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Original Research Article

ROLE OF SELECTED HEMATOLOGICAL PARAMETERS IN PROGNOSTICATION OF SARS COV2 INFECTION IN HOSPITALISED PATIENTS

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Abstract

Background: Coronavirus disease (COVID) is a viral infection which spread worldwide within a short span of time. One of the major challenges encountered during this pandemic was the unpredictability with which the patients developed complications. The aim and objective are to estimate baseline hematological parameters in patients hospitalised with COVID and study selected haematological parameters with relation to patient outcome. **Materials and Methods:** This is a retrospective study conducted in a tertiary care teaching institute. Patient data of all confirmed cases of COVID admitted from 1st February 2020 to 31st August 2020 was collected from electronic medical records. Statistical analysis of data was done using SPSS. ROC curve was plotted and logistic regression analysis performed to determine the association of demographic and haematological parameters with severity of disease. **Result:** During the study period, 416 patients were hospitalised with COVID, among whom 235 patients were categorised as severe and 181 as non severe. Hematological parameters like RDW-CV, total leucocyte count, absolute neutrophil count, platelet count, ferritin and indices like neutrophil-lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR) and systemic immune inflammatory index (SII) were found to be higher in the severe group when compared to the non-severe group. Based on logistic regression analysis, age and NLR were found to be the most relevant factors predictive of progression to severity. **Conclusion:** Baseline hematological investigations are a valuable tool in the management of SARS CoV2 infection. Age and neutrophil lymphocyte ratio may be used as prognostic markers to predict severity of COVID 19.

INTRODUCTION

An outbreak of pneumonia cases was reported in Wuhan in China in December 2019. The causative organism was identified by deep gene sequencing as a novel enveloped RNA betacorona virus which has been named the severe acute respiratory syndrome virus 2 (SARS COV2). The resultant viral disease was designated as coronavirus disease 2019 (COVID-19) by World Health Organisation on January 30, 2020.[1] As this disease is widely transmitted during the presymptomatic and early symptomatic phase there was a rapid increase in the number of cases within a short while. By March 2020, 114 countries worldwide were affected, prompting the World Health Organisation to declare it as a pandemic.[2] By September 2021, over 220 million confirmed cases and over 4.5 million deaths were reported globally.

Although the primary organ affected is the lung, the manifestations of the disease vary widely from a mild upper respiratory infection to a severe potentially fatal multisystem disease. Around 50% of the COVID patients may be asymptomatic carriers or presymptomatic patients. Only mild flu like symptoms is manifested during the early phase of the infection. The progression from mild disease to severe respiratory distress can be rapid and unexpected. Severe cases are complicated by septic shock, multiorgan dysfunction and disseminated intravascular coagulation leading to mortality.[1,3] A major challenge in a pandemic of this proportion is to sort out the critically ill patients from the tremendous population of the infected and provide invaluable medical care to the needy. Rapid diagnosis and

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triaging of the patients will prove beneficial in optimum utilisation of available resources. Ministry of Health and Family Welfare, Government of India has issued a detailed clinical management protocol for COVID 19 patients, according to which the patients with mild disease may be cared for at home or at a COVID care centre whereas those with severe disease should be managed in a hospital.[4]

The nonspecific presenting symptoms can be interpreted more efficiently with the support of haematological markers. Hematological abnormalities have been found to be associated with disease progression, morbidity and mortality.[5] Various biomarkers involving erythrocyte, leucocyte and platelet parameters like Neutrophil lymphocyte ratio (NLR), Platelet lymphocyte ratio (PLR) and Systemic Immune-Inflammatory Index (SII) have been suggested as diagnostic indicators as well as prognostic parameters for early identification of potential complications.[1,2,3,6] This study explores the possibility of utilising various hematological parameters for predicting the prognosis of COVID 19 patients.

MATERIALS AND METHODS

The study was a retrospective single centre study conducted in a tertiary care hospital. The study protocol was approved by the institutional ethics committee. All adult patients who were admitted with a diagnosis of COVID 19 infection from February 2021 to August 2021 were included in the study. Paediatric patients and known cases of haematological malignancy were excluded from the study. The diagnosis of COVID infection was made by Real Time Polymerase Chain Reaction (RTPCR) on nasopharyngeal swab specimens. The medical records of these patients were reviewed. A detailed proforma for entering the patient data, the study parameters and clinical outcome was used to collect the information. The data collected included demographic data, medical history, clinical features, laboratory investigations and outcome events like ICU admission, ventilator use and death.

The patients were classified into severe and non-severe categories based on their clinical features. Severe disease was defined as - Fever or suspected respiratory infection, plus one of the following: respiratory rate>30/ min, severe respiratory distress or SpO2< or equal to 90% on room air. This criterion was according to the clinical management protocol of Covid 19 issued by Ministry of Health and Family Welfare, Government of India. Patients who were positive for Covid 19 infection but failed to fulfil the criteria for severe disease were included in the non-severe category.[4]

Complete blood count was performed on Erba Mannheim ELITE 580 hematology analyser and coagulation parameters on mini VIDAS multiparametric immunoanalyser from samples taken on the day of admission.

Hematological ratios like Neutrophil lymphocyte ratio (NLR), Platelet lymphocyte ratio (PLR) and Systemic Immune- Inflammatory Index (SII) were calculated from the values obtained. Neutrophil lymphocyte ratio was defined as absolute neutrophil count divided by absolute lymphocyte count. Platelet lymphocyte ratio was defined as total platelet count divided by absolute lymphocyte count. Systemic immune-inflammatory index was calculated as the product of absolute neutrophil count and total platelet count divided by absolute lymphocyte count.[3] Red cell distribution width (RDW) was measured by the hematology analyser as two parameters- coefficient of variation (RDW-CV) and standard deviation (RDW-SD), both of which were included in the study.

Descriptive analysis was performed on all the variables. Continuous variables were presented as means and standard deviations and categorical variables were presented as percentages in each category. Students t-test was used to compare continuous variables in severe and non severe categories. P value < 0.05 was considered as statistically significant. ROC curve was plotted to determine cut off values of NLR, PLR and SII. [Figure 1] Binary logistic regression was done to determine the significance of age, gender and other significant factors. All statistical analysis was performed using IBM SPSS 20 software.

RESULTS

Among the 416 patients included in the study, there were 220 (52.88%) males and 196 (47.12%) females. The ‘severe’ category comprised of 235 (56.49%) patients and the ‘non severe’ category consisted of 181 (43.51%) patients. [Table 1] Mean age of the patients was 57.13 years. Patients with severe disease (Mean age- 61.26) were older compared to those with non- severe disease. (Mean age-51.76) (p value-0.007). Severe category included more men than women, but no significant association was found between gender and severity of disease.

The difference in haematological parameters between severe and non-severe groups are shown in [Table 2]. There was no significant difference in haemoglobin values between severe and non-severe groups. RDW-CV was significantly higher in the severe group as compared to the non-severe group (p value-0.04), whereas RDW-SD showed no significant difference between the two groups.

Total leucocyte count, absolute neutrophil count, platelet count and ferritin were found to be significantly higher in severe groups than in the non-severe group. (p value<0.05) Absolute lymphocyte count was found to be lower in severe group than in non-severe group. (p value<0.001) No significant difference was noted between the two groups for absolute eosinophil count and D dimer.

Mean values of Neutrophil lymphocyte ratio (NLR), Platelet lymphocyte ratio (PLR) and Systemic

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Immune-Inflammatory index (SII) were also found to be higher in the severe group as compared to the non-severe group. (p value <0.05)

As there are no universally accepted cut off values for the haematological parameters under study to differentiate between severe and non-severe cases of Covid infection, a receiver operating characteristic (ROC) curve was plotted to obtain optimum cut off values for absolute neutrophil count (ANC), absolute lymphocyte count, platelet count, NLR, PLR, SII and RDW. [Figure 1] The findings were significant (p value<0.05) in case of absolute neutrophil count, absolute lymphocyte count, NLR, PLR and SII only.

