Multi-inflammatory Index as a Novel Mortality Predictor in Critically Ill COVID-19 Patients

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Abstract

Aim: Systemic inflammation has a crucial role in the pathogenesis and mortality of Coronavirus disease 2019 (COVID-19). Multi-inflammatory index (MII) is a novel index related with systemic inflammation. In this study, we investigated the relationship between MII and in-hospital mortality in COVID-19 patients admitted to the intensive care unit (ICU).
Methods: We retrospectively analyzed the medical records of COVID-19 patients followed-up in the ICU of our institution between 01.04.2020 and 01.10.2021. Patients were classified into two groups according to mortality status as survivors and non-survivors. Various inflammatory parameters of the groups were compared and their efficacy in predicting mortality was investigated.
Results: Out of 348 study patients, 86 cases (24.7%) were in the survived group and 262 cases (75.3%) were in the dead group. The median age of the mortal group was significantly higher than that of the survived group (65.5 vs 76, $P < .001$). Multiple logistic regression analysis revealed that among all the included inflammatory parameters, MII showed the best efficacy for predicting mortality (OR: 0.999; 95% CI: 0.9991-0.9998; $P = .003$).
Conclusion: MII, a new combination of Neutrophil to lymphocyte ratio (NLR) and C-reactive protein (CRP), is a simple and practical biomarker that can help us in the prediction of mortality in COVID-19 patients followed-up in the ICU.

Keywords

coronavirus disease 2019, mortality, intensive care unit, multi-inflammatory index

Introduction

Coronavirus disease 2019 (COVID-19) which is still a global threat is a highly contagious viral disease primarily affecting the respiratory system. The causative agent is a novel coronavirus named as SARS-CoV-2. The disease has spread all over the world within a very short time period which has seriously affected health, social life, education, and economy. The most important cause of short term morbidity and mortality is viral pneumonia which can immediately progress to acute respiratory distress syndrome.[1]

Neutrophils are the most important cells which firsly appear in infections. They protect against viral invasion, prevent viral replication and spreading. At the same time, neutrophils have negative effects on the host during viral infection.[2]

Immune response against viral infection is mainly established by lymphocytes. In COVID-19 patients, decrease in lymphocyte count may be related to lymphocyte consumption, destruction of lymphatic tissues, and cytokine-induced T-cell apoptosis. Severe lymphopenia is a sign of worse outcome in COVID-19.[3]

C-reactive protein (CRP) is one of the positive acute phase proteins. It is produced in the liver against infection and inflammation. Previous studies showed that CRP levels seriously increase in critical situations such as cancers and critical infections as well as COVID-19.[4,5]

In symptomatic patients with COVID-19, SARS-CoV-2 triggers the inflammation cascade which leads to increase in the levels of inflammatory biomarkers such as CRP and ferritin, which is usually balanced by the the host's immune system whereas in some individuals SARS-CoV-2 causes excessive release of proinflammatory cytokines resulting in hyperinflammation which can not be controlled by the host's immune

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system.[6] Levels of the coagulation parameters such as fibrinogen and D-dimer also increase as the disease progresses while lymphocyte counts and albumin levels gradually decrease. Systemic inflammatory burden and subsequent disseminated thrombosis as a result of severe sepsis eventually cause cytokine storm which is implicated to be responsible for the clinical deterioriation of COVID-19 patients.[7,8]

Severe COVID-19 cases developing hyperinflammation and cytokine storm have greater levels of systemic inflammatory markers. Neutrophil to lymphocyte ratio (NLR), mean platelet volume to platelet ratio (MPR), mean platelet volume to lymphocyte ratio (MLR) and platelet to lymphocyte ratio (PLR) are novel systemic inflammatory markers. These hemogram based inflammatory parameters are strong predictors of mortality in critically ill patients as well as COVID-19.[9-14]

Multi-inflammatory index (MII) is a novel inflammation related index created firstly by Gardini et al.[15] It is calculated by the multiplication of NLR and CRP which were previously studied individually in COVID-19 patients. Both of them were found useful in predicting mortality.[5]

COVID-19 patients admitted to intensive care unit (ICU) carry high risk for mortality, so it is important to predict mortality earlier in this critical population. MII is a combination of both NLR and CRP,[15] hence we investigated the role of MII in predicting mortality in COVID-19 patients in the ICU.

