Inflammation-based Indices Predicting Mortality in COVID-19

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ABSTRACT

Efficiency of various inflammation-based indices, including neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), lymphocyte/monocyte ratio (LMR), C-reactive protein/lymphocyte ratio (CLR), albumin/globulin ratio (AGR), haemoglobin, albumin, lymphocyte, and platelet (HALP), systemic immune-inflammatory index (SII) and prognostic nutritional index (PNI), was examined in predicting mortality in COVID-19 patients. The study population consisted of 827 COVID-19 patients, including 733 survivors and 94 non-survivors. Compared with the survivor group, the NLR, PLR, CLR, and SII values of the non-survivor group were markedly higher; however, the LMR, PNI, HALP and AGR values were markedly lower. Multivariate analysis identified PNI, NLR, CLR, older age, male gender and dyslipidemia as independent factors for mortality in COVID-19 patients. PNI had the largest area under the curve to predict mortality, followed by CLR, NLR, and other indexes. This data revealed that PNI, NLR, and CLR are independent factors of mortality in COVID-19 patients among inflammation-based indexes.

Key Words: *COVID-19 mortality, Prognostic nutritional index, C-reactive protein/lymphocyte ratio, Neutrophil/lymphocyte ratio.*

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The COVID-19 infection, which first started in Wuhan, China at the end of 2019, soon spread to other countries, causing a pandemic. The course of COVID-19 disease ranges from asymptomatic or mild infection to critical illness that can lead to death.[1]

Accumulating evidence has revealed that severe systemic inflammation and poor nutritional status lead to a worse prognosis in patients infected with COVID-19. And various inflammation and nutrition-based markers, namely, neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), lymphocyte/-monocyte ratio (LMR), C-reactive protein/lymphocyte ratio (CLR), albumin/globulin ratio (AGR), systemic immune-inflammatory index (SII), and prognostic nutritional index (PNI) have been confirmed to be correlated with disease progression and death in COVID-19 patients.[2-4] The HALP score, which includes haemoglobin, albumin, lymphocyte, and platelet parameters, is a new index that reflects both nutritional and inflammatory status.[5]

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However, the HALP index has not been evaluated in COVID-19 patients so far. Moreover, it is unclear which inflammation-based index more strongly predicts mortality in COVID-19 patients. The aim of this study was to compare the predictive power of different inflammation-based indexes (NLR, PLR, LMR, CLR, AGR, PNI, SII and HALP score) to predict mortality in COVID-19 patients.

This retrospective study included 827 patients who applied to Şanlıurfa Training and Research Hospital due to COVID-19, between May 2020 and December 2020. All participants had positive COVID-19 PCR test results. The patients included in the study were outpatients and inpatients, and none of them was vaccinated. Exclusion criteria in the study were age under 18 years, pregnancy, chronic liver disease, chronic kidney failure, haematological disorder, neoplastic disease, and missing laboratory data. Eligible patients were classified into two groups as survivors (n=733) and non-survivors (n=94). The Harran University Ethics Committee approved this study (reference no. HRU.22/07/16).

Demographic information, coexisting conditions and laboratory findings at admission to the hospital were retrieved from hospital records. Albumin, total protein and CRP concentrations were run on the Cobas 8000 instrument (Roche, Germany), while neutrophil, lymphocyte, monocyte, haemoglobin, and platelet counts were determined by Sysmex XN-1000 instrument (Sysmex, Japan). Afterwards, eight inflammation-based biomarkers (NLR, PLR, LMR, CLR, AGR, PNI, SII, and HALP score) were derived from the combination of laboratory parameters.[2-5]

Table I: Demographic characteristics and laboratory findings of COVID-19 patients on admission.