The parameters for which the area under curve (AUC) was greater than 0.5 included age, absolute neutrophil count, NLR, PLR and SII. [Table 3] The optimum cut off values for these parameters were identified by means of Youden cut offs as 52.5, 5272/cmm, 3.58, 158.95 and 445.09 x 103

Binary logistic regression was performed to determine the association of age, gender, NLR, PLR, SII and RDW on severity of COVID infection. Based on the results, only age (p value< 0.001) and NLR (p value- 0.017) showed significant association with disease severity. [Figure 2 and 3]

Table 1: Gender wise distribution of cases

	Male	Female	Total
Non severe	91	90	181 (43.5%)
Severe	129	106	235 (56.5%)
Total	220 (52.9%)	196 (47.1%)	416

Table 2: Hematological parameters in COVID patients

Lab value (Mean+/-SD)	All patients (n=416)	Non severe (n=181)	Severe (n=185)	p value
Hemoglobin	12.87(+/-1.80)	12.91(+/-1.81)	12.84(+/-1.81)	0.593
RDW-CV	14.52(+/-6.30)	13.99(+/-1.31)	14.93(+/-8.29)	0.048
RDW-SD	43.29(+/-4.34)	43.06(+/-4.54)	43.47(+/-4.19)	0.367
Total leucocyte count	8633.16 (+/-4737.28)	7634.33 (+/-4096.22)	9402.48 (+/-5052.49)	0.001
ANC	6827.97(+/-4645.48)	5535.94(+/-3789.78)	7823.11 (+/-4993.92)	0.000
ALC	1422.33(+/-807.706)	1677.21 (+/-886.16)	1226.03(+/-681.18)	0.000
AEC	80.29(+/-185.49)	80.07 (+/- 129.17)	80.46 (+/-219.52)	0.445
Platelet count	2.27(+/-2.4)	2.14 (+/- 0.65)	2.54 (+/-3.14)	0.028
ESR	62.17(+/-41.79)	47.07(+/-35.43)	73.79(+/-42.65)	0.001
NLR	6.89(+/-8.01)	4.38 (+/- 4.22)	8.82 (+/- 9.57)	0.000
PLR	0.23(+/-0.30)	0.17 (+/- 0.12)	0.27 (+/- 0.38)	0.004
SII	1866.76(+/-3814.35)	989.87(+/-1140.70)	2542.15 (+/-4873.33)	0.000
D dimer	1875.99 (+/-5997.25)	1730.29 (+/-7802.44)	1988.22 (+/-4114.51)	0.800
Ferritin	604.65(+/-764.57)	399.92 (+/-566.09)	762.33 (+/-856.06)	0.000

Footnote- RDW-CV: Red cell distribution width-Coefficient of variation, RDW-SD: Red cell distribution width-Standard Deviation, ANC: Absolute neutrophil count, ALC: Absolute leucocyte count, AEC: Absolute eosinophil count, ESR: Erythrocyte sedimentation rate, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, SII: Systemic inflammatory index

Table 3: Area under curve of NLR, PLR, SII, RDW-SD, RDW-CV and age in predicting severity in patients with COVID infection

Test Variables	Area	Standard Error	Asymptotic significance	Asymptotic 95% Confidence interval	
				Lower bound	Upper bound
Age	0.661	0.027	0.000	0.608	0.714
NLR	0.711	0.025	0.000	0.662	0.761
PLR	0.658	0.027	0.000	0.606	0.710
SII	0.699	0.026	0.000	0.648	0.749
RDW-CV	0.545	0.028	0.114	0.490	0.610
RDW-SD	0.543	0.028	0.136	0.487	0.598

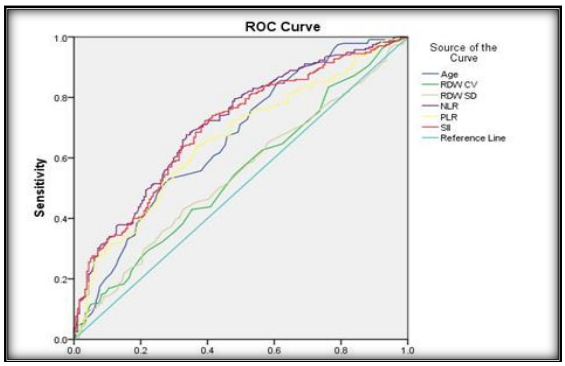

Figure 1: Receiver operating characteristic curves (ROC) curves of NLR, PLR, SII, RDW-SD,RDW-CV, and age in predicting severity in patients with COVID infection

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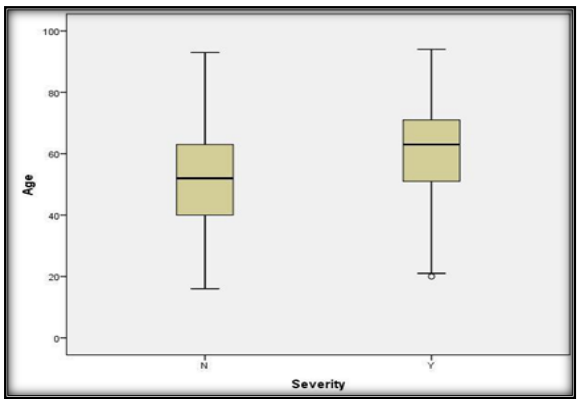

Figure 2: Box and whisker plot showing age distribution of Covid patients with non-severe and severe disease Footnote: N- nonsevere, Y- severe

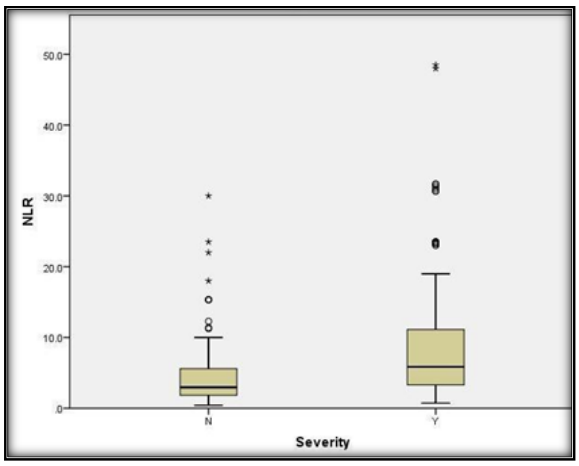

Figure 3: Box and whisker plot showing distribution of NLR value in Covid patients with non-severe and severe disease. Footnote: N- nonsevere, Y- severe

DISCUSSION

The first case of COVID 19 infection in India was identified in January 2020. Since then there was a steep rise in the number of COVID 19 patients. The number of cases as well as the number of deaths was increasing day by day. The outbreak of this infection resulted in saturation of hospitals with patients, overwhelming our healthcare system. Around half of the patients were asymptomatic or mildly symptomatic in the early phase.[7] The initial manifestations in most of the patients were fever and cough, whereas gastrointestinal manifestations were found in some patients. Although the disease affects all the organ systems, lung is the major target organ. Severe lung injury and acute respiratory distress syndrome is the leading cause of death.[8]

Erythrocytes play a significant role in the pathophysiology of COVID 19. Thomas et al has hypothesised that COVID 19 infection results in damage of erythrocyte structural proteins and remodelling of membrane phospholipids.[9] Other consequences of COVID infection such as coagulopathy and hemolysis have may also contribute to derangement of red blood cell morphology.[10]