Materials and Methods

We retrospectively analyzed the data of COVID-19 patients followed-up in the adult ICU of our institution between 01.04.2020 and 01.10.2021. COVID-19 was diagnosed with positive nasopharyngeal swab PCR result. Criteria for ICU admission were sepsis, septic shock, respiratory failure (requiring mechanical ventilation), acute respiratory distress syndrome, or multiple organ failure. Some patients were excluded from the study due to pregnancy, cirrhosis, nephrotic syndrome, hematological disease, terminal malignancy and absent laboratory results.

Table 1. Comparison of the Median age and Demographic Data of the Study Groups.

Variable	Survived (n = 86)	Mortal (n = 262)	P value
Age (years)	65.50 (55.25-79.25)	76 (68.75-83)	<.001
Gender, n (%)			
Male	49 (57)	156 (59.5)	.769
Female	37 (43.02)	106 (40.5)	
DM, n (%)	22 (25.6)	96 (36.6)	.080
HT, n (%)	48 (55.9)	167 (63.7)	.236
COPD, n (%)	11(12.8)	58 (22.1)	.083
CVD, n (%)	20 (23.3)	99 (37.8)	.019
CRF, n (%)	7 (8.1)	44 (16.8)	.072
Malignancy, n (%)	2 (2.3)	22 (8.4)	.092

Abbreviations: DM, diabetes mellitus; HT, hypertension; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; CRF, chronic renal failure.

Venous blood samples were collected from all patients at the entry to ICU. Complete blood count parameters were measured in the tubes containing ethylenediamine tetraacetic acid (EDTA) as an anticoagulant by Sysmex XN-1000 hematology analyzer. Biochemical tests other than ferritin and troponin were measured in the tubes containing clot activator by *Abbott Architect c8000* analyzer after centrifugation. Ferritin and troponin were tested in the tubes containing clot activator by Abbott Architect i2000SR analyzer after centrifugation. Coagulation parameters were tested in the tubes containing sodium citrate as an anticoagulant by *Sysmex CS-2500 system*.

Different treatment protocols were administered during the course of the pandemic. *From the beginning until the end of the study, hydroxychlorine, hydroxychlorine plus favipiravir, favipiravir, and favipiravir plus high dose corticosteroids were used against COVID-19, respectively.*

The patients were divided into two groups according to mortality status as survivors and non-survivors. Demographic and clinical data, routine laboratory results and various inflammatory parameters of the groups were compared.

The formulas of the inflammatory parameters are as follows:

Hemogram Derived Inflammatory Parameters

Neutrophil to lymphocyte ratio (NLR) = Neutrophil count/lymphocyte count

Platelet to lymphocyte ratio (PLR) = Platelet count/lymphocyte count

Mean platelet volume to platelet ratio (MPR) = Mean platelet volume/platelet count

Mean platelet volume to lymphocyte ratio (MLR) = Mean platelet volume/lymphocyte count

Albumin Based Inflammatory Parameters

Urea to albumin ratio (UAR) = Urea/albumin

Lactate dehydrogenase-to albumin ratio (LAR) = Lactate dehydrogenase/albumin

C-reactive protein to albumin ratio (CAR) = CRP/albumin

D-dimer to albumin ratio (DAR) = D-dimer/albumin

Procalcitonin to albumin ratio (PAR) = Procalcitonin/albumin

Fibrinogen to albumin ratio (FAR) = Fibrinogen/albumin

Prognostic Inflammatory Indexes

Multi-inflammatory index (MII) = NLR × CRP[15]

Prognostic nutritional index (PNI) = 10 × serum albumin (g/dL) + 0.005 × lymphocyte count (/mm^3)[16]

Systemic inflammatory index (SII) = neutrophil count × PLR[17]

Platelet mass index (PMI) = MPV × platelet count

The local ethics committee of Bolu Abant Izzet Baysal University Medical Faculty approved the study (Decision number: 2021/259).

Table 2. Comparison of the Means of Hemoglobin and Albumin and Median of the Other Laboratory Data of the Study Groups.

Variable	Survived group (n = 86)	Mortal group (n = 262)	P value
WBC (K/uL)	11.090 (7.578-16.87)	12.02 (7.645-17.725)	.606
Neutrophil (K/uL)	9.490 (6.148-15.005)	10.625(6.528-15.790)	.363
Lymphocyte (K/uL)	0.8 (0.5275-1.2550)	0.65 (0.3775-1.11)	.009
Monocyte (K/uL)	0.58 (0.2600-0.8625)	0.44 (0.23-0.76)	.139
Hemoglobin (g/dL)	12.608 ± 2.47	11.96 ± 2.373	.030
RDW (%)	14.3 (13.2-15.5)	14.7 (13.7-16.725)	.017
Platelet (K/uL)	251 (188-325)	208 (130.5-304.25)	.001
MPV (fL)	10.6 (9.8-11.4)	11.2(10.225-12.175)	<.001
PDW	12.8 (11.3-14.8)	13.35 (11.7-16.5)	.041
LDH (U/L)	435(335.8-584)	543(373.5-728.3)	.002
CRP (mg/L)	79.5 (31.63-160.1)	113 (64.75-169.25)	.010
ESR	43.5 (31-71)	47 (29-80.25)	.425
Procalcitonin (ng/mL)	0.21 (0.08-0.56)	0.485 (0.185-1.685)	.001
Albumin (g/dL)	3.2562 ± 0.5112	2.97 ± 0.4923	<.001
INR	1.16 (1.075-1.3050)	1.27 (1.14-1.435)	<.001
Fibrinogen (mg/dL)	542 (383.7-703.2)	556 (422.9-693.2)	.558
D-dimer (mg/L)	2.2 (1.1-4.93)	2.76 (1.53-5.575)	.047
Ferritin (µg/L)	468 (181.5-986.9)	703 (348.3-1601.6)	<.001
Troponin (ng/L)	25 (5.7-146)	49 (17.7-231)	.002
Glucose (mg/dL)	133 (104.8-194)	151 (115.75-213)	.175
Urea (mg/dL)	47.5 (34-92)	73 (49-122)	<.001
Creatinine (mg/dL)	0.88 (0.69-1.495)	1.165(0.85-2.103)	<.001
ALT (U/L)	31.5 (18-48)	30 (18-56)	.529
AST (U/L)	38 (22-55.25)	42.5 (25.8-69)	.040
UAR	15.1 (10.1-26.63)	24.77 (15.86-44.66)	<.001
LAR	143.78 (101.38-187.88)	186.83 (126.6-235.11)	<.001
DAR	0.725 (0.362-1.58)	0.883 (0.502-1.988)	.012
FAR	173.21 (107.79-218.58)	185.61 (141.2-237.48)	.037
CAR	26.92 (10.11-48.46)	40.41 (21.7-58.24)	.001
PAR	0.0787(0.0242-0.224)	0.169 (0.0579-0.604)	<.001
PNI	37.325 (33.875-41.303)	33.55 (29.588-37.675)	<.0001
SII	2796 (1517-5121)	3086 (1426-6827)	.445
MII	745 (244-2108)	1689 (724-3714)	<.0001
PMI	2619 (2120-3458)	2418 (1609.4-3192.5)	.008
NLR	10.59 (6.3-20.9)	14.86 (8.43-29.36)	.006
PLR	304.6 (184.1-500.4)	311.1 (182.3-523.9)	.782
MPR	0.04041(0.3169-0.05484)	0.0507(0.03529-0.08502)	<.001
MLR	13.714(8.871-19.863)	16.57 (9.93-29.91)	.007

