 ± 9.49% and 10.87 ± 8.06%, respectively. The Neutrophil-to-Lymphocyte Ratio (N/L Ratio) was calculated at 5.21 ± 2.62, and the Platelet-to-Lymphocyte Ratio (P/L Ratio) averaged 250.45 ± 170.26. D Dimer levels were recorded at 972.02 ± 2,119.06 ng/mL, and C - reactive protein (CRP) levels were observed at 2,739.70 ± 3,143.19 mg/L (Table 2).

Table 2: Laboratory Parameters of study participants

Laboratory Parameter	Mean ± SD
Platelets	211438.94 ± 103690.20
Haemoglobin	11.48 ± 1.92
TLC	11478.95 ± 4757.94
Neutrophil Count	82.43 ± 9.49
Lymphocyte Count	10.87 ± 8.06
N/L Ratio	5.21 ± 2.62
P/L Ratio	250.45 ± 170.26
D DIMER	972.02 ± 2119.06
CRP	2739.70 ± 3143.19

Through the application of multivariate logistic regression, solely anemia, elevated NLR, elevated PLR, and heightened D-dimer levels demonstrated a significant association with the severity of disease (Table 3).

Table 3: Logistic regression for predictors of severity of disease

Factors	Multivariate Analysis	
	OR (95% CI)	p value
Age (≥ 55 years)	0.95 (0.550–1.6)	0.651
Gender Male	1.5 (0.78–2.9)	0.109
Fever	1.2 (0.59–2.7)	0.621
Constitutional symptoms	1.4 (0.79–2.8)	0.274
Cough	0.9 (0.58–1.8)	0.788
Dyspnea	2.1 (1.2–4.5)	< 0.05
Presence of comorbidity	2.8 (1.2–5.6)	< 0.05
Anemic (HB < 12 g/dl)	3.1 (1.6–5.7)	< 0.05
WBCs Low (< 4) [(Ref. = 4–10*10³/µl)]	1.8 (0.75–4.3)	0.396
WBCs High (> 10)	1.15 (0.61–2.1)	0.807
High NLR (> 8)	6.5 (2.3–15.2)	< 0.05
High PLR (> 192)	2.8 (1.2–6.4)	< 0.05
High D-dimer (> 0.9 mg/L)	1.8 (1.1–3.4)	< 0.05
High CRP (> 23 mg/dl)	1.4 (0.78–2.2)	0.421

Discussion

The global surge in COVID-19 cases is significantly impacting healthcare systems, particularly the availability of ICU beds. Consequently, timely identification of severe cases is essential for swift patient triage. Factors such as clinical presentation, comorbidities, radiological infiltration extent, and blood oxygen saturation can guide the decision to admit COVID-19 patients to ICUs. Additionally, various laboratory parameters play a crucial role in assessing the severity of the disease.

This study involved 118 patients, with 50 (42.37%) requiring ICU admission. Those admitted to the ICU were predominantly older males with a higher frequency of fever, dyspnea, and cough, along with comorbid conditions. Key indicators such as anemia, leukocytosis, lymphopenia, elevated NLR and PLR, and increased levels of CRP, and D-dimer were significantly associated with ICU admission. However, multivariate regression analysis identified only high NLR (> 8.5), PLR (> 193), and D-dimer (> 1 mg/l) as significant risk factors for severe COVID-19 infection requiring ICU admission.

Complete blood count serves as a vital diagnostic tool for COVID-19, aiding in both diagnosis and severity assessment. Anemia is linked to an increased risk of severe infection through mechanisms including reduced oxygen delivery due to low hemoglobin levels, aggravating hypoxemia and playing a role in multi-organ failure. Additionally, SARS-CoV-2 interaction with erythrocyte receptors may lead to hemolysis, contributing to the severity of COVID-19 infection [14-16].

Leukocytosis and lymphopenia are identified as potential hazard factors for severe COVID-19 infection and poor outcomes. A recent meta-analysis of 10 studies indicated that lower lymphocyte and higher leukocyte counts were associated with severe infection. Lymphopenia, previously used as a prognostic biomarker in other infectious diseases, may result from direct infection of lymphocytes, lymphatic tissue destruction, lymphocyte apoptosis due to inflammation, or metabolic abnormalities such as lactic acidosis inhibiting lymphocytes. Despite their association with severe COVID-19 infection in this study, neither leukocytosis nor lymphopenia emerged as

significant risk factors in multivariate regression analysis [17-19].