Red cell distribution width (RDW) is a quantitative estimation of the heterogeneity of the circulating erythrocyte population. Automated analysers express RDW as coefficient of variation (RDW-CV) and as standard deviation (RDW-SD). RDW has been suggested as a prognostic factor in respiratory and cardiovascular diseases like chronic obstructive pulmonary disease (COPD), pneumonia, pulmonary embolism, cardiac failure as well as haematolymphoid malignancies.[11] In COVID 19 infection, which is associated with accelerated turnover of leucocytes and platelets, it is implied that there is delayed erythrocyte clearance. There is a decrease in the cellular volume as part of aging process of RBC. Hence the persistence of older erythrocytes in peripheral blood results in wider volume variance measurable as elevated RDW.[10]

Poulazadeh et al names RDW-SD as a more reliable indicator of disease severity in COVID 19 rather than RDW-CD. It is noted that RDW-SD is high in elderly patients and those with hypertension and cardiovascular disorders and thus indicative of general health status.[12] A retrospective cohort study by Foy et al has noted the prognostic value of RDW-CV in predicting mortality among COVID patients. This study has noted that an RDW of greater than 14.5% at hospital admission is associated with greater risk of mortality, especially among younger patients.[11] In our study, there is a significant difference between RDW-CV (p value<0.05) and no significant difference in RDW-SD between severe and non severe groups. Sarkar et al affirms the association of elevated RDW in COVID 19 related morbidity and mortality despite the varying cut off values.[13]

Neutrophilia has been associated with severe bacterial infections and lymphocytosis with viral infections. Neutrophilia in COVID infection is suggested to be an expression of cytokine storm leading to the hyperinflammatory state characteristic of its pathogenesis.[14,15] Neutrophils can be triggered by virus associated inflammatory mediators such as interleukin 6, interleukin 8, tumour necrosis factor alpha and granulocyte colony stimulating factor.[6] Tomar et al explains the role of neutrophils in the immunopathology of COVID 19. Neutrophilic infiltration at the site of viral entry, subsequent degranulation and formation of Neutrophil Extracellular traps contribute to an exaggerated immune response. Neutrophil extracellular traps trigger cytokine storm, microthrombi formation and activation of complement cascade thus resulting in acute respiratory distress syndrome, systemic inflammatory response syndrome and impairments in microcirculation.[16]

Lymphocytes play a major role in regulating inflammatory response. Corona virus disease has been shown to have high rate of lymphocyte infection in the early phase. T lymphocytes are instrumental in the destruction of viral particles. Lymphopenia in COVID is postulated to reflect a defective immune response to viral entry. Cytopathic destruction of

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lymphocytes, along with infection of bone marrow precursor cells contributes to lymphocyte depletion in peripheral blood as well as in the reticuloendothelial system.[17] During viral infections, T lymphocytes inhibit the overactive innate immune responses. Dysregulation of the innate immune system results in excessive inflammatory cell infiltration and subsequent cytokine storm which is the cause of severe morbidity and mortality in COVID 19.[1] Waris et al speculates that lymphocyte depletion is directly proportional to the severity of Covid infection.[2]

Neutrophil lymphocyte ratio (NLR) is associated with systemic inflammatory status has been associated with a prognostic role in cardiovascular disorders, autoimmune diseases, neoplasms and bacterial infections, especially pneumonia. This ratio has recently been utilised to predict the severity of Covid infections.[14,18] Waris et al comments that NLR value greater than 3 can be considered as a sign of infection and NLR greater than 9 can be considered an indicator of sepsis.[2] Cut off values of NLR varies in different studies.(Liu-3.13, Yang- 3.3, Kazancioglu-3.58, Kong-5, Fois-6.2, Xia-7.25, Citu-9.1)[1,6,18-22] Our study yielded a cut off value of 3.58 which is comparable with similar studies. It is suggested that high NLR value in conjunction with age can be practical tools in predicting severity of COVID 19 infection.[6,18] Fois et al reports that NLR is a sensitive biomarker having more superior prognostic potential than independent neutrophil and lymphocyte counts.[20] Xia et al has identified NLR as the biomarker with the greatest specificity in predicting diseased deterioration.[21]