Abbreviations: WBC, white blood cell; RDW, red cell distribution width; MPV, mean platelet volume; PDW, platelet distribution width; LDH, lactate dehydrogenase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; INR, international normalized ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; UAR, urea to albumin ratio; LAR, Lactate dehydrogenase to albumin ratio; DAR, D-dimer to albumin ratio; FAR, fibrinogen to albumin ratio; CAR, C-reactive protein to albumin ratio; PAR, procalcitonin to albumin ratio; PNI, prognostic nutritional index; SII, systemic inflammatory index; MII, Multi-inflammatory index; PMI, Platelet mass index; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; MPR, mean platelet volume to platelet ratio; MLR, mean platelet volume to lymphocyte ratio.

Statistical Analysis

Statistical analyzes were conducted using R statistical software version 4.1.2.[18] Variables showing normal distribution were expressed as mean ± SD and compared with independent samples t-test. Variables not showing normal distribution were expressed as median (IQR) and compared with Mann–Whitney U test. Categorical variables were expressed as numbers and percentages while compared with χ2 test. Multiple logistic regression analysis was used to determine the independent predictors of mortality. The odds ratio (OR) and 95% confidence interval (CI) were calculated for each independent variable. A P value < .05 was accepted as statistically significant.

Results

Although 380 patients were admitted to our ICU during the study period, 32 patients were discarded from the study according to exclusion criteria. Hence, 348 patients were enrolled in this study. Of these patients, 205 were male (59%) and 143 were female (41%). The median age of the patients was 74 (65-83). There were 86 cases (24.7%) in the survived group

Table 3. Factors Related with Mortality in ICU COVID-19 Patients.

Variable	Odds ratio	95% CI	P value
Age (years)	1.0729	1.0414-1.1097	<.001*
MPV (fL)	1.2675	0.8837-1.8519	.205
RDW (%)	1.0728	0.8493-1.3924	.576
LDH (U/L)	0.9969	0.9875-1.0054	.504
CRP (mg/L)	1.0185	0.9954-1.0430	.123
Procalcitonin (ng/mL)	1.4065	0.5605-4.2722	.508
Ferritin (µg/L)	1.0003	0.9996-1.0011	.421
Troponin (ng/L)	1.0000	0.9999-1.0000	.275
UAR	1.0007	0.9764-1.0275	.959
LAR	1.0177	0.9930-1.0478	.204
DAR	1.0044	0.8967-1.1678	.944
FAR	0.9987	0.9912-1.0061	.726
CAR	0.9806	0.9145-1.0543	.587
PAR	0.3891	0.0195-5.4453	.502
PNI	1.0109	0.9461-1.1124	.761
MII	0.9995	0.9991-0.9998	.003*
PMI	1.0000	0.9995-1.0005	.964
NLR	1.0771	1.0166-1.1506	.018*
PLR	0.9985	0.9953-1.0018	.356
MLR	1.0606	0.9832-1.1596	.166

Abbreviations: MPV, mean platelet volume; RDW, red cell distribution width; LDH, lactate dehydrogenase; CRP, C-reactive protein; UAR, urea to albumin ratio; LAR, Lactate dehydrogenase to albumin ratio; DAR, D-dimer to albumin ratio; FAR, fibrinogen to albumin ratio; CAR, C-reactive protein to albumin ratio; PAR, procalcitonin to albumin ratio; PNI, prognostic nutritional index; MII, Multi-inflammatory index; PMI, Platelet mass index; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; MLR, mean platelet volume to lymphocyte ratio.

and 262 cases (75.3%) in the dead group. The median age of the mortal group was significantly higher than that of the survived group (65.5 vs 76, $P < .001$). There was not a statistically significant difference between the groups with respect to gender ($P = .769$). Diabetes mellitus (DM), hypertension (HT), chronic obstructive pulmonary disease (COPD), chronic renal failure (CRF) and malignancy were found to be more frequent in the dead group, however the differences were not statistically significant ($P = .080$, $P = .236$, $P = .083$, $P = .072$, $P = .092$, respectively). On the other hand, cardiovascular disease (CVD) was more frequent in the dead group and the difference was statistically significant ($P = .019$). Demographic data were presented in Table 1.

