RESEARCH ARTICLE

Pattern of cytopenias and systemic immune-inflammation index among hospitalised patients of COVID-19

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Abstract

Objective: To compare the extent of cytopenias and systemic immune inflammation index of hospitalised coronavirus disease-2019 patients during the first and second/third waves of the pandemic.

Method: The retrospective, cross-sectional study was conducted in October 2021 at Fatima Memorial Hospital, Lahore, Pakistan, and comprised data of hospitalised coronavirus disease-2019 patients regardless of age and gender from May 2020 to June 2021. Data was segregated into first wave that lasted from May to July 2020, second wave that lasted from early November to mid-December 2020, and third wave that ranged from mid-March to June 2021. For comparison purposes, the data of first wave was in group A, while data of second and third waves was pooled into group B. Age, gender, comorbidities, requirement of ventilator support and outcome of the patients was noted. Inflammatory markers were compared on the basis of complete blood count and systemic immune-inflammation index data. Data was analysed using SPSS 25.

Results: Of the 202 patients, 90(44.5%) were in group A and 112(55.4%) were in group B. There were 108(53.5%) males and 94(46.5%) females. The median age in males was 58 years (interquartile range: 21 years) and it was 56 years (interquartile range: 21 years) in females. Neutrophilia (p<0.001), leukocytosis (p<0.001) and lymphocytopenia (p<0.001) had direct association with increased systemic immune-inflammation. Raised systemic immune-inflammation also had an association with increased requirement of ventilator support (p=0.2) and increased mortality (p=0.001). There were more females, more critical patients, more patients with anaemia, leukopenia, lymphocytopenia and thrombocytopenia in group B compared to group A (p<0.05). Need for ventilator support and mortality were also higher in group B compared to group A (p<0.05).

Conclusion: All the indicators analysed were worse during the second and third waves of coronavirus disease-2019 compared to the first wave of the pandemic.

Keywords: COVID-19, Thrombocytopenia, Leukopenia, Lymphopenia, Cytopenia. (JPMA 74: 911; 2024)

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused the global pandemic of coronavirus disease-2019 (COVID-19) which resulted in considerable morbidity and mortality across the world.[1] As per the World Health Organisation (WHO) data, there were over 500 million confirmed cases and over 6 million deaths reported worldwide.[2]

COVID-19 is highly communicable and contagious disease and can lead to diversity of symptoms, including mild fever, dry cough, myalgia and headache as well as gastrointestinal symptoms, including abdominal pain, diarrhoea and vomiting, and respiratory symptoms leading to a critical stage needing expert management at intensive care units (ICUs).[3] Hospitalisation of patients was seen with worsening clinical symptoms, like life-threatening respiratory failure with pulmonary decline. This usually happens when a high level of pro-inflammatory cytokines are released which lead to tissue damage.[4]

Relationship of COVID-19 with laboratory parameters have been well-established by many studies.[5,6] Respiratory system is the main system involved in COVID-19, but multi-systemic involvement was also seen, like the haemopoietic system in which blood count anomalies, like neutrophilia and lymphopenia, were particularly seen in COVID-19 patients which also had a prognostic significance.[7]

Higher values of neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR) and platelets-to-lymphocytes ratio (PLR) can be useful predictive inflammatory markers for the disease course, and their increased levels were directly proportional to disease severity and poor outcome in COVID-19 patients. Systemic immune-inflammatory index (SII) has served as an expedient, affordable and noninvasive prognostic marker for patients of solid malignancy and carcinomas.[8,9]

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Moreover, SII also has positive prognostic value in COVID-19 patients and help in assessing the length of hospital stay (LOS) and predicts the mortality in these patients.[10]

Pakistan had its first confirmed case of COVID-19 in February 2020 and the first wave lasted till July 2020. The second wave lasted from November to December 2020 and the third wave from mid-March to June 2021. The fourth wave, which was presumed to be caused by the delta variant of SARS-CoV-2, lasted from July to September 2021. As per data till April 20, 2022, there were over 1.5 million confirmed COVID-19 cases and over 30,000 deaths reported in Pakistan.[11]

The current study was planned to compare the extent of cytopenias and SII of hospitalised COVID-19 patients during the first and second/third waves of the pandemic in a Pakistani setting.