Normal values of Neutrophil-to-Lymphocyte Ratio (NLR) in adults range between 1.0 and 2.3. The cut-off value for NLR predicting severe COVID-19 infection varies widely in the literature, ranging from 3.13 to 9.38. In this study, the optimal cut-off point predicting severe COVID-19 infection was > 8.5. A large cohort study on a similar population found a statistically significant strong association of in-hospital mortality with a neutrophil-lymphocyte ratio > 3.1. The lack of a universal definition for severe COVID-19 infection and variability in outcome measures across studies may explain this wide range. However, there is consensus on the value of an elevated baseline NLR in predicting severe COVID infection [20-22].

Platelet-to-Lymphocyte Ratio (PLR), a simple and cost-effective method calculated from CBC, is less commonly used but could be valuable in predicting COVID-19 severity. Recent meta-analyses showed that cases with severe COVID-19 had higher admission levels of PLR. Additionally, platelet count and dynamic fluctuations during management may offer insights into prognosis and illness severity. Cytokine storms in affected patients were associated with higher platelet count and longer hospitalization, making PLR a potential indicator in monitoring COVID-19 patients [23-25].

In terms of inflammatory biomarkers associated with COVID-19, meta-analyses observed higher concentrations of C-reactive protein (CRP) among patients with severe infection. In this study, higher CRP levels were found in severe COVID-19 cases admitted to the ICU. However, it did not emerge as a predictor for severity in multivariate regression analysis, even with a relatively high and sensitive—though not specific—cut-off point [26-28].

COVID-19 can impact coagulation and hemostasis through various mechanisms, leading to abnormal bleeding risk and thromboembolism. Main coagulation biomarker disturbances, including higher serum D-dimer levels, longer prothrombin time (PT), and lower platelet counts, were observed in COVID-19 cases. D-dimer levels correlate with disease severity and serve as a reliable prognostic indicator for hospital mortality in admitted patients with COVID-19. Elevated D-dimer levels signify a hyperfibrinolysis state and increased inflammatory burden induced by SARS-COV-2 infection [29-31].

Conclusion

Anemia, elevated neutrophil-to-lymphocyte ratio > 8.5, platelet-to-lymphocyte ratio > 193, and elevated D-dimer level > 1 mg/L at the time of admission serve as potential predictors for severe COVID-19, indicating a need for ICU admission. Future studies should assess the linear change of NLR, PLR, and D-dimer during disease progression.

References

1. Knight SR, Ho A, Pius R, Buchan I, Carson G, Drake TM, et al. Risk stratification of patients admitted to hospital with COVID-19 using the ISAR IC WHO Clinical Characterisation Protocol: development and validation of the 4C Mortality Score. BMJ. 2020; 370:m3339.
2. Diao B, Wang C, Tan Y, Chen X, Liu Y, Ning L, et al. Reduction and functional exhaustion of T cells in patients with coronavirus disease 2019 (COVID-19). Front Immunol. 2020; 11: 827.
3. Ruan Q, Yang K, Wang W, Jiang L, Song J. Correction to: Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020; 46(6):1294–1297.
4. Yuan J, Zou R, Zeng L, Kou S, Lan J, Li X, et al. The correlation between viral clearance and biochemical outcomes of 94 COVID-19 infected discharged patients. Inflamm Res. 20 20; 69(6):599–606.
5. J-j Z, Dong X, Y-y C, Y-d Y, Yang Y-b, Y-q Y, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020; 75(7):1730–1741.
6. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395(10223):497–506.
7. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020; 18(4):844–847.
8. Li Y, Hu Y, Yu J, Ma T. Retrospective analysis of laboratory testing in 54 patients with severe- or critical-type 2019 novel coronavirus pneumonia. Lab Invest. 2020; 100 (6):794–800.
9. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 20 20; 395(10229):1054–1062.
10. Assandri R, Buscarini E, Canetta C, Scartabellati A, Viganò G, Montanelli A. Laboratory biomarkers predicting COVID-19 severity in the emergency room. Arch Med Res. 2020; 51(6):598–599.
11. Hashem MK, Khedr EM, Daef E, et al. Prognostic biomarkers in COVID-19 infection: value of anemia, neutrophil-to-lymphocyte