When hemogram based inflammatory parameters were evaluated it was seen that NLR, MPR and MLR were significantly higher in the mortal group compared with the survived group. All of the albumin based inflammatory parameters (UAR, LAR, CAR, DAR, FAR and PAR) were significantly higher in the mortal group compared with the survived group. When prognostic inflammatory indexes were examined, it was seen that PNI, PMI and and MII were significantly higher in the mortal group compared with the survived group. Laboratory data of the study groups were summarized in Table 2.

Multiple logistic regression analysis revealed that age (OR: 1.072; 95% CI: 1.0414-1.1097; $P < .001$), NLR (OR: 1.077; 95% CI: 1.0166-1.1506; $P = .018$), and MII (OR: 0.999; 95%

CI: 0.9991-0.9998; $P = .003$) were independent predictors of mortality. Among all inflammatory parameters, MII showed the best performance in predicting mortality (Table 3).

Discussion

First time with this study, we found MII as an independent predictor of mortality in ICU COVID-19 cases. In addition to this new finding, we also found in our study that advanced age and increased NLR level were the other independent mortality predictors as in agreement with the previous literature.[5]

As the neutrophil count usually increases and lymphocyte count decreases in COVID-19, elevated NLR predicts disease severity and mortality.[5] Apart from NLR, many other inflammatory parameters showing systemic inflammation were found to be useful in predicting mortality in COVID-19 patients.[19–29] The common mechanism of the effect of these parameters to the disease mortality is that systemic inflammation has a crucial role in the pathogenesis and mortality of COVID-19.[6,8]

Hemogram based inflammatory parameters were previously investigated in COVID-19 patients. For example, in a previous study elevated NLR and MPR were found to be associated with mortality.[19] Consistently, our study supported that these hemogram based parameters were significantly higher in mortal cases compared with survived ones.

Albumin based inflammatory parameters (UAR, LAR, CAR, DAR, FAR and PAR) were also studied in critical illnesses as well as COVID-19 and they were all found to be useful in the prediction of prognosis.[20–26] Consistent with these studies, we also found that albumin based inflammatory parameters were significantly higher in mortal cases compared with survived ones.

CRP is a positive acute phase protein which was also associated with the prognosis in COVID-19. Elevated CRP levels were related with poor prognosis and mortality.[5] Our study also showed that CRP levels were significantly increased in mortal COVID-19 cases compared with survived ones.

Various prognostic indexes such as SII, PNI and PMI give an idea about the prognosis of critical diseases as well as COVID-19.[27–29] In our study, PNI and PMI were found to be useful in the discrimination of mortal COVID-19 cases from survived ones.

MII is a novel prognostic index that was firstly created by Gardini et al.[15] They found it useful in determining the prognosis in colorectal cancer patients. A recent study suggested that this new index plays an important role in distinguishing massive and non-massive pulmonary embolism.[30] In our study, we searched the relationship between MII and ICU mortality in COVID-19 patients and we found that MII was higher in the mortal group which can serve as an independent predictor of in-hospital mortality.

Our study has some limitations. First, this is a retrospective study with single center data and relatively small number of

patients. Second, there was some missing data for a few patients, Third, all patients did not receive the same treatment, different treatment strategies were administered because of changing treatment protocols during the pandemic. Lastly, serial measurement of laboratory parameters were not evaluated. However, to the best of our knowledge, our study is the first to demonstrate the relationship between MII and mortality status in critically ill COVID-19 patients.

In conclusion, MII is a simple and practical biomarker that can help us in the early determination of poor prognosis in COVID-19. It is easily obtained from NLR and CRP. Furthermore, it was found superior to NLR or CRP alone in the discrimination of mortal COVID-19 cases. We believe that physicians should be more careful in the management of COVID-19 cases with rising MII levels. More comprehesive and large scale studies are required to validate our results.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

The local ethics committee of Bolu Abant Izzet Baysal University Medical Faculty approved the study (Decision number: 2021/259).