Materials and Methods

The retrospective, cross-sectional study was conducted in October 2021 at the Department of Pathology in collaboration with the Department of Medicine, Fatima Memorial Hospital, Lahore, Pakistan, and comprised data of hospitalised COVID-19 patients regardless of age and gender from May 2020 to June 2021. Data was segregated into first wave that lasted from May to July 2020, second wave that lasted from early November to mid-December 2020, and third wave that ranged from mid-March to June 2021. For comparison purposes, the data of first wave was in group A, while data of second and third waves was pooled together into group B. The data was retrieved using consecutive nonprobability sampling technique after approval from Fatima Memorial college of medicine and dentistry institutional ethics review board (FMH-08-2021-IRB934-M). The study was in line with the Strengthening the Reporting of Cohort Studies in Surgery (STROCSS) criteria.[12]

Being a country with low socioeconomic status with resource limitations, gene sequencing was notperformed to detect the type of different variants of the virus. Diagnosis of COVID-19 had been confirmed on the basis of positive polymerase chain reaction (PCR) finding on nasal swab. Data of patients with chronic liver disease (CLD) and known haematological disorders was excluded.

Data retrieved included age, gender, comorbidities, requirement of ventilator support and outcome of the patients. Inflammatory markers were calculated from complete blood count (CBC) values. SII, which is an indicator related to inflammation that can mirror the immune and inflammation state of a patient 10, was calculated on the basis of absolute platelet count(APC), absolute neutrophil count (ANC) and absolute lymphocyte count (ALC) (APC x ANC / ALC), and SII >600 was labelled as raised and a bad prognostic marker.[13] For the purpose of the current study, patients with SII <600 were placed in group I, and patients with SII >600 in group II. CBC was performed on Sysmex XN-10 USA, (Five part haematology analyzer). Reference cut-off values to label cytopenia were taken from WHO and literaure.[14,15] NLR was calculated, and value >3 was considered raised. PLR was calculated as APC / ALC, and raised PLR was taken as >149 for males and >172 for females.[16] MLR was also calculated as absolute monocyte count (AMC) / ALC, and 0.23 was considered the cut-off level.[17] Patients with oxygen saturation (SaO_2) <94% and >50% lung involvement were considered to have severe disease, and patients requiring either invasive or non-invasive ventilator support with other complications were labelled as critical disease.[18]

Data was analysed using SPSS 25. Data was stratified according to age, gender, SII and different waves of COVID-19. Categorical variables were expressed as frequencies and percentages, while quantitative variables were expressed as median with interquartile range (IQR). Continuous variables were analysed using Mann-Whitney U test, while categorical variables were analysed using Chi-square and Fischer exact tests. NLR, PLR, MLR and SII were derived from the same CBC parameters, so no statistical comparison was done between SII and these inflammatory markers. P<0.05 was considered significant.

Results

Of the 202 patients, 90(44.5%) were in group A and 112(55.4%) were in group B. There were 108(53.5%) males and 94(46.5%) females. The median age in males was 58 years (IQR: 21 years) and it was 56 years (IQR: 21 years) in females. There were 173(85.6%) patients with severe disease and 29(14.4%) had critical disease. Mortality was the outcome in 25(14.5%) patients with severe disease and 22(75.9%) patients with critical disease (p<0.001).

Overall,74(36.6%) patients had no co-morbidities, 49(24.3%) had one co-morbidity and 79(39.1%) had two or more co-morbidities. The most frequent co-morbidity was hypertension (HTN) in 99(49%) patients, followed by diabetes mellitus (DM) in 94(46.5%), ischaemic heart disease (IHD) in 23(11.4%), chronic kidney disease (CKD) in 16(7.9%), asthma in 8(4%), chronic obstructive pulmonary disease (COPD) in 5(2.5%) and malignancy in 4(2%) patients. Ventilator support was required in 29(14%) cases, and mortality was the outcome in 47(23.3%) patients. Among the mortalities, 10(21.3%) patients had no co-morbidities, while 37(78.7%) had one or more co-morbidities.

