Original Article

DOI: 10.7860/JCDR/2024/69032.19433

Pathology Section

Assessing the Predictive Value of Haematological Parameters (NLR, LMR, PLR) for COVID-19 Disease Severity as quantified by CT Severity Scores: A Prospective Cohort Study

KOVURI UMADEVI[1], LAVANYA MOTRAPU[2], KASTURI DINESH[3], NAGARJUNA CHARY RAJARIKAM[4], MOHD IMRAN ALI[5]

(cc) BY-NC-ND

ABSTRACT

Introduction: In the relentless global battle against the Coronavirus Disease-2019 (COVID-19) pandemic, accurate prediction of disease severity remains a critical challenge, with profound implications for patient outcomes and healthcare resource allocation. As the virus continues to evolve and pose new threats, the need for reliable prognostic indicators becomes increasingly urgent. Effective identification of patients at high-risk of developing severe illness not only facilitates timely intervention and personalised treatment strategies but also optimises healthcare resource utilisation. In this context, the exploration of novel biomarkers and predictive models holds immense promise for enhancing ones understanding of disease progression and improving clinical decision-making.

Aim: To study the association between haematological parameters, including Neutrophil-to-Lymphocyte Ratio (NLR), Lymphocyte-to-Monocyte Ratio (LMR), and Platelet-to-Lymphocyte Ratio (PLR), with Computed Tomography Scan Severity Score (CTSS) in COVID-19 patients.

Materials and Methods: A prospective cohort study was conducted from March 2021 to July 2022 at Government General Hospital (GGH) Nizamabad, Telangana, India. The study encompassed all three COVID-19 waves, included a sample size of 159 Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) positive patients, excluding pregnant women and children under 10 years. Upon admission, CTSS and ratios of NLR, LMR, and PLR were recorded in an MS Excel sheet before any medical intervention and then analysed using Statistical Package for Social Sciences (SPSS) software 22.0.

Results: The study comprised 159 patients with a mean age of 50.86±13.89 years (ranging from 16 to 85), predominantly male 90 (56.61%). The highest infection rate 85 (53.45%) was in the 41-60 years age group. The NLR was significantly elevated from a mean value of 4.58 to 11.24 (r value=0.78, p-value=<0.001), and LMR notably reduced from 8.27 to 3.80 (r value=0.67, p-value=0.003) in correlation with the severity as indicated by CTSS. Although PLR values were higher in severe cases, increasing from 173.07 in mild cases to 272.29 in severe cases, there was no significant correlation with CTSS (r-value=-0.78, p-value=0.177).

Conclusion: CTSS emerges as a valuable radiological biomarker for predicting COVID-19 severity. However, due to its cost and limited availability in grassroots-level hospitals, there is a need for alternative severity prediction models. Present study proposes a predictive model using NLR and LMR biomarkers as alternatives to CTSS for assessing COVID-19 severity.

Keywords: Coronavirus disease-2019, Lymphocyte-to-monocyte ratio, Neutrophil-to-lymphocyte ratio, Platelet-to-lymphocyte ratio

INTRODUCTION

The world has been grappling with the COVID-19 pandemic for over two and a half years, a crisis that has now transitioned into an endemic stage. Since the virus's emergence in December 2019, extensive research has been conducted to understand its structure, mechanism, family, origin, and variants [1-4]. Vaccination against COVID-19 has significantly altered the virus's impact, but the longevity of vaccine protection is still under investigation [5]. Despite a global stabilisation in the virus's impact, the emergence of vaccine-resistant variants continues to be a concern [6]. The World Health Organisation (WHO) emphasises testing and isolation as key strategies to curb the virus's transmission [7]. Testing is crucial not only for identifying COVID-19 but also for assessing the severity of the infection. Diagnostic methods like Polymerase Chain Reaction (PCR) and Rapid Antigen Tests (RAT) are pivotal for detecting SARS-CoV-2, but their scope is limited to disease identification and they are plagued by issues like false negatives and the need for advanced laboratories and skilled technicians [7,8]. Computed Tomography (CT) scans provide a direct assessment of viral impact on the lungs and alveolar damage. The CTSS is a valuable diagnostic tool in this regard, using a 25-point scale to categorise disease severity: <7 as mild, 7-18 as moderate, and >18 as severe [9,10]. CT scans are integral for initial lung assessments, monitoring virus replication, complication prediction, treatment planning, and post-diagnosis follow-up [11,12]. While CT imaging is quick, safe, and painless, it faces practical limitations such as limited availability in primary health centres, the need for specialised equipment and personnel, and a radiation dose of approximately 8mSv per full chest scan [13,14]. Given the limitations of CT scans and the unpredictable nature of COVID-19 complications, there is a growing need for a cost-effective, easy-to-use diagnostic tool for daily patient monitoring [15]. Short-term prognostic markers have emerged as essential tools in tracking disease progression [16]. Biomarkers from peripheral blood specimens have shown significant potential in COVID-19 diagnosis. COVID-19 is a multisystem syndrome involving complex immunological, inflammatory, and coagulative responses [17,18]. Biomarkers, categorised into haematological, inflammatory, coagulation, cardiac, hepatic, muscle, renal, and electrolytic types