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References

1. Du RH, Liang LR, Yang CQ, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study [published correction appears in *Eur Respir J*. 2020 Sep 24;56(3):]. *Eur Respir J*. 2020;55(5):2000524. Published 2020 May 7. doi:10.1183/13993003.00524-2020.

2. Naumenko V, Turk M, Jenne CN, Kim SJ. Neutrophils in viral infection. *Cell Tissue Res*. 2018;371(3):505-516. doi:10.1007/s00441-017-2763-0.

3. Tan L, Wang Q, Zhang D, et al. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study [published correction appears in Signal Transduct Target Ther. 2020 Apr 29;5(1):61]. *Signal Transduct Target Ther*. 2020;5(1):33. Published 2020 Mar 27. doi:10.1038/s41392-020-0148-4.

4. Ryoo SM, Han KS, Ahn S, et al. The usefulness of C-reactive protein and procalcitonin to predict prognosis in septic shock patients: a multicenter prospective registry-based observational study. *Sci Rep*. 2019;9(1):6579. Published 2019 Apr 29. doi:10.1038/s41598-019-42972-7.

5. Ergenç H, Ergenç Z, Dog An M, Usanmaz M, Gozdas HT. C-reactive protein and neutrophil-lymphocyte ratio as predictors of mortality in coronavirus disease 2019. *Rev Assoc Med*
Bras (1992). 2021;67(10):1498-1502. doi:10.1590/1806-9282.20210679.

6. Boechat JL, Chora I, Morais A, Delgado L. The immune response to SARS-CoV-2 and COVID-19 immunopathology – current perspectives. *Pulmonology*. 2021;27(5):423-437. doi:10.1016/j.pulmoe.2021.03.008.

7. Khinda J, Janjua NZ, Cheng S, van den Heuvel ER, Bhatti P, Darvishian M. Association between markers of immune response at hospital admission and COVID-19 disease severity and mortality: a meta-analysis and meta-regression. *J Med Virol*. 2021;93-(2):1078-1098. doi:10.1002/jmv.26411.

8. Zanza C, Romenskaya T, Manetti AC, et al. Cytokine storm in COVID-19: immunopathogenesis and therapy. *Medicina (Kaunas)*. 2022;58(2):144. Published 2022 Jan 18. doi:10.3390/medicina58020144.

9. Yoldas H, Karagoz I, Ogun MN, et al. Novel mortality markers for critically ill patients. *J Intensive Care Med*. 2020;35(4):383-385. doi:10.1177/0885066617753389.

10. 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(6):e23809. doi:10.1002/jcla.23809.

11. Erdogan A, Can FE, Gönüllü H. Evaluation of the prognostic role of NLR, LMR, PLR, and LCR ratio in COVID-19 patients. *J Med Virol*. 2021;93(9):5555-5559. doi:10.1002/jmv.27097.

12. Seyit M, Avci E, Nar R, et al. 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;45:569. doi:10.1016/j.ajem.2020.12.069.

13. Asan A, Üstündağ Y, Koca N, et al. Do initial hematologic indices predict the severity of COVID-19 patients? *Turk J Med Sci*. 2021;51(1):39-44. Published 2021 Feb 26. doi:10.3906/sag-2007-97.

14. Carpio-Orantes LD, García-Méndez S, Hernández-Hernández SN. Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio and systemic immune-inflammation index in patients with COVID-19-associated pneumonia. Índices neutrófilo/linfocito, plaqueta/linfocito e inmunidad/inflamación sistémica en pacientes con neumonía por COVID-19. *Gac Med Mex*. 2020;156(6):527-531. doi:10.24875/GMM.M21000480.

15. Casadei Gardini A, Scarpi E, Valgiusti M, et al. Prognostic role of a new index (multi inflammatory index) in patients with metastatic colorectal cancer: results from the randomized ITACa trial. *Ther Adv Med Oncol*. 2020;12:1758835920958363. Published 2020 Sep 28. doi:10.1177/1758835920958363.