There were more males in group A, while there were more females in group B (p=0.001). In group A, 83(92.2%) patients had a severe disease and 7(7.8%) had critical disease, while in group B, the corresponding values were 90(80.4%) 22(19.6%) (p=0.01). Leukopenia, lymphocytopenia and thrombocytopenia were more prevalent in group B compared to group A (p<0.05). Overall, anaemia was found in 42(37.5%) patients, and 6(5.4%) of them required packed cell volume (PCV) transfusion. Anaemia was more prevalent in group B 25(27.8%), but it was not statistically significant (p=0.09). Raised ANC, NLR, MLR, PLR and SII values were directly associated with severity of COVID-19 infection and these inflammatory markers showed no significant intergroup variations (Table).

High-resolution computed tomography (HRCT) score was only available for group B, which was 15 (IQR: 8). No patient with HRCT <8 or between 8-15 needed ventilator support. There were 58(51.7%) patients with HRCT >15, and 22(37.9%) of them required ventilator support. Ventilator support was needed in 7(7.8%) group A patients and 22(19.6%) group B patients (p=0.002). Prevalence of mortalities was significantly high in group B compared to group A (p<0.001).

On the basis of SII value, there were 54(26.7%) patients in group I and 148(73.2%) in group II. Median age of group I was 50years (IQR: 28 years) and it was 58 years (IQR: 20 years) in group II (p=0.2). There were 29(53.7%) males in group I and 9(53.4%) in group II (p=0.9). Anaemia was seen in 18 (33.3%) group I patients and 49 (33.1%) in group II (p=0.5). Leukopenia was seen in 11(20%) patients in group I, while no patient in group II had leukopenia. Leukocytosis was seen in 11(20.4%) and 89 (60.1%) patients in groups I and II, respectively (p<0.001). ANC was increased in 6(11.1%) patients of group I and 88 (59.5%) of group II (p<0.001). ANC showed a significant association with SII (p<0.001). Lymphopenia was present in 3(5.6%) patients of group I and 59(39.9%) of group II (p<0.001). AMC was markedly reduced in 23(42.6%) patients of group I and 74(50%) of group II (p=0.04). Thrombocytopenia was seen in 17(31.5%) and 14(9.5%) patients of groups I and II, respectively (p=0.001) (Figure). Group I had 50(92.6%) patients with severe disease and 4(7.4%) critical cases, while in group II there were 123(83.1%) severe disease and 25(16.9%) critical disease patients (p=0.06). Requirement of ventilatory support (p=0.3) and mortality (p<0.001) were more prevalent in group II.