[19], play a crucial role in understanding the disease's impact on the body [20]. This study, conducted in Nizamabad, India, brings a fresh perspective by evaluating haematological markers (NLR, LMR, PLR) as predictors for COVID-19 severity, offering an innovative alternative to CTSS. Focusing on accessible blood biomarkers, it addresses the need for practical severity assessment tools in resource-limited settings. The research enriches the global understanding of COVID-19 haematological effects from a unique regional standpoint, advancing the field by providing valuable insights into alternative diagnostic strategies.

MATERIALS AND METHODS

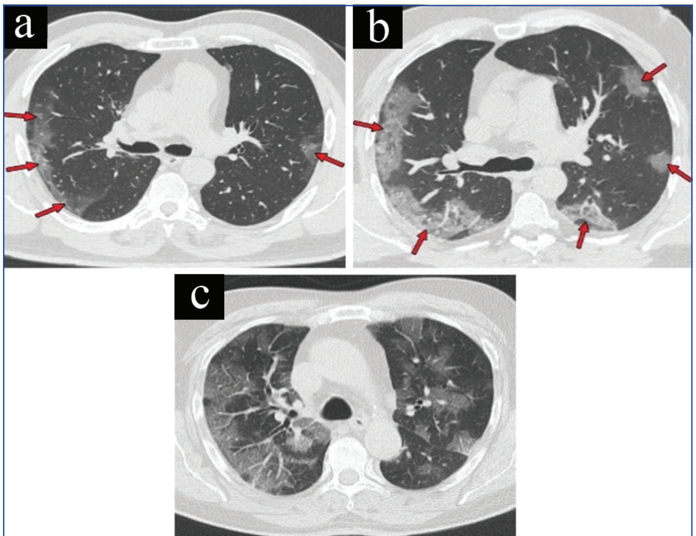
The study was a prospective cohort study analysis conducted at Government General Hospital, Nizamabad, Telangana, India from March 2021 to July 2022, including 159 patients. Approval for the study was granted by the Institutional Ethical Committee of Government Medical College Nizamabad, Telangana State, India, with the registration number ECR/144/INST/TG/2019.

Inclusion criteria: COVID-19 patients confirmed positive by RT-PCR testing were included in the study.

Exclusion criteria: Pregnant women and individuals below the age of 10 years were excluded from the study.

Data collection: Patient data collected included demographic information (age, gender), clinical symptoms (fever, cough, myalgia, headache, eye burning sensation), medical history (diabetes, hypertension), and personal, travel, and contact history. Haematological parameters were measured using Sysmex xn-1000, and peripheral smears were examined on admission day before any treatment intervention. Data were recorded in a Microsoft Excel sheet for analysis. Ratios for NLR, LMR, and PLR were calculated based on their absolute counts. CTSS was assessed in accordance with WHO criteria using a Siemens 16-slice CT scanner [21].

CTSS, as per WHO guidelines, was categorised into three groups: mild (CTSS 1-< 7/25), moderate (CTSS 7-18/25), and severe (CTSS >18-25/25) as shown in [Table/Fig-1]. In this study, the extent of lung involvement was quantified by assigning 5 points to each affected lobe, with a total of 5 lobes in the lungs, culminating in a maximum score of 25 points [21].



[Table/Fig-1]: CTSS of (a) Mild; (b) Moderate; and (c) Severe COVID-19 patients. Red arrows indicating ground glass opacities.

The NLR normal reference range is 1-3, LMR normal reference is 2-6, and PLR normal reference is 100-200 [3]. These ratios were then categorised according to the WHO chest CTSS Score.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS software version 22.0. Categorical and continuous variables were expressed as percentages and mean±standard deviation, respectively. The analysis included age-wise and gender-wise comparisons. Descriptive statistical analyses were conducted, including the calculation of the mean, standard error of mean, standard deviation, and the minimum and maximum values, as well as the lower and upper bounds for NLR, LMR, and PLR, utilising SPSS software. The mean differences in NLR, LMR, and PLR across the mild, moderate, and severe categories of CTSS were examined using the one-way ANOVA, and correlation was assessed using Spearman rank analysis A p-value of <0.05 is deemed statistically significant. Subsequently a Games-Howell post-hoc test was conducted to compare mean differences between three different groups (grades) in the study. In this context, CTSS Mild is considered as Grade 1, Moderate as Grade 2, and Severe as Grade 3.

RESULTS

COVID-19 patients with varying degrees of COVID-19 severity, as classified by their CTSS, were analysed and are presented in [Table/Fig-2]. The cohort comprised 90 (56.61%) males and 69 (43.39%) females, with the highest infection rate observed in the 41-60 years age group, accounting for 86 (54.1%). Regarding the CTSS categories, the majority of patients, 98 (61.64%), fell into the moderate category. The mild and severe categories included 27 (16.98%) and 34 (21.38%) of the patients, respectively.

Age group (years)	Male	Female	CTSS mild category	CTSS moderate	CTSS severe	Total cases
10-20	0	02	02	00	00	02 (1.26%)
21-30	10	3	03	08	02	13 (8.176%)
31-40	16	6	03	13	06	22 (13.836%)
41-50	25	16	08	25	08	41 (25.786%)
51-60	25	20	05	28	12	45 (28.3%)
61-70	9	17	04	18	04	26 (16.352%)
>70	5	5	02	06	02	10 (6.289%)
	90 (56.61%)	69 (43.39%)	27 (16.98%)	98 (61.64%)	34 (21.38%)	159

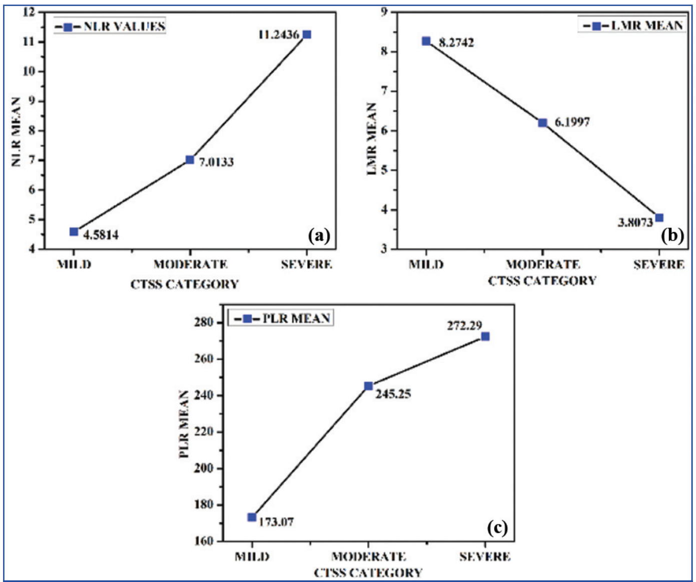
[Table/Fig-2]: Showing distribution of cases as per age, gender and CTSS.

[Table/Fig-3] presents a comparison of the mean values of NLR, LMR, and PLR across different CTSS categories: mild, moderate, and severe. In the mild category, the mean NLR value is 4.58±2.17, while it is 7.01±4.66 in the moderate category and 11.24±8.29 in the severe category. This increasing trend in NLR with the escalating severity of the disease was statistically significant, as indicated by a p-value of 0.000, determined through ANOVA testing, and an r-value of 0.78. [Table/Fig-4a] illustrates this rising trend of NLR corresponding to an increase in disease severity. Similarly, the mean LMR value in the mild category is 8.27±6.85, but it decreases to 6.19±5.43 in the moderate category and further to 3.80±3.10 in the severe category with a p-value of 0.003 and an r-value of 0.67 [Table/Fig-4b] visually represents this decreasing trend of LMR with the increasing severity of the disease.

In the mild category, the study observed a mean Platelet-Lymphocyte Ratio (PLR) value of 173.07±128.25, which increased to 245.25±215.11 in the moderate category and further to 272.29±256.42 in the severe category. Although there is an upward trend in PLR values in more severe cases, this increase did not show a significant correlation with the severity of the disease, evidenced by a p-value of 0.177 and an r-value of -0.78. [Table/Fig-4c] displays the trend line for PLR values across mild, moderate, and severe categories.

CTSS category	Minimum	Maximum	Mean±Standard Deviation	Standard Error	One-way ANOVA p-value
NLR-Neutrophil Lymphocyte Ratio					
Mild	1.71	9.88	4.58±2.17	0.42	<0.001
Moderate	0.84	23	7.01±4.66	0.47	
Severe	1.96	31.66	11.24±8.29	1.42	
LMR: Lymphocyte monocyte ratio					
Mild	2.16	35	8.27±6.85	1.32	0.003
Moderate	0.0003	30	6.19±5.43	0.54	
Severe	1	16	3.81±3.10	0.53	
PLR: Platelet lymphocyte ratio					
Mild	33.15	685.18	173.07±128.25	24.68	0.177
Moderate	28.28	1436.78	245.25±215.11	21.72	
Severe	44.19	1401.86	272.29±256.42	43.97	

[Table/Fig-3]: Statistical analyses of NLR, LMR, as well as PLR and their comparison with CTSS.