	Survival Group (n=733)	Non-survival Group (n=94)	p-value
Age, years	47 (33-62)	72 (62-78)	<0.001[a]
Gender			
Male, n (%)	346 (47.2)	62 (66)	0.001[b]
Female, n (%)	387 (52.8)	32 (34)	
Co-existing conditions			
Diabetes, n (%)	124 (16.9)	27 (28.7)	0.005[b]
Hypertension, n (%)	191 (26.1)	52 (55.3)	<0.001[b]
Cardiovascular disease, n (%)	81 (11.1)	28 (29.8)	<0.001[b]
Dyslipidemia, n (%)	85 (11.6)	30 (31.9)	<0.001[b]
Chronic pulmonary disease, n (%)	98 (13.4)	17 (18.1)	0.214[b]
Cerebrovascular disease, n (%)	17 (2.3)	7 (7.4)	0.013[c]
Rheumatological diseases, n (%)	12(1.6)	1 (1.1)	1.000[c]
Laboratory Findings			
Neutrophil count, $x10^3/\mu L$	3.71 (2.71-5.40)	8.33 (4.92-13.05)	<0.001[a]
Lymphocyte count, $x10^3/\mu L$	1.55 (1.16-2.09)	1.01 (0.65-1.50)	<0.001[a]
Monocyte count, $x10^3/\mu L$	0.52 (0.38-0.72)	0.46 (0.27-0.76)	0.051[a]
Haemoglobin count, g/dl	13.65 ± 1.65	13.36 ± 1.98	0.175[d]
Platelet count, $x10^3/\mu L$	230 (193-275)	211 (167-299)	0.172[a]
Albumin, g/dL	4.38 (4.04-4.65)	3.54 (3.18-3.84)	<0.001[a]
Globulin, g/dL	3.24 (2.94-3.56)	3.24 (2.93-3.54)	0.956[a]
CRP, mg/L	9.4 (2.5-33.7)	100.5 (50.6-185.7)	<0.001[a]
Inflammation-based indexes			
NLR	2.30 (1.48-3.91)	6.95 (4.56-14.53)	<0.001[a]
PLR	145 (108-190)	221 (136-338)	<0.001[a]
CLR	6.2 (1.3-25.3)	96.5 (42.2-219.4)	<0.001[a]
LMR	3.15 (2.12-4.28)	2.25 (1.55-3.74)	<0.001[a]
PNI	43.8 (40.4-46.5)	35.4 (31.8-38.4)	<0.001[a]
SII	522 (327-952)	1646 (835-3527)	<0.001[a]
HALP	40.09 (28.04-57.36)	21.06 (12.09-36.1)	<0.001[a]
AGR	1.35 ± 0.25	1.09 ± 0.21	<0.001[d]

The data were presented as median (25-75 percentile), mean±SD or numbers (%), as appropriate. [a]Mann-Whitney U-test; [b]χ^2 test; [c]Fisher's exact test; [d]Independent t-test. CRP: C-reactive protein; NLR: neutrophil/lymphocyte ratio; PLR: Platelet/lymphocyte ratio; LMR: lymphocyte/monocyte ratio; CLR: C-reactive protein/lymphocyte ratio; PNI: prognostic nutritional index; SII: systemic immune inflammatory index; HALP (Haemoglobin, albumin, lymphocytes, and platelets); AGR: albumin/globulin ratio.

Statistical calculations were carried out with SPSS (version 21.0) software. Statistical significance was considered as $p< 0.05$. The normality of the variables was checked with the Kolmogorov-Smirnov test. Categorical variables were assessed using either the χ^2 test or Fisher's exact test. Continuous variables with or without normal distribution were compared using the independent t-test and Mann-Whitney U-test, respectively. Independent factors for mortality in patients infected with COVID-19 were determined by univariate analysis and multivariate regression analysis with the enter method. The performance of inflammation-based indexes in predicting mortality in patients suffering from COVID-19 was evaluated by ROC analysis.

Demographic characteristics and laboratory findings of cases with COVID-19 are presented in Table I. Considering the inflammation-based indexes, the values of NLR, PLR, CLR and SII were markedly higher in the non-survivor group than in the survivor group. However, LMR, PNI, HALP and AGR values were markedly lower in the non-survivor group.

Univariate analysis revealed that age, gender, presence of diabetes, hypertension, cardiovascular disease, dyslipidemia, chronic pulmonary disease, cerebrovascular disease, and 8 inflammation-based indexes (NLR, PLR, CLR, LMR, PNI, SII, HALP and AGR) were associated with in-hospital death. Then, in multivariate analysis performed with significant variables determined in univariate analysis, age >57 years (Odds ratio [OR]: 3.86, 95% CI: 1.77-8.44, p=0.001), male gender (OR: 2.03, 95% CI: 1.11-3.72, p=0.022), dyslipidemia (OR: 2.52, 95% CI: 1.05-6.04, p=0.038), PNI ≤40.03 (OR: 5.89, 95% CI: 2.40-14.48, p<0.001), NLR >4.78 (OR: 4.21, 95% CI: 1.69-10.50, p=0.002), and CLR >16.65 (OR: 3.60, 95% CI: 1.35-9.60, p=0.011) were found to be independent predictors for death.