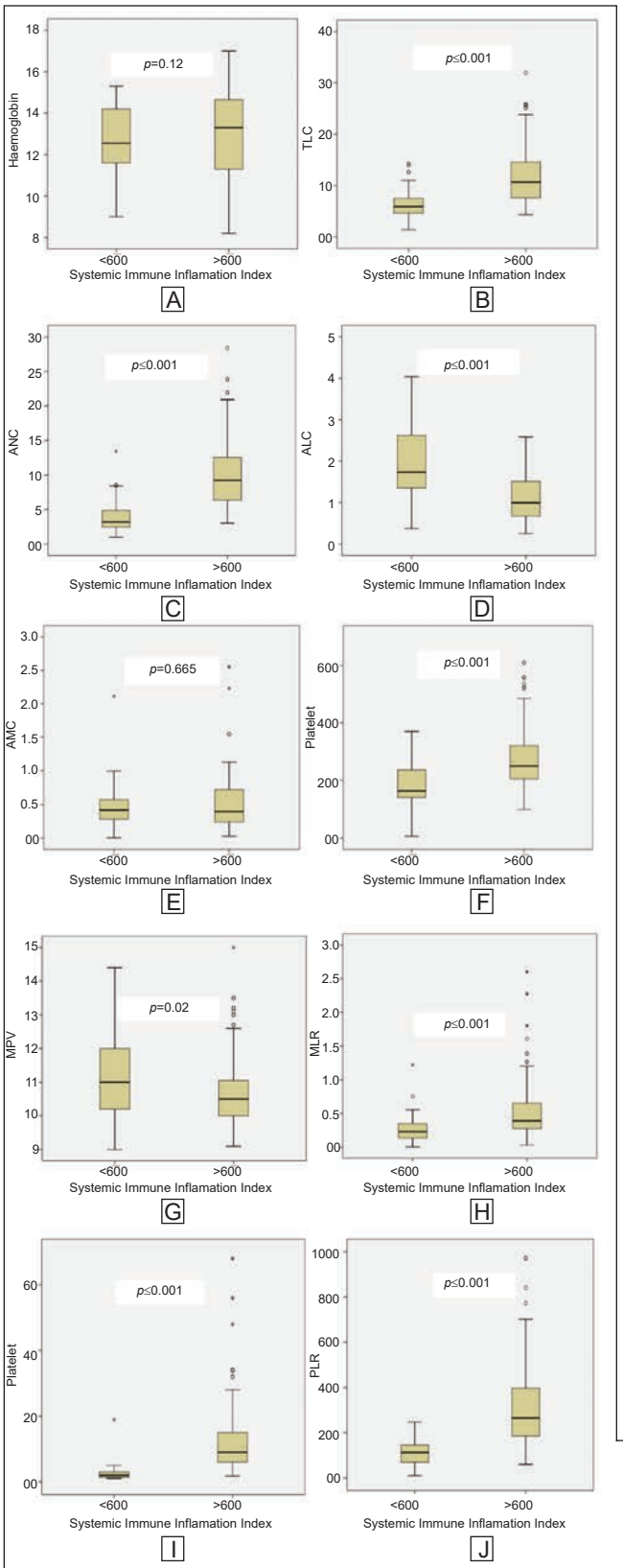
Table: Median (IQR) values of haematological parameters and their comparison between the first and second/third waves of COVID-19.

	Parameters	Units	Cut off values	Median (IQR) (n= 202)	First wave (n=90)	Second/third waves (n=112)	*p*-value
1	Gender		Male,		60 (66.7%)	48 (42.9%)	0.001
			Female		30 (33.3%)	64 (57.1%)	
2	Hb	g/dl	<13, <11.7	13.2(3.2)	25 (27.8%)	42 (37.5%)	0.09
			>13, >11.7		65 (72.2 %)	70(62.5%)	
3	TLC	109/l	<4	9.64(6.4)	1 (1.1%)	10 (8.9%)	0.001
			4-10		51(56.7%)	40(35.7%)	
			>10		38(42.2%)	62 (55.4%)	
4	ANC	109/l	<0.5	7.8(6.4)	0 (0%)	2 (1.8%)	0.2
			0.5-8		52 (57.8%)	54 (48.2%)	
			>8		38 (42.2%)	56 (50%)	
5	ALC	109/l	<0.8	1.25(0.99)	18 (20%)	44(39.3%)	0.003
			0.8-5		72 (80%)	68 (60.7%)	
6	AMC	109/l	<0.4	0.4(0.4)	43 (47.8%)	54 (48.2%)	0.98
			0.4-1		40 (44.4%)	50 (44.6%)	
			>1		7 (7.8%)	8 (7.1%)	
7	NLR	Ratio	<3	6.5(9)	34 (37.8%)	26(23.2%)	0.24
			>3		56 (62.2%)	86 (76.8%)	
8	Platelets	109/l	<150	234.5(130)	3 (3.3%)	28 (25%)	<0.001
			>150		87 (96.7%)	84 (75%)	
9	MPV	fl	<11.5	10.5(1.4)	72 (80%)	80 (71.4%)	0.19
			>11.5		18 (20%)	32 (28.6%)	
10	MLR		<2.3	0.35(0.33)	26 (28.9%)	24 (21.4%)	0.145
			>2.3		64 (78.1%)	88 (78.6%)	
11	PLR	Ratio	<149, <172	207.2(174.7)	35(38.9%)	30 (26.8%)	0.067
			>149, >172		55 (61.1%)	82 (73.2%)	
12	SII	Ratio	<600	1613(2475.9)	26 (28.9%)	28 (25%)	0.53
			>600		64 (71.1%)	84 (75%)	