Thrombocytopenia is a feature of severity in all viral infections including COVID. Waris et has suggested that a mean platelet count is decreased in COVID 19 patients with severe clinical manifestations.[2] However, elevation of platelet count may be reflective of the degree of cytokine storm in severely ill patients. Frater et al reports the incidence of thrombocytopenia in majority of COVID cases and thrombocytosis in a few.[15] Qu et al suggests that thrombocytopenia in COVID 19 may be attributable to viral invasion of bone marrow resulting in hematopoietic inhibition and retention and depletion of platelets in lung tissue due to extensive alveolar damage. Anti platelet auto antibody formation triggered by SARS-COV2 infection can also contribute to immune mediated platelet destruction.[23] Platelet lymphocyte ratio is more valuable as a prognostic tool as it represents both thrombotic and inflammatory pathways. Seyit et al advocates the use of PLR in the diagnosis and follow of COVID patients along with NLR.[24] The cut off value of PLR obtained in our study (158.51) is comparable with the values in similar studies. (Seyit-102.8, Yang-180, Kazancioglu- 230, Fois-240).[6,19,20,24]

In acute viral infections, eosinophils have been found to accumulate in the affected tissue to combat infection, resulting in decrease of peripheral blood eosinophil count. Sun et al explains the incidence of peripheral blood eosinopenia in COVID patients by this mechanism and proposes eosinopenia as an indicator of poor outcome.[8] Li et al recommends eosinopenia as an early marker for emergence of radiological features characteristic of COVID infection.[25] Our study has not found a significant association between absolute eosinophil count and severity of disease.

Sysmetic Inflammatory Index (SII) is a biomarker which includes three relevant peripheral blood parameters- neutrophil count, lymphocyte count and platelet count. As it effectively summarises the balance between host immune status and the inflammatory response to infection, SII has been as a prognostic indicator in sepsis as well as in neoplastic conditions like small cell carcinoma and hepatocellular carcinoma.[20,26] SII has been put forward as a diagnostic parameter for COVID 19 by Usul et al.[3] Fois et al demonstrates the role of SII in early identification of high risk patients, with a cut off value of 1835. A high value of SII insinuates a possibility of respiratory complications leading to poor prognosis.[20] Some studies have suggested the use of SII along with NLR owing to the greater sensitivity of the former.[21] Xue et al proposes SII as a promising indicator of severity superior to NLR.[27] A review article on systemic inflammation markers suggests the use of SII among other markers for prognostic use.[28] Our study indicates a significant association between SII and disease severity, with a suggested cut off value of 703.33x 103. However, the cut off value of SII to anticipate complications are seen to vary widely in different studies. (Xue-809.02, Xia- 887.20, Fois-1835).[20,21,27]

Based on logistic regression analysis, age and NLR show superior prognostic possibility in progression to disease severity. The other parameters included in this analysis were RDW-CV, RDW-SD, PLR and SII, all of which were not found to be significant in prediction of severity. Hence we suggest that patients older than 52.5 years and those with NLR greater than 3.58 on admission need to be stringently monitored for deterioration of clinical condition. This finding is in accordance with a similar study by Yang et al which gives a similar cut off for age and NLR.[6] Karimi et al after a review of multiple novel systemic inflammatory markers also concludes that NLR appears to have a higher prognosticating potential when compared to PLR and SII.[28]

There are mainly three limitations to this study. This is a single centre study carried out on limited number of patients. These patients have been followed up for the duration of their hospital admission only and later complications have not been considered. We have assessed the association of baseline haematological parameters at the time of admission with severity of disease. The variation in haematological parameters throughout the course of hospital admission has not been taken into account. Multicentre studies with regular monitoring of laboratory parameters and long term follow up of patients may yield valuable

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information regarding the impact of haematological indices in the prognosis of patients with Covid infection.