[Table/Fig-4]: a) Depicting increasing trend of NLR with an increase in severity of disease; b) Depicting decreasing trend of LMR with an increase in severity of disease, and c) Showing line trend of mild, moderate, and severe PLR values.

A Games-Howell post-hoc test was conducted to compare mean differences between three different groups (grades) in the study. [Table/Fig-5] provides mean differences between each pair of groups, along with their standard errors, significance levels (Sig.), and 95% Confidence Intervals (CI). For NLR, the mean difference between grade 1 and grade 2 is 2.39599, with a standard error of 0.90434.

Variable	Comparison	Mean difference	Standard error	p-value	95% Confidence Interval
NLR	Grade 1 vs. Grade 2	2.39599	0.90434	0.027	(0.2259, 4.5661)
NLR	Grade 1 vs. Grade 3	6.24062	1.27534	<0.001	(3.1640, 9.3172)
LMR	Grade 1 vs. Grade 2	2.41559	0.96579	0.040	(0.0913, 4.7399)
LMR	Grade 1 vs. Grade 3	4.80183	1.11752	<0.001	(2.1123, 7.4913)

[Table/Fig-5]: Showing statistical summary of Games-Howell Post-Hoc comparisons for NLR and LMR across grades 1, 2, and 3.

Similarly, the mean difference between Grade-1 and Grade-3 was 6.24062, with a standard error of 1.27534. This difference was also statistically significant (p-value<0.001). For LMR, the mean difference between Grade-1 and Grade-2 is 2.41559, with a standard error of 0.96579. This difference was statistically significant at the 0.05 level (p-value=0.040). Similarly, the mean difference between Grade-1 and Grade-3 was 4.80183, with a standard error of 1.11752. This difference was also statistically significant p-value<0.001.

DISCUSSION

This study involved 159 COVID-19 patients from the first, second, and third waves in India. The Government General Hospital, Nizamabad, saw a rapid surge in cases and hospitalisations, posing a challenge in predicting disease severity. CTSS was used as a benchmark for comparison. Managing severely affected patients was particularly challenging due to the common risk of multiple organ failures noted throughout the disease course. During the second wave, existing treatment protocols and patient risk assessment models proved inadequate.

The average age of COVID-19 positive patients in this study was 50.86±13.89 years, ranging from 16 to 85 years. This finding was compared with other researchers as shown in [Table/Fig-6] [22-24].

Mean age of positivity (years)	Present study, 2024	Yang X et al., [22] 2020	Yang AP et al., [23] 2020	Hashem Mk et al., [24] 2021
	50.86±13.8	59.7±13.3	46.4±17.6	57.4±14

[Table/Fig-6]: Showing comparison of mean age of positivity with other studies [22-24].

In present study cohort, 110 (69.18%) of the patients presented with symptoms like fever, cough, and sore throat, while 30.82% experienced other symptoms such as eye burning sensation, diarrhoea, anosmia, shortness of breath, etc. Among those admitted, 50 out of 159 patients had co-morbidities, with hypertension present in 42% of these patients, diabetes in 32%, and other conditions in 26%. [Table/Fig-7] compares our study's findings with those of Hashem MK et al., who categorised patients into non-severe and severe based on WHO interim guidance and Chinese COVID-19 treatment guidelines [24].

	Present study			Hashem MK et al., [24]	
Parameters	Mean±SD Mild (n=27)	Mean±SD Moderate (n=98)	Mean±SD Severe (n=34)	Mean±SD in non severe cases (n=69)	Mean±SD in severe cases (n=24)
NLR	4.58±2.17	7.01±4.66	11.24±8.29	4.8 ±3.5	20.7±24.1
LMR	8.27±6.85	6.19±5.43	3.81±3.10	4.1±6.0	2.1±1.6
PLR	173.07± 128.25	245.25± 215.11	272.29± 256.42	176.7± 84.2	436.5± 329.2