COVID-19: Coronavirus disease-2019, IQR: Interquartile range, Hb: Haemoglobin, TLC: Total leukocyte count, ANC: Absolute neutrophilic count, ALC: Absolute lymphocyte count, AMC: Absolute monocyte count, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MPV: Mean platelet volume, MLR: Monocyte-to-lymphocyte ratio, SII: Systemic immune inflammation index.

Discussion

The clinical spectrum of coronavirus ranges from asymptomatic or mild disease to fatal and life-threatening illness. Laboratory findings responsible for worst outcome include lymphopenia, thrombocytopenia, elevated liver enzyme, lactate dehydrogenase (LDH), inflammatory markers, D-Dimers, prothrombin time, troponin, creatinine phosphokinase and acute kidney injury. Due to high infectivity and mortality rates of COVID-19, early diagnosis of the disease is essential.[19] Results of the current study showed that co-morbidities and deranged haematological parameters had direct impact on the severity and outcome of the disease in COVID-19 patients. The study reported higher percentage of infectivity in males during the first wave, while during the second/third wave phase,



infectivity was more prevalent in females. A study also showed higher prevalence of female hospitalisation than males during the second wave.[20] Among co-morbidities, Hypertension was the most prevalent, followed by DM, IHD, CKD, asthma, COPD and malignancy. A study also concluded that HTN, DM and cardiovascular diseases (CVDs) were the most frequent co-morbidities among COVID-19 patients.[21] It was observed in the current study that mortality was higher in patients who had co-morbidities. Higher number of mortalities in patients with co-morbidities was also reported earlier.[22] A meta-analysis illustrated that higher mortality was seen in patients with co-morbidities, like HTB, DM and respiratory diseases.[23]

SII is used for risk stratification of patients and has an important role in prognosticating the outcomes related to COVID-19.[24] In the current study, patients with high SII (≥600) showed higher mortality and required increased ventilator support. Hong Li et al. reported the same findings.[25] Infectious diseases cause inflammation which has a significant role in the progression of viral pneumonia, including COVID-19. There is an immune response imbalance due to weak adaptive immune response seen in severe inflammation. Circulating biomarkers, like NLR, PLR and MLR, in COVID-19 represented inflammation and immune status as predictors of prognosis. Elevated NLR was associated with poor prognosis and severe disease in COVID-19. NLR was seen elevated in patients with raised SII. Yang AP et al. found a positive association of elevated NLR with severity of disease and poor prognosis. Similarly, elevated PLR value suggested an overactive inflammatory response and was associated with severe disease and poor prognosis.[26] In the current study, PLR was found elevated in patients with high SII and had statistical significance. Simadibrata et al. suggested that elevated PLR in COVID-19 patients could reflect cytokine storm.[27] In the current study, raised SII showed a direct association with increased mortality. Fois AG et al. also reported significantly higher value, among other markers, of SII in non-survivors compared to survivors.[28] High SII was also directly associated with the requirement of invasive and non-invasive ventilator support in the current study, and the same was concluded by a study that had 326 COVID-19 patients.[25]

Data of comparative studies on haematological parameters between first and subsequent waves is limited. The current

Figure: Association of systemic immune inflammation Index (SII) with haematological parameters in the first and second/third waves of coronavirus disease-2019 (COVID-19), including (A) haemoglobin (Hb), (B) total leucocyte count (TLC), (C) absolute neutrophil count (ANC), (D) absolute lymphocyte count (ALC), (E) absolute monocyte count (AMC), (F) platelet count, (G) mean platelet volume (MPV), (H) monocyte-to-lymphocyte ratio (MLR) (I) neutrophil-to-lymphocyte ratio (NLR), and (J) platelet-to-lymphocyte ratio (PLR).