ratio, platelet-to-lymphocyte ratio, and D-dimer. Egypt J Bronchol. 2021; 15:29.
12. World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: interim guidance, 13 March 2020. World Health Organization. https://apps.who. int/iris/ handle/10665/331446. Published 2020.
13. Masoud H, Elassal G, Hassany M, Shawky A, Hakim M, Zaky S, et al. Management Protocol for COVID-19 Patients MoHP Protocol for COVID19 November 2020. 2020.
14. Hemauer SJ, Kingeter AJ, Han X, Shotwell MS, Pandharipande PP, Weavind LM. Daily lowest hemoglobin and risk of organ dysfunctions in critically ill patients. Crit Care Med. 2017;45(5):e479–e484
15. Cavezzi A, Troiani E, Corrao S. COVID-19: hemoglobin, iron, and hypoxia beyond inflammation. A narrative review. Clin Pract. 2020; 10(2):1271.
16. Hariyanto TI, Kurniawan A. Anemia is associated with severe coronavirus disease 2019 (COVID-19) infection. Transfus Apher Sci. 2020; 102926.
17. Yamada T, Wakabayashi M, Yamaji T, Chopra N, Mikami T, Miyashita H, Miyashita S. Value of leukocytosis and elevated C-reactive protein in predicting severe coronavirus 2019 (COVID-19): A systematic review and meta-analysis. Clin Chim Acta. 2020; 509:235–243.
18. Huang G, Kovalic AJ, Graber CJ. Prognostic Value of Leukocytosis and Lymphopenia for Coronavirus Disease Severity. Emerg Infect Dis. 2020; 26(8):1839–1841.
19. Tan L, Wang Q, Zhang D, Ding J, Huang Q, Tang Y-Q, Wang Q, Miao H. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. Signal Transduct Target Ther. 2020; 5(1):33.
20. Wang S, Fu L, Huang K, Han J, Zhang R, Fu Z. Neutrophil-to-lymphocyte ratio on admission is an independent risk factor for the severity and mortality in patients with coronavirus disease 2019. J Infect. 2021; 82(2):e16-e8.
21. Zahorec R, Hulin I, Zahorec P. Rationale use of neutrophil-to-lymphocyte ratio for early diagnosis and stratification of COVID-19. Bratisl Lek Listy. 2020; 121(7):466–470.
22. Asem N, Hassany M, Taema K, Masoud H, Elassal G, Kamal E, et al. Demographic and clinical features associated with in-hospital mortality in Egyptian COVID-19 patients: a retrospective cohort study 2021.
23. Chan AS, Rout A. Use of Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios in COVID-19. J Clin Med Res. 2020; 12(7):448–453.
24. Simadibrata DM, Pandhita BAW, Ananta ME, Tango T. Platelet-to-lymphocyte ratio (PLR), a novel biomarker to predict the severity of COVID-19 patients: a systematic review and meta-analysis. J Intensive Care Soc. 2020: 175 1143720969587.
25. Qu R, Ling Y, Zhang Y-h-z, Wei L-y, Chen X, Li X-m, et al. Platelet-to-lymphocyte ratio is associated with prognosis in patients with coronavirus disease-19. J Med Virol. 2020; 92 (9):1533–1541.
26. Tan C, Huang Y, Shi F, Tan K, Ma Q, Chen Y, Jiang X, Li X. C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early. J Med Virol. 2020; 92(7):856–862.
27. Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chem Lab Med (CCLM). 2020; 58(7):1021–1028.
28. Elshazli RM, Toraih EA, Elgaml A, El-Mowafy M, El-Mesery M, Amin MN, et al. Diagnostic and prognostic value of hematological and immunological markers in COVID-19 infection: A meta-analysis of 6320 patients. PLoS One. 2020; 15(8):e0238160.
29. Yao Y, Cao J, Wang Q, Shi Q, Liu K, Luo Z, Chen X, Chen S, Yu K, Huang Z, Hu B. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case control study. J Intensive Care. 2020; 8(1):49.
30. Danwang C, Endomba FT, Nkeck JR, Wouna DLA, Robert A, Noubiap JJ. A meta-analysis of potential biomarkers associated with severity of coronavirus disease 2019 (COVID-19). Biomarker Res. 2020; 8(1):37.
Yu H-H, Qin C, Chen M, Wang W, Tian D-S. D-dimer level is associated with the severity of COVID-19. Thromb Res. 2020; 195:219–225.