[Table/Fig-7]: Comparison of NLR and LMR mean values with other studies

Comparing present findings with those of other researchers, Prakash Rao VV reported mean NLR values of 5.6 for mild and 9.2 for moderate disease upon admission [25]. Kurri N et al., observed NLR values of 7.9 in survivors versus 11.8 in non-survivors [26]. Toori KU et al., noted a progressive increase in NLR from 1.92 in asymptomatic patients to 9.9 in severe cases [27]. Present study aligns with these findings, indicating a significant rise in NLR with increased disease severity. The uniqueness of present study lies in providing NLR mean values across mild, moderate, and severe categories in comparison with CTSS, a facet scarcely explored in existing research. Treatment largely depended on independent predictors, including clinical and CT topographic biomarkers. An ideal severity prediction model would optimally use hospital resources. Several researchers have developed prediction models, considering CTSS as a standard radiographic scoring, associating it with individual haematological and inflammatory biomarkers. However, these models mainly focused on mild cases and were unreliable for moderate and severe cases, where clinical progression often extends beyond lung involvement to affect the heart, kidneys, and other organs. Therefore, robust alternative disease prediction models are needed to analyse virus severity and identify patients at high-risk of multiple organ failure or mortality. Present study focuses on haematological biomarkers such as NLR, LMR, and PLR ratios, derived from complete blood counts, a basic screening procedure in any diagnostic protocol. Authors have associated these ratios with CTSS, proposing a novel approach that provides effective calibration in predicting disease severity in COVID-19 patients. While most Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infections are mild to moderate, a small number progress to severe pneumonia, pulmonary oedema, Acute Respiratory Distress Syndrome (ARDS), or multiple organ failure, necessitating Intensive Care Unit (ICU) admission and resulting in high mortality [28]. The immune response to SARS-CoV-2 infection is crucial, as inadequate adaptive responses and uncontrolled inflammatory innate responses can cause tissue damage. Acute COVID-19 is often the result of tissue-directed immunopathology, especially in the lungs, rather than the virus itself [29,30]. Excessive inflammation, driven by a dysregulated immune response, contributes significantly to coronavirus-mediated lung damage and systemic pathology. Neutrophils (NEU) play a critical role in immune system activation and migration, producing reactive oxygen species that can cause cellular DNA damage and free the virus, leading to antibody-dependent cell-mediated cytotoxicity [31].

NEU also interact with various cell populations, producing cytokines and effector molecules like Vascular Endothelial Growth Factor (VEGF), which stimulate tumour angiogenesis, growth, and metastasis [32,33]. Elevated levels of VEGF-A and VEGF-C expression have been reported in COVID-19 patients [33]. Lymphopenia, characterised by a decrease in lymphocyte counts, particularly in CD4+ T cells and B cells, is a common feature in COVID-19 patients, indicating abnormal immune function [34-36]. André S et al., noted that CD4 and CD8 T cells in COVID-19 patients are prone to apoptosis [37]. Microbial infection induces neutrophil recruitment [38], and impaired lymphocytes in COVID-19 patients can lead to microbial infection, promoting NEU activation and recruitment [39]. Some critically ill patients develop bacterial superinfections, exacerbating the disease. COVID-19 infections typically start with droplet inhalation and upper respiratory airway infection. The virus initially targets Angiotensin Converting Enzyme 2 (ACE2) expressing nasopharyngeal epithelium, with local tissue macrophages responding to infected cells via cytokine responses [40]. Monocytes, dendritic cells, and tissue macrophages can bind the virus via lectin-like receptors such as CD169 and transport it to regional lymph nodes [41]. Thrombocytopenia in COVID-19 patients has been linked to lung damage, with lung tissue and pulmonary endothelial cell injuries causing platelet activation, aggregation, and thrombus formation [42-44]. Huang C et al., suggested that patients with COVID-19 exhibit high levels of cytokines like Interleukin (IL-1), Interferon (IFN) and others, contributing to Th1 activation [45]. However, severe cases show higher concentrations of cytokines like G-CSF, IP-10, MCP-1, MIP-1, and TNF-alpha, indicating that a cytokine storm is associated with disease severity. Infections with 2019-nCoV cause cytokine storms, exacerbating the inflammatory response and stimulating platelet release, indicating a poor prognosis. The objective of this study was to develop a novel predictive model correlating NLR, LMR, and CTSS for assessing the severity of COVID-19 in patients. By examining how these haematological biomarkers change across different CTSS categories, the study intends to develop a comprehensive predictive model that can accurately predict disease severity upon admission. Further research is suggested to explore the relationship between PLR and CTSS, potentially leading to a triple haematological biomarker combination for predicting disease severity in future waves of COVID-19 or similar emerging epidemics. Understanding risk factors for mortality and predicting severe COVID-19 cases upon admission are emphasised as crucial for patient isolation and early preventive measures.

Limitation(s)

The study relies on data from a single centre, potentially limiting generalisability, as well as the possibility of selection bias and a limited sample size, which could compromise the representativeness and statistical power of the findings.

CONCLUSION(S)

This study highlights the potential of haematological biomarkers, particularly NLR and LMR, as accessible tools for predicting the severity of COVID-19. Authors found significant correlations between changes in NLR and LMR with disease severity, as measured by CTSS, suggesting their usefulness in risk stratification, especially in resource-limited settings. While PLR did not show a significant correlation in present study analysis, further investigation is warranted. Present study findings emphasise the importance of ongoing research to refine predictive models incorporating these biomarkers, aiding clinicians in early identification and management of severe COVID-19 cases, ultimately improving patient outcomes and guiding public health interventions.