study concluded that lymphocytopenia and thrombocytopenia were more prevalent during the phase of second/third waves. The findings of the current study concurred with the study conducted on Romanian patients which found prevalence of lymphopenia and thrombocytopenia during the second wave.[29] Rahim S et al. also found lymphopenia as a prominent finding during the second wave.[30] Anaemia was found to be more prevalent during the second/third waves in the current study, but it was not significant statistically and was corrected by blood transfusion.

In the current study, leukopenia was also observed during the second/third waves of COVID-19. Li YX et al. concluded that leukopenia, lymphocytopenia and eosinophil cytopenia were more prominent findings in COVID-19 patients than non-COVID-19 patients.[31]

Utility of other inflammatory markers, like NLR, PLR, MLR and SII, have established a positive role in predicting the severity and course of disease along with directing the management plans for the COVID-19 patients as well as prognosis.[32] These inflammatory markers showed a strong association with disease course, severity and outcome of COVID-19 disease, but no significant difference was found between the different waves of COVID-19 in the current study. Increased invasive and non-invasive ventilatory support requirement and an increased number of critical patients were observed during the second/third wave of COVID-19 in comparison with the first wave.

More mortalities were noted in the current study during the second/third waves of COVID-19. The same results were concluded by Kumar G et al. in India, where mortality increased by 3.1% during the second wave of COVID-19.[33] Increased in-hospital deaths were also observed by Jassat W et al. during the second wave in South Africa.[34] However, the findings differed from a study which concluded that fewer deaths occurred during the second wave compared to the first wave of COVID-19.[35]

The current study has limitations. It was unable to detect the different variants and mutations of coronavirus that were detected worldwide. As such, it was impossible to categorise the haematological parameters according to specific variants of COVID-19.

Although this was a single-centre study, the results can be applicable to COVID-19 patients of other ethnic origins.

Conclusion

SII was found to be a good, expedient and non-invasive predicting tool in COVID -19 prognosis. It was directly associated with cytopenias, severity of disease, ICU admissions, ventilator support as well as outcome of the disease. SII can be used as a useful inflammatory marker for COVID-19 prognosis.