CONCLUSION

Covid 19 infection has varying manifestations involving different systems. Early identification of potential complications will enable optimum channelization of health facilities. The current study stresses the importance of haematological indices like RDW, NLR, PLR and SII with relation to severity of infection. The study postulates that age and NLR are independent prognostic biomarkers for Covid 19 patients.

REFERENCES

1. Kong M, Zhang H, Cao X, Mao X, Lu Z. Higher level of neutrophil-to lymphocyte ratio is associated with severe COVID-19. Epidemiology and Infection 148, e139, 1-6. https://doi.org/10.1017/S0950268820001557
2. Waris A, Din M, Khalid A, et al. Evaluation of hematological parameters as an indicator of disease severity in Covid-19 patients: Pakistan's experience. J Clin Lab Anal. 2021;35:e23809. https://doi.org/10.1002/jcla.23809
3. Usul, E¸San I, Bekgöz ¸ Sahin, A. Role of hematological parameters in COVID-19 patients in the emergency room. Biomark. Med. 2020, 14, 1207–1215.
4. Clinical management Protocol:COVID-19. Government of India. Ministry of Health and Family Welfare. Directorate Generalof Health Services. Version 4. June 27, 2020.
5. Liao D, Zhou F, Luo L, Xu M, Wang H, Xia J et al. Haematological characteristics and risk factors in the classification and prognosis evaluation of COVID-19: a retrospective cohort study. Lancet Haematol. 2020 Sep;7(9):e671-e678.doi;10.1016/s2352-3026(20)30217-9.
6. Yang AP, Liu JP, Tao WQ, Li HM. The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. International Immunopharmacology. 84 (2020) 106504
7. Rahman M.A, Shanjana Y, Tushar M.I, Mahmud T, Rahman GMS, Milan ZH, et al. (2021) Hematological abnormalities and comorbidities are associated with COVID-19 severity among hospitalized patients: Experience from Bangladesh. PLoS ONE. 2021, 16(7): e0255379. https://doi.org/10.1371/journal.pone.0255379
8. Sun S, Cai X, Wang H, He G, Lin Y, Lu B et al. Abnormalities of peripheral blood system in patients with COVID-19 in Wenzhou, China. Clin Chim Acta. 2020 Aug; 507:174-180. doi:10.1016/j.cca.2020.04.024
9. Thomas T, Stefanoni D, Dzieciatkowska M, et al. Evidence of structural protein damage and membrane lipid remodeling in red blood cells from COVID- 19 patients. J Proteome Res. 2020;19(11):4455- 4469. https://doi.org/10.1021/acs.jproteome.0c00606
10. Patel HH, Patel HR, Higgins JM. Modulation of red blood cell population dynamics is a fundamental homeostatic response to disease. Am. J. Hematol. 90(5), 422–428 (2015).
11. Foy BH, Carlson JCT, Reinertsen E, Valls RPI, Lopez RP,Palanques-Tost E et al. Association of Red Blood Cell Distribution Width with Mortality Risk in Hospitalized Adults with SARS-CoV2 Infection. JAMA Netw Open. 2020 Sep 1;3(9):e2022058. doi:10.1001/jamanetworkopen.2020.22058.
12. Pouladzadeh M, Safdarian M, Choghakabodi PM, Amini F, Sokooti A. Validation of red cell distribution width as a COVID-19 severity screening tool. Future Sci OA. 2021 Apr 20;7(7): FSO712. Doi:10.2144/fsoa-2020-01999.
13. Sarkar S, Kannan S, Khanna P, Singh AK. Role of red blood cell distribution width, as a prognostic indicator in COVID-19: A systematic review and metaanalysis. Rev Med Virol. 2021;e2264. https://doi.org/ 10.1002/rmv.2264
14. Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis. 2020;71(15):762-768. https://doi.org/10.1093/cid/ciaa248
15. Frater JL, Zini G, d'Onofrio G, Rogers HJ. COVID-19 and the clinical hematology laboratory. Int JLab Hematol. 2020;42(Suppl. 1):11–18. https://doi.org/10.1111/ijlh.13229
16. Tomar, B.; Anders, H.-J.; Desai, J.; Mulay, S.R. Neutrophils and Neutrophil Extracellular Traps Drive Necroinflammation in COVID-19. Cells 2020, 9, 1383.
17. Gu J, Korteweg C. Pathology and pathogenesis of severe acute respiratory syndrome. The American Journal of Pathology.2007 April; 170(4): 1136–1147.
18. Liu J, Liu Y, Xiang P, et al. Neutrophil-to-Lymphocyte ratio predicts critical illness patients with 2019 coronavirus disease in the early stage. J Transl Med. 2020;18:1-2.
19. Kazancioglu S, Bastug A, Ozbay BO, Kemirtlek N, Bodur H (2020). The role of haematological parameters in patients with COVID-19 and influenza virus infection. Epidemiology and Infection 148, e272, 1–8. https://doi.org/10.1017/S095026882000271X
20. 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 Dec 4;25(23):5725. doi:10.3390/molecules25235725
21. Xia W, Tan Y, Hu S, Li C, Jiang T. Predictive Value of Systemic Immune-Inflammation index and Neutrophil-to-Lymphocyte Ratio in Patients with Severe COVID-19. Clinical and Applied Thrombosis/Hemostasis. 2022;28. doi:10.1177/10760296221111391
22. Citu C., Gorun F., Motoc A., Sas I., Gorun O.M., Burlea B., Tuta-Sas I., Tomescu L., Neamtu R., Malita D., et al. The Predictive Role of NLR, d-NLR, MLR and SIRI in COVID-19 Mortality. Diagnostics 2022, 12, 122. https://doi.org/10.3390/diagnostics12010122
23. Qu R, Ling Y, Zhang YH,Wei LY, Chen X, Li XM, et al. Platelet-to-lymphocyte ratio is associated with prognosis in patients with coronavirus disease-19. J Med Virol. 2020 Sep;92(9):1533-1541. https://doi.org/10.1002/jmv.25767
24. Seyit M., Avci E., Nar R., Senol H., Yilmaz A., Ozen M., Oskay A., Aybek H. Neutrophil to Lymphocyte Ratio, Lymphocyte to Monocyte Ratio and Platelet to Lymphocyte Ratio to Predict the Severity of COVID-19. Am. J. Emerg. Med. 2021, 40, 110–114
25. Li Q, Ding X, Xia G, Chen H-G, Chen F, Xu L et al. Eosinopenia and elevated C-reactive protein facilitate triage of COVID-19 patients in fever clinic: a retrospective case-control study. EClinicalMedicine 2020, 23, 100375. https://doi.org/10.1016/j.eclinm.2020.100375
26. Hu B, Yang XR, Xu Y, Sun YF, Sun C, Guo W, et al. Systemic Immune-Inflammation Index Predicts Prognosis of Patients After Curative Resection for Hepatocellular Carcinoma. Clin Cancer Res an Off J Am Assoc Cancer Res (2014) 20(23):6212–22. doi: 10.1158/1078-0432.CCR-14-0442
27. Xue G, Gan X, Wu Z, Xie D, Xiong Y, Hua L, et al. Novel Serological Biomarkers for Inflammation in Predicting Disease Severity in Patients With COVID-19. International Immunopharmacology. Int Immunopharmacol (2020) 89(Pt A):107065. doi: 10.1016/j.intimp.2020.107065
28. Karimi A, Shobeiri P, Kulasinghe A, Rezaei N (2021) Novel Systemic Inflammation Markers to Predict COVID-19 Prognosis. Front. Immunol. 12:741061. doi: 10.3389/fimmu.2021.741061

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