Acknowledgements

Dr. Kovuri Umadevi extends special thanks to Dr. Dola Sundeep, a research scholar from IIITDM Kurnool, for his contributions in drafting the manuscript.

REFERENCES

[1] Boopathi S, Poma AB, Kolandaivel P. Novel 2019 Coronavirus structure, mechanism of action, antiviral drug promises and rule out against its treatment. J Biomol Struct Dyn. 2021;39(9):3409-18. Available from: https://doi.org/10.1080/07391102.2020.1758788.
[2] Wang MY, Zhao R, Gao LJ, Gao XF, Wang DP, Cao JM. SARS-CoV-2: Structure, biology, and structure-based therapeutics development. Front Cell Infect Microbiol. 2020;10:587269. Available from: https://doi.org/10.3389/fcimb.2020.587269.
[3] Luo H, He L, Zhang G, Yu J, Chen Y, Yin H, et al. Normal reference intervals of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, and systemic immune inflammation index in healthy adults: A large multi-center study from western China. Clin Lab. 2019;65(3).
[4] Umadevi K, Sundeep D, Varadharaj EK, Sastry CC, Shankaralingappa A, Chary RN, et al. Precision detection of fungal co-infections for enhanced COVID-19 treatment strategies using FESEM imaging. J Microbiol. 2024:01-05.
[5] Deb B, Vilvadrinath R, Goel S. COVID-19 variants that escape vaccine immunity: Global and Indian context-are more vaccines needed? J Biosci. 2021;46:112. Available from: https://doi.org/10.1007/s12038-021-00226-7.
[6] Gómez CE, Perdiguero B, Esteban M. Emerging SARS-CoV-2 variants and impact in global vaccination programs against SARS-CoV-2/COVID-19. Vaccines (Basel). 2021;9(3):243. Available from: https://doi.org/10.3390/vaccines9030243.
[7] Sundeep D, Varadharaj EK, Umadevi K, Jhansi R. Role of nanomaterials in screen printed electrochemical biosensors for detection of COVID-19 and for post-covid syndromes. ECS Advances. 2023;2(1):016502. Available from: https://doi.org/10.1149/2754-2734/acb832.
[8] Udugama B, Kadhiresan P, Kozlowski HN, Malekjahani A, Osborne M, Li VYC, et al. Diagnosing COVID-19: The disease and tools for detection. ACS Nano. 2020;14(4):3822-35. Available from: https://doi.org/10.1021/acsnano.0c02624.
[9] Yang R, Li X, Liu H, Zhen Y, Zhang X, Xiong Q, et al. Chest CT Severity Score: An imaging tool for assessing severe COVID-19. Radiol Cardiothorac Imaging. 2020;2(2):e200047. Available from: https://doi.org/10.1148/ryct.2020200047.
[10] Gurumurthy B, Das SK, Shetty S, Veerabhadrappa RC, Kosinepalli SS, Dharamaraju SH. CT severity score: An imaging biomarker to estimate the severity of COVID-19 pneumonia in vaccinated and non-vaccinated population. Egypt J Radiol Nucl Med. 2022;53(1):88. Available from: https://doi.org/10.1186/s43055-022-00768-2.
[11] Kevadiya BD, Machhi J, Herskovitz J, Oleynikov MD, Blomberg WR, Bajwa N, et al. Diagnostics for SARS-CoV-2 infections. Nat Mater. 2021;20(5):593-605. Available from: https://doi.org/10.1038/s41563-020-00906-z.
[12] Francone M, Iafrate F, Masci GM, Coco S, Cilia F, Manganaro L, et al. Chest CT score in COVID-19 patients: Correlation with disease severity and short-term prognosis. Eur Radiol. 2020;30(12):6808-17. Available from: https://doi.org/10.1007/s00330-020-07033-y.
[13] Fred HL. Drawbacks and limitations of computed tomography: Views from a medical educator. Tex Heart Inst J. 2004;31(4):345-48.
[14] Mardian Y, Kosasih H, Karyana M, Neal A, Lau CY. Review of current COVID-19 diagnostics and opportunities for further development. Front Med (Lausanne). 2021;8:615099. Available from: https://doi.org/10.3389/fmed.2021.615099.
[15] Shang Y, Pan C, Yang X, Zhong M, Shang X, Wu Z, et al. Management of critically ill patients with COVID-19 in ICU: Statement from front-line intensive care experts in Wuhan, China. Ann Intensive Care. 2020;10(1):73. Available from: https://doi.org/10.1186/s13613-020-00689-1.
[16] Feng Z, Yu Q, Yao S, Luo L, Zhou W, Mao X, et al. Early prediction of disease progression in COVID-19 pneumonia patients with chest CT and clinical characteristics. Nat Commun. 2020;11(1):4968. Available from: https://doi.org/10.1038/s41467-020-18786-x.
[17] Schultze JL, Aschenbrenner AC. COVID-19 and the human innate immune system. Cell. 2021;184(7):1671-92. Available from: https://doi.org/10.1016/j.cell.2021.02.029.