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References

1. Townsend L, Fogarty H, Dyer A, Martin-Loeches I, Bannan C, Nadarajan P, et al. Prolonged elevation of D-dimer levels in convalescent COVID-19 patients is independent of the acute phase response. J Thromb Haemost 2021;19:1064-70. doi: 10.1111/jth.15267
2. World Health Organization (WHO). Weekly epidemiological update on COVID-19. [Online] 2021 [Cited October 25]. Available from URL: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---19-october-2021
3. Kumar R, Singh V, Mohanty A, Bahurupi Y, Gupta PK. Corona health-care warriors in India: knowledge, attitude, and practices during COVID-19 outbreak. J Educ Health Promot 2021;10:44. doi: 10.4103/jehp.jehp_524_20
4. Zafer MM, El-Mahallawy HA, Ashour HM. Severe COVID-19 and Sepsis: Immune Pathogenesis and Laboratory Markers. Microorganisms 2021;9:159. doi: 10.3390/microorganisms9010159
5. Taj S, Kashif A, Arzinda Fatima S, Imran S, Lone A, Ahmed Q. Role of hematological parameters in the stratification of COVID-19 disease severity. Ann Med Surg (Lond) 2021;62:68-72. doi: 10.1016/j.amsu.2020.12.035
6. Bairwa M, Kumar R, Beniwal K, Kalita D, Bahurupi Y. Hematological profile and biochemical markers of COVID-19 non-survivors: A retrospective analysis. Clin Epidemiol Glob Health 2021;11:100770. doi: 10.1016/j.cegh.2021.100770
7. Agbuduwe C, Basu S. Haematological manifestations of COVID-19: From cytopenia to coagulopathy. Eur J Haematol 2020;105:540-6. doi: 10.1111/ejh.13491
8. Yang R, Chang Q, Meng X, Gao N, Wang W. Prognostic value of Systemic immune-inflammation index in cancer: A meta-analysis. J Cancer 2018;9:3295-302. doi: 10.7150/jca.25691
9. Ali S, Ashraf , Ahmad I, Rahman N, Zeb S, Abbas M. Prognostic value of the SII Systemic Immune-Inflammation Index a novel biomarker in coronavirus disease 2019 patient's disease progression to fatality. Rawal Med J 2023;48:63-9.
10. Zinellu A, Scano V, Masotto E, De Riu G, Vaira LA, Carru C, et al. The Systemic Inflammation Index on admission is independently associated with length of stay in hospitalized COVID-19 patients. Minerva Respir Med 2021;60:65-72. DOI: 10.23736/S2784-8477.21.01932-5. Pubmed result not found
11. Government of Pakistan. COVID-19 dashboard. [Online] 2022 [Cited 2022 June 15]. Available from URL: https://nhsrc.gov.pk/ProjectDetail/M2QzOWJmMjUtZTU3MC00NmFkLWE4YmMtZDFhMmRlOGU2NGRh
12. Mathew G, Agha R, Albrecht J, Goel P, Mukherjee I, Pai P, et al. STROCSS 2021: Strengthening the reporting of cohort, cross-sectional and case-control studies in surgery. Int J Surg 2021; 96:e106165. doi: 10.1016/j.ijsu.2021.106165
13. Demir H, Katırcılar Y, Beypınar İ, Karagöz Eren S, İnanç M. Prognostic Value of Systemic Immune Index in Patients with Metastatic Gastric Cancer. Eur Arch Med Res 2021;37:95-100. DO I: 10.4274/eamr.galenos.2020.36449
14. World Health Organization (WHO). Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. [Online] 2011

[Cited 2021 October 18]. Available from URL: https://iris.who.int/bitstream/handle/10665/85839/WHO_NMH_NHD_MNM_11.1_eng.pdf