16. Onodera T, Goseki N, Kosaki G. Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients. *Nihon Geka Gakkai Zasshi*. 1984;85(9):1001-1005. Article in Japanese.

17. Feng JF, Chen S, Yang X. Systemic immune-inflammation index (SII) is a useful prognostic indicator for patients with squamous cell carcinoma of the esophagus. *Medicine (Baltimore)*. 2017;96(4):e5886. doi:10.1097/MD.0000000000005886.

18. R Core Team. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing; 2021. https://www.R-project.org/.

19. Mobarki AA, Dobie G, Saboor M, et al. MPR And NLR as prognostic markers in ICU-admitted patients with COVID-19 in Jazan, Saudi Arabia. *Infect Drug Resist*. 2021;14:4859-4864. Published 2021 Nov 23. doi:10.2147/IDR.S342259.

20. Ata F, As AK, Engin M, Kat NK, Ata Y, Turk T. Can blood urea nitrogen-to-albumin ratio predict mortality in patients with moderate-to-severe COVID-19 pneumonia hospitalized in the

intensive care unit? *Rev Assoc Med Bras (1992)*. 2021;67-(10):1421-1426. doi:10.1590/1806-9282.20210610.

21. Lee BK, Ryu S, Oh SK, et al. Lactate dehydrogenase to albumin ratio as a prognostic factor in lower respiratory tract infection patients. *Am J Emerg Med*. 2022;52:54-58. doi:10.1016/j.ajem.2021.11.028.

22. Li Y, Li H, Song C, et al. Early prediction of disease progression in patients with severe COVID-19 using C-reactive protein to albumin ratio. *Dis Markers*. 2021;2021:6304189. Published 2021 Dec 3. doi:10.1155/2021/6304189.

23. Küçükceran K, Ayranci MK, Girişgin AS, Koçak S. Predictive value of D-dimer/albumin ratio and fibrinogen/albumin ratio for in-hospital mortality in patients with COVID-19. *Int J Clin Pract*. 2021;75(7):e14263. doi:10.1111/ijcp.14263.

24. Afşin A, Tibilli H, Hoşoğlu Y, et al. Fibrinogen-to-albumin ratio predicts mortality in COVID-19 patients admitted to the intensive care unit [published online ahead of print, 2021 Dec 9]. *Adv Respir Med*. 2021. doi:10.5603/ARM.a2021.0098

25. Chen H, Liu Q, Wang L. An analysis of the 28-day mortality risk factors in acute respiratory distress syndrome patients and the establishment of prediction models. *Am J Transl Res*. 2021;13(6):6937-6944.

26. Chen L, Wu X, Qin H, et al. The PCT to albumin ratio predicts mortality in patients with acute kidney injury caused by abdominal infection-evoked sepsis. *Front Nutr*. 2021;8:584461. doi: 10.3389/fnut.2021.584461.

27. Nalbant A, Demirci T, Kaya T, Aydın A, Altındiş M, Güçlü E. Can prognostic nutritional index and systemic immune-inflammatory index predict disease severity in COVID-19? *Int J Clin Pract*. 2021;75(10):e14544. doi:10.1111/ijcp.14544.

28. Fois AG, Paliogiannis P, Scano V, et al. The systemic inflammation index on admission predicts in-hospital mortality in COVID-19 patients. *Molecules*. 2020;25(23):5725. Published 2020 Dec 4. doi:10.3390/molecules25235725.

29. Yurekli UF, Liste U, Ertunc B, Tercan M, Tahtabasi M. Could platelet mass index (PMI) be a new prognostic biomarker for COVID-19? *Ann Clin Anal Med*. 2022;13(1):72-75. doi:10.4328/ACAM.20850.

30. Boyuk F. The role of the multi-inflammatory index as a novel inflammation-related index in the differential diagnosis of massive and non-massive pulmonary embolism. *Int J Clin Pract*. 2021;75(12):e14966. doi:10.1111/ijcp.14966.