[18] Samprathi M, Jayashree M. Biomarkers in COVID-19: An up-to-date review. Front Pediatr. 2021;8:607647. Available from: https://doi.org/10.3389/fped.2020.607647.

[19] 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. 2020;58(7):1021-28. Doi: 10.1515/cclm-2020-0369. Available from: https://doi.org/10.1515/cclm-2020-0369.

[20] Ansar W, Ghosh S. Inflammation and inflammatory diseases, markers, and mediators: Role of CRP in some inflammatory diseases. In: Biology of C Reactive protein in health and disease. Springer, New Delhi. 2016. Available from: https://doi.org/10.1007/978-81-322-2680-2_4.

[21] Yang R, Li X, Liu H, Zhen Y, Zhang X, Xiong Q, et al. Chest CT severity score: An imaging tool for assessing severe COVID-19. Radiology: Cardiothoracic Imaging. 2020;2(2):e200047.

[22] Yang X, Yu Y, Xu J, Shu H, Liu H, Wu Y, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: A single-centered, retrospective, observational study. The Lancet Respir Med. 2020;8(5):475-81. Available from: https://doi.org/10.1016/S2213-2600(20)30079-5.

[23] Yang AP, Liu JP, Tao WQ, Li HM. The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. Int Immunopharmacol. 2020;84:106504. Available from: https://doi.org/10.1016/j.intimp.2020.106504.

[24] Hashem MK, Khedr EM, Daef E, Mohamed-Hussein A, Mostafa EF, Hassany SM, 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(1):01-09. Available from: https://doi.org/10.1186/s43168-021-00075-w.

[25] Prakash Rao VV. Utility of Neutrophil-Lymphocyte Ratio (NLR) as an indicator of disease severity and prognostic marker among patients with COVID-19 infection in a tertiary care centre in Bangalore-A retrospective study. J Assoc Physicians India. 2022;70(4):11-12.

[26] Kurri N, Tyagi B, Singhal E, Gupta N, Agarwal AK, Gupta V, et al. Assessing the impact of inflammatory markers and CT severity score on disease severity of COVID-19 patients admitted to ICU at a tertiary hospital. J Assoc Physicians India. 2021;69(6):41-49.

[27] Toori KU, Qureshi MA, Chaudhry A, Safdar MF. Neutrophil to lymphocyte ratio (NLR) in COVID-19: A cheap prognostic marker in a resource constraint setting. Pak J Med Sci. 2021;37(5):1435-39. Available from: https://doi.org/10.12669/pjms.37.5.4194.

[28] Umadevi K, Nagarjunachary R, Lavanya M, Ali MI, Begum F, Vadana SP. Red cell distribution width, platelet distribution width, and plateletcrit as indicators of prognosis in COVID-19 patients-A single-center study. Asian J Med Sci. 2023;14(6):13-17.

[29] Jesenak M, Brndiarova M, Urbancikova I, Rennerova Z, Vojtkova J, Bobcakova A, et al. Immune parameters and COVID-19 infection-associations with clinical severity and disease prognosis. Front Cell Infect Microbiol. 2020;10:364. Available from: https://doi.org/10.3389/fcimb.2020.00364.

[30] Ricci D, Etna MP, Rizzo F, Sandini S, Severa M, Coccia EM. Innate immune response to SARS-CoV-2 infection: From cells to soluble mediators. Int J Mol Sci. 2021;22(13):7017. Available from: https://doi.org/10.3390/ijms22137017.

[31] Kusumanto YH, Dam WA, Hospers GA, Meijer C, Mulder NH. Platelets and granulocytes, in particular the neutrophils, form important compartments for circulating vascular endothelial growth factor. Angiogenesis. 2003;6(4):283-87. Available from: https://doi.org/10.1023/B:AGEN.0000029415.62384.ba.

[32] Hanrahan V, Currie MJ, Gunningham SP, Morrin HR, Scott PA, Robinson BA, et al. The angiogenic switch for vascular endothelial growth factor (VEGF)-A, VEGF-B, VEGF-C, and VEGF-D in the adenoma-carcinoma sequence during colorectal cancer progression. J Pathol. 2003;200(2):183-94. Available from: https://doi.org/10.1002/path.1339.

[33] Kim SL, Lee ST, Trang KT, Kim SH, Kim IH, Lee SO, et al. Parthenolide exerts inhibitory effects on angiogenesis through the downregulation of VEGF/VEGFRs in colorectal cancer. Int J Mol Med. 2014;33(5):1261-67. Available from: https://doi.org/10.3892/ijmm.2014.1669.