15. Bates I. Reference Ranges and Normal Values. In: Bain BJ, Bates I, Laffan MA, eds. Dacie and Lewis Practical Haematology, 12th ed. Amsterdam, Netherlands: Elsevier, 2017; pp 8-17.
16. Wu L, Zou S, Wang C, Tan X, Yu M. Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratio in Chinese Han population from Chaoshan region in South China. BMC Cardiovasc Disord 2019;19:125. doi: 10.1186/s12872-019-1110-7
17. Peng J, Qi D, Yuan G, Deng X, Mei Y, Feng L, et al. Diagnostic value of peripheral hematologic markers for coronavirus disease 2019 (COVID-19): A multicenter, cross-sectional study. J Clin Lab Anal 2020;34:e23475. doi: 10.1002/jcla.23475
18. National Institutes of Health (NIH). Clinical Spectrum of SARS-CoV-2 Infection. [Online] 2022 [Cited 2022 July 11]. Available from URL: https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/
19. McIntosh K, Gandhi RT. COVID-19: Clinical features. [Online] 2022 [Cited 2022 June 15]. Available from URL: https://www.uptodate.com/contents/covid-19-clinical-features
20. Quaresima V, Scarpazza C, Sottini A, Fiorini C, Signorini S, Delmonte OM, et al. Sex differences in a cohort of COVID-19 Italian patients hospitalized during the first and second pandemic waves. Biol Sex Differ 2021;12:45. doi: 10.1186/s13293-021-00386-z
21. Sharif N, Opu RR, Ahmed SN, Sarkar MK, Jaheen R, Daullah MU, et al. Prevalence and impact of comorbidities on disease prognosis among patients with COVID-19 in Bangladesh: A nationwide study amid the second wave. Diabetes Metab Syndr 2021;15:102148. doi: 10.1016/j.dsx.2021.05.021
22. Ejaz H, Alsrhani A, Zafar A, Javed H, Junaid K, Abdalla AE, et al. COVID-19 and comorbidities: Deleterious impact on infected patients. J Infect Public Health 2020;13:1833-9. doi: 10.1016/j.jiph.2020.07.014
23. Gold MS, Sehayek D, Gabrielli S, Zhang X, McCusker C, Ben-Shoshan M. COVID-19 and comorbidities: a systematic review and meta-analysis. Postgrad Med 2020;132:749-55. doi: 10.1080/00325481.2020.1786964
24. Mangoni AA, Zinellu A. Systemic inflammation index, disease severity, and mortality in patients with COVID-19: a systematic review and meta-analysis. Front Immunol 2023;14:1212998. doi: 10.3389/fimmu.2023.1212998
25. Li H, Huang J, Pan W, Zhang C, Chang X, Yang B. Systemic Immune-Inflammatory Index predicts prognosis of patients with COVID-19: a retrospective study. Res Sq 2020. Doi: 10.21203/rs.3.rs-30701/v1 [Preprint]
26. 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. doi: 10.1016/j.intimp.2020.106504
27. Simadibrata DM, Pandhita BAW, Ananta ME, Tango T. Platelet-to-lymphocyte ratio, a novel biomarker to predict the severity of COVID-19 patients: A systematic review and meta-analysis. J Intensive Care Soc 2022;23;20-6. Doi: 10.1177/1751143720969587.
28. Fois AG, Paliogiannis P, Scano V, Cau S, Babudieri S, Perra R, et al. The Systemic Inflammation Index on Admission Predicts In-Hospital Mortality in COVID-19 Patients. Molecules 2020;25:5725. doi: 10.3390/molecules25235725
29. Mocanu A, Noja GG, Istodor AV, Moise G, Leretter M, Rusu LC, et al. Individual Characteristics as Prognostic Factors of the Evolution of Hospitalized COVID-19 Romanian Patients: A Comparative Observational Study between the First and Second Waves Based on Gaussian Graphical Models and Structural Equation Modeling. J Clin Med 2021;10:1958. doi: 10.3390/jcm10091958
30. Rahim S, Dhrolia M, Qureshi R, Nasir K, Ahmad A. A Comparative Study of the First and Second Waves of COVID-19 in Hemodialysis Patients From Pakistan. Cureus 2022;14:e21512. doi: 10.7759/cureus.21512
31. Li YX, Wu W, Yang T, Zhou W, Fu YM, Feng QM, et al. Characteristics of peripheral blood leukocyte differential counts in patients with COVID-19. Zhonghua Nei Ke Za Zhi 2020;59:372-4. doi: 10.3760/cma.j.cn112138-20200221-00114.
32. Usul E, Şan İ, Bekgöz B, Şahin A. Role of hematological parameters in COVID-19 patients in the emergency room. Biomark Med 2020;14:1207-15. doi: 10.2217/bmm-2020-0317
33. Kumar G, Mukherjee A, Sharma RK, Menon GR, Sahu D, Wig N, et al. Clinical profile of hospitalized COVID-19 patients in first & second wave of the pandemic: Insights from an Indian registry based observational study. Indian J Med Res 2021;153:619-28. doi: 10.4103/ijmr.ijmr_1628_21
34. Jassat W, Mudara C, Ozougwu L, Tempia S, Blumberg L, Davies MA, et al. Difference in mortality among individuals admitted to hospital with COVID-19 during the first and second waves in South Africa: a cohort study. Lancet Glob Health 2021;9:e1216-25. doi: 10.1016/S2214-109X(21)00289-8
35. Iftimie S, López-Azcona AF, Vallverdú I, Hernández-Flix S, de Febrer G, Parra S, et al. First and second waves of coronavirus disease-19: A comparative study in hospitalized patients in Reus, Spain. PLoS One 2021;16:e0248029. doi: 10.1371/journal.pone.0248029

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AK: Concept, design, data analysis, writing.
ST: Data interpretation, literature review.
SSC, SM: Data collection, literature review.
AZKC: Data collection, interpretation, writing.
AL: Proof reading, final approval.