ROC analysis results showed that PNI, CLR and NLR had the highest area under the curve (AUC) to predict mortality. The optimal threshold level was 40.03 for PNI (AUC: 0.897, 95%CI: 0.874-0.917, sensitivity, Se:90.43%, specificity, Sp:77.63%); 16.65 for CLR (AUC:0.887, 95%CI: 0.863-0.908, Se:93.62%, Sp:67.39%); 4.78 for NLR (AUC: 0.838, 95%CI: 0.812-0.863, Se:74.47%, Sp:81.58%); 1222 for SII (AUC: 0.806, 95%CI: 0.777-0.833, Se:64.89%, Sp:83.63%); 1.208 for AGR (AUC: 0.790, 95%CI: 0.761-0.817, Se:77.66%, Sp:69.58%); 21.27 for HALP (AUC: 0.752, 95%CI: 0.721-0.781, Se:52.13%, Sp:86.49%); 189 for PLR (AUC: 0.693, 95%CI: 0.660-0.724, Se:60.64%, Sp:75.03%), and 2.51 for LMR (AUC: 0.640, 95%CI: 0.607-0.673, Se:59.57%, Sp: 66.58%), respectively (p= 0.001 for all).

The PNI, which consists of lymphocytes and albumin, is an effective index used to assess inflammation and nutritional conditions.[2,3] Wang *et al*. demonstrated that low PNI at admission is an independent factor for mortality in subjects suffering from

COVID-19.[2] Similarly, Aciksari *et al*. showed, PNI less than equal to 40.2 to be associated with increased mortality with an OR of 10.85.[3] Consistent with these findings, the present study detected that PNI ≤40.03 was an independent predictor of mortality in COVID-19 subjects. This study also revealed that PNI has the highest AUC among inflammation-based indices for predicting mortality. These outcomes indicate that the PNI index, which integrates both immune and nutritional conditions, is an important indicator for predicting mortality in these patients.

CLR obtained by using lymphocytes and CRP is one of the inflammation-related indexes reflecting the systemic inflammatory response in the organism.[6] Jemaa *et al*. noted that high CLR is related to a worse prognosis in COVID-19 subjects. They also revealed that CLR levels returned to normal more rapidly in surviving COVID-19 subjects, but remained elevated in non-survivors.[6] In this study, the non-survivors had a higher CLR than the survivors. This elevation in CLR was associated with high CRP levels and low lymphocyte count. In ROC analysis, when the cut-off value of CLR was above 16.65, the AUC was 0.887, indicating that the CLR has good predictive power. It was also found that CLR more than 16.65 was an independent prognostic factor with an OR of 3.60 for mortality.

NLR, which is a systemic inflammatory indicator, is a commonly used index that is easily obtained by dividing neutrophils by lymphocyte count.[6] Numerous studies have shown that an increase in NLR is associated with a higher risk of mortality and disease progression in COVID-19 patients.[3,4,6] These results are in line with the findings of previous studies in which NLR was an independent factor of death in COVID-19 patients with an OR of 4.21 in multivariate regression.

HALP, PLR, LMR, SII, and AGR are other inflammation-related indexes. In this study, there were significant differences between survivors and non-survivors in terms of these indices. The predictive performance of the AGR, HALP, PLR, and LMR indices for mortality was fair or weak as they had AUC values less than 0.800. The AUC values of SII were greater than 0.800, indicating good performance in predicting mortality, but this index on admission was not identified as an independent factor of mortality.

This study is limited by the retrospective investigation of the medical data of COVID-19 patients in a single institute. This study revealed that low PNI and high NLR and CLR are related to higher COVID-19 mortality. Advanced age, male gender, and presence of dyslipidemia were other independent factors of mortality. Assessment of these indicators can assist physicians in identifying high-risk cases with COVID-19, thereby minimising mortality rates.

DISCLOSURE:
This work was presented as a poster at the 33th National Biochemistry Congress in October 2022 (Izmir-Cesme, Turkey).

ETHICAL APPROVAL:
This study was approved by the Turkish Ministry of Health and the Harran University Ethics Committee (Approval No. HRU.22/07/16).

PATIENTS' CONSENT:
Because this study was retrospective, the condition of patients' consent was waived.

COMPETING INTEREST:
The authors declared no competing interest.

AUTHORS' CONTRIBUTION:
GC: Concept, design, analysis/interpretation, literature search, and manuscript writing.
TDC: Data collection/processing, analysis/interpretation, literature search, and manuscript writing.
AB: Data collection/processing, analysis/interpretation, and critical review.
MO: Data collection/processing and critical review.
All the authors have read and approved the final version of the manuscript.

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