[34] Liu J, Li S, Liu J, Liang B, Wang X, Wang H, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. EBioMedicine. 2020;55:102763. Available from: https://doi.org/10.1016/j.ebiom.2020.102763.

[35] Belaid B, Lamara Mahammad L, Mihi B, Rahali SY, Djidjeli A, Larab Z, et al. T cell counts and IL-6 concentration in blood of North African COVID-19 patients are two independent prognostic factors for severe disease and death. J Leukoc Biol. 2022;111(1):269-81. Available from: https://doi.org/10.1002/JLB.4COVA1020-703R.

[36] Wen XS, Jiang D, Gao L, Zhou JZ, Xiao J, Cheng XC, et al. Clinical characteristics and predictive value of lower CD4+ T cell level in patients with moderate and severe COVID-19: A multicenter retrospective study. BMC Infect Dis. 2021;21(1):57. Available from: https://doi.org/10.1186/s12879-020-05741-w.

[37] André S, Picard M, Cezar R, Roux-Dalvai F, Alleaume-Butaux A, Soundaramourty C, et al. T cell apoptosis characterizes severe COVID-19 disease. Cell Death Differ. 2022;29(8):1486-99. Available from: https://doi.org/10.1038/s41418-022-00936-x.

[38] Reusch N, De Domenico E, Bonaguro L, Schulte-Schrepping J, Baßler K, Schultze JL, et al. Neutrophils in COVID-19. Front Immunol. 2021;12:652470. Available from: https://doi.org/10.3389/fimmu.2021.652470.

[39] Yang L, Liu S, Liu J, Zhang Z, Wan X, Huang B, et al. COVID-19: Immunopathogenesis and Immunotherapeutics. Signal Transduct Target Ther. 2020;5(1):128. Available from: https://doi.org/10.1038/s41392-020-00243-2.

[40] Toniato E, Ross R, Kritas SK. How to reduce the likelihood of coronavirus-19 (CoV-19 or SARS-CoV-2) infection and lung inflammation mediated by IL-1. J Biol Regul Homeost Agents. 2020;34(2):10. 23812/Editorial-Conti-2.

[41] Bedin AS, Makinson A, Picot MC, Mennechet F, Malergue F, Pisoni A, et al. Monocyte CD169 expression as a biomarker in the early diagnosis of coronavirus disease 2019. J Infect Dis. 2021;223(4):562-67. Available from: https://doi.org/10.1093/infdis/jiaa724.

[42] Poon TC, Pang RT, Chan KA, Lee NL, Chiu RW, Tong YK, et al. Proteomic analysis reveals platelet factor 4 and beta-thromboglobulin as prognostic markers in severe acute respiratory syndrome. Electrophoresis. 2012;33(12):1894-900. Available from: https://doi.org/10.1002/elps.201200002.

[43] Pilaczyńska-Cemel M, Gołda R, Dąbrowska A, Przybylski G. Analysis of the level of selected parameters of inflammation, circulating immune complexes, and related indicators (neutrophil/lymphocyte, platelet/lymphocyte, CRP/CIC) in patients with obstructive diseases. Cent Eur J Immunol. 2019;44(3):292-98. Available from: https://doi.org/10.5114/ceji.2019.87498.

[44] Shinya K, Gao Y, Cilloniz C, Suzuki Y, Fujie M, Deng G, et al. Integrated clinical, pathologic, virologic, and transcriptomic analysis of H5N1 influenza virus-induced viral pneumonia in the rhesus macaque. J Virol. 2012;86(11):6055-66. Available from: https://doi.org/10.1128/JVI.00365-12.

[45] 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. Available from: https://doi.org/10.1016/S0140-6736(20)30183-5.

PARTICULARS OF CONTRIBUTORS:

1. Senior Resident, Department of Pathology, Government Medical College Nizamabad, Telangana, India.
2. Associate Professor, Department of Pathology, Government Medical College Nizamabad, Telangana, India.
3. Assistant Professor, Department of Pathology, Government Medical College Nizamabad, Telangana, India.
4. Professor and Head, Department of Pathology, Government Medical College Nizamabad, Telangana, India.
5. Associate Professor, Department of Pathology, Government Medical College Nizamabad, Telangana, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Kovuri Umadevi,
Government General Hospital, Beside Bustand, Khaleelwadi-503001,
Nizamabad, Telangana, India.
E-mail: dr.umadevik113@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]

- Plagiarism X-checker: Dec 12, 2023
- Manual Googling: Mar 22, 2024
- iThenticate Software: Mar 25, 2024 (10%)

ETYMOLOGY: Author Origin

EMENDATIONS: 6

AUTHOR DECLARATION:

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Dec 11, 2023**
Date of Peer Review: **Feb 02, 2024**
Date of Acceptance: **Mar 28, 2024**
Date of Publishing: **May 01, 2024**