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A new COVID-19 prediction scoring model for in-hospital mortality: experiences from Turkey, single center retrospective cohort analysis

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Abstract. – OBJECTIVE: Although many studies reported prognostic factors proceeding to severity of COVID-19 patients, in none of the article a prediction scoring model has been proposed. In this article a new prediction tool is presented in combination of Turkish experience during pandemic.

MATERIALS AND METHODS: Laboratory and clinical data of 397 over 798 confirmed COVID-19 patients from Gülhane Training and Research Hospital electronic medical record system were included into this retrospective cohort study between the dates of 23 March to 18 May 2020. Patient demographics, peripheral venous blood parameters, symptoms at admission, in hospital mortality data were collected. Non-survivor and survivor patients were compared to find out a prediction scoring model for mortality.

RESULTS: There was 34 [8.56% (95% CI:0.06-0.11)] mortality during study period. Mean age of patients was 57.1±16.7 years. Older age, comorbid diseases, symptoms, such as fever, dyspnea, fatigue and gastrointestinal and WBC, neutrophil, lymphocyte count, C-reactive protein, neutrophil-to-lymphocyte ratio of patients in non-survivors were significantly higher. Univariate analysis demonstrated that OR for prognostic nutritional index (PNI) tertile 1 was 18.57 (95% CI: 4.39-78.65, $p<0.05$) compared to tertile 2. Performance statistics of prediction scoring method showed 98% positive predictive value for criteria 1.

CONCLUSIONS: It is crucial to constitute prognostic clinical and laboratory parameters for faster delineation of patients who are prone to worse prognosis. Suggested prediction scoring method may guide healthcare professional to discriminate severe COVID-19 patients and provide prompt intensive therapies which is highly important due to rapid progression leading to mortality.

Key Words:
COVID-19, Prognostic Nutritional Index, Hospital Mortality, Neutrophil-to-Lymphocyte ratio, Prognosis, Mortality Prediction Model, High Sensitive-Modified Glasgow Prognostic Score.

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Introduction

SARS-CoV-2 known as novel coronavirus was first identified in Wuhan, China, at the end of 2019[1]. Due to rapid outbreak in China and followed by other countries throughout the World, this contagious disease has raised worldwide concerns. As of May 21, 2020, 153548 patients have been diagnosed as COVID-19 in Turkey, 4249 (2.77%) of them progressed to mortality[2]. Since no standardized treatment protocols are available in current practice, it is highly important to delineate risk factors leading worse prognosis in COVID-19 patients[3,4].

Due to rapid spread and heavy damage of COVID-19, it is crucial to constitute prognostic clinical and laboratory parameters for faster delineation of patients who are prone to worse prognosis. Potential prognostic inflammation markers are signs of systemic inflammatory response. Roles of these inflammatory molecules and cells in progression of COVID-19 have been showed previously[4-11]. However, the importance of prognostic inflammation markers for the survival of COVID-19 patients has not been scrutinized previously. Thus, this retrospective cohort study was conducted to delineate prognostic significance of baseline blood inflammation biomarkers or several ratios for overall survival rate. Furthermore, this study investigated prognostic laboratory results and clinical features with description of risk factors and a prediction scoring model associated with in-hospital mortality of patients with COVID-19.

In the present study, primary endpoint was to detect whether prognostic nutritional index (PNI), neutrophil (NEU)-to-lymphocyte (LYM) ratio (NLR) and high sensitive modified Glasgow prognostic score (HS-mGPS) can be used as a valuable predictor of in-hospital mortality. Secondary endpoint was whether these ratios in combination with some clinical parameters can have a role to constitute a prediction scoring method.

Materials and Methods

This retrospective cohort study was approved by Ethics Committee of Health Sciences University, Gülhane School of Medicine (2020-152) and conducted in line with ethical standards of Declaration of Helsinki. Confirmed COVID-19 cases from 23 March to 18 May, 2020 were included consecutively. Anonymous clinical and laboratory findings were collected. Therefore, there was no requirement for informed consent. Ankara as capital of Turkey has a population of 5,504,000 people. Gülhane Training and Research Hospital is one of biggest and oldest hospital in Ankara and Turkey with more than 1500 bed capacity has been assigned as pandemic hospital for COVID-19 treatment.

Turkish Ministry of Health dictated rules for diagnosis and treatment guidelines of COVID-19 during pandemic according to interim guidance of WHO.

Clinical and laboratory data have been obtained from hospital electronic data system. Patients who are pregnant, younger than 18 years old, with missing baseline data or being transferred to other designated hospitals and died on admission were not enrolled. Through this exclusion criteria 401 patients were excluded and 397 patients were included in final analyses (Figure 1). COVID-19 patients were divided into 2 groups as patients who died in hospital (non-survivors) and discharged from hospital after recovery (survivors).

PNI was computed by using following formula: "Serum albumin levels (g/dl) x 10 + total lymphocyte count in peripheral blood (per mm^3) x 0.005"[12]. Patients were allocated into two tertiles according to median as low PNI (Tertile 1=28.3-44.7) and high PNI (Tertile 2=44.7-60.1) groups.

Three types of GPS score were reported previously as traditional Glascow prognostic score (GPS), modified GPS (m-GPS) and high-sensitivity modified GPS (HS-mGPS) based on mainly CRP cut-off value. For HS-mGPS, in which 3 mg/L (rather than 10 mg/L), it is used as CRP cut-off value[13]. Currently, HS-mGPS was used in this study.

NLR, d-NLR and Systemic immune-inflammation index (SII) were calculated according to previous studies[5,13].

In order to make a baseline for further studies, it is decided to constitute a prediction scoring method to detect in-hospital mortality by using parameters, such as existence of any comorbidity, symptoms fever, and dyspnea on admission, being in NLR tertile 2 (NLR value: 3.2-38.8), being in PNI tertile 1 (PNI value: 28.3-44.7), and HS-mGPS scores 1 and 2. Two criteria have been decided according to HS-mGPS scores 1 or 2; and all these parameters were tested according to their existence or absence by using score 1 and 2 separately. Score 1 is accepted as criteria 1 and score 2 is accepted as criteria 2.

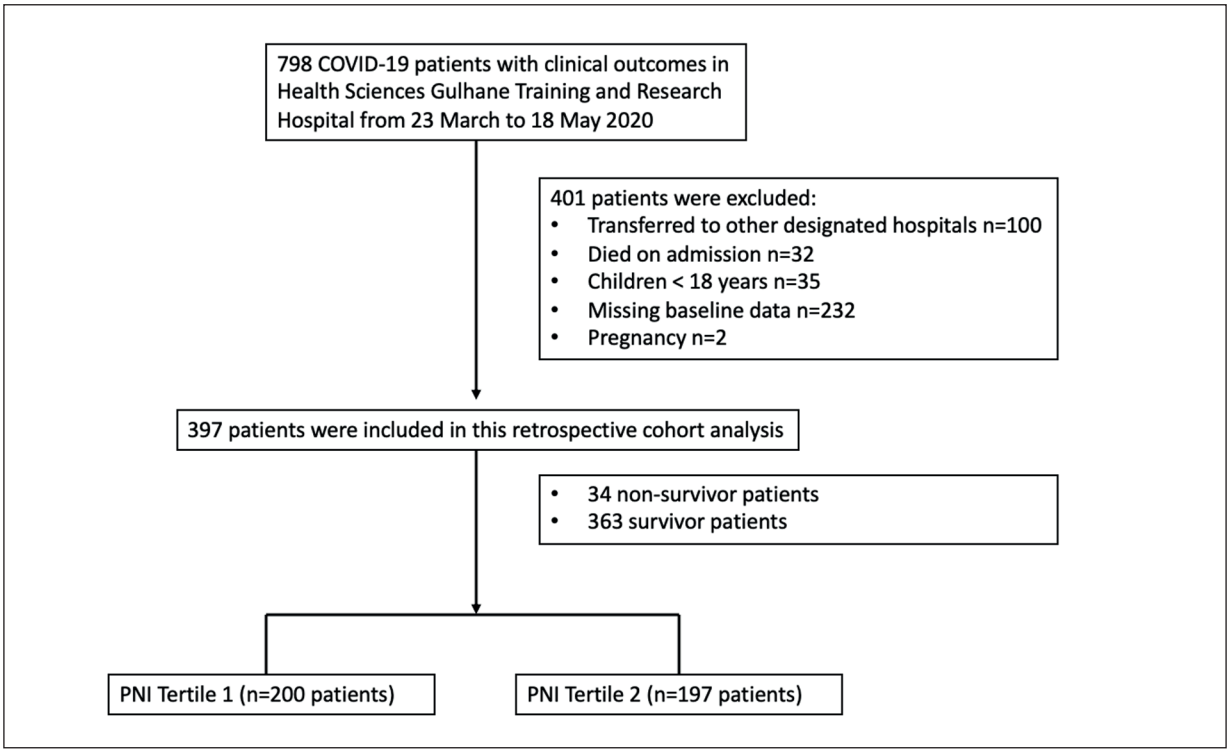

Figure 1. Study Population. PNI: Protein nutritional index.

Statistical Analysis

Parametric tests were used, without normality tests due to suitability according to the Central Limit Theorem[14]. Mean and standard deviation, median and (25%-75%) values, minimum and maximum values are given, while statistical data of continuous structure are given, frequency and percentage values are given, while statistics of categorical variables are made, while analyzing data. Student's *t*-test statistic is given, to compare two averages of independent groups. Repeated ANOVA test statistic is given, comparing more than two group averages dependent. Chi-square test statistics were used to evaluate the relationship between categorical variables. Exposure ratio (odds ratio) was given for non-survival variables that are thought to be related. Negative Prediction Value, Positive Prediction Value, Accuracy, and Diagnostic Odds Rate statistics were determined. Criteria Obtained from Risk Factors affecting non-survival status. Significance level was taken as $p<0.05$. In this study, MedicReS Good Biostatistical Consultancy Standards were used (www.e-picos.com, NY, New York software and MedCalc statistics).

Results

Demographic findings and clinical features of the patient cohort are shown in Table I. Mean age was 57.1±16.7 years [55, 47-70 (Median, 25%-75%)]. Older age, comorbid diseases, symptoms such as fever, dyspnea, fatigue and gastrointestinal and WBC count, neutrophil count, CRP, SII, NLR, and d-NLR of patients in non-survivors were significantly higher. However, there was no significant difference in terms of gender. Total in-hospital death number was 34 [8.56% (95% CI:0.06-0.11)]. The most common symptoms on admission were fever (n=261, 65.7%) and cough (n=195, 49.1%). In 80.6% and 51.6% of patients, lymphopenia and neutrophilia were respectively observed. Non-survivor patients showed significantly higher rates in occurrence of Chronic Obstructive Pulmonary Disease (COPD; Non-survivor: 13/34, Survivor: 26/363, $p<0.0001$), Chronic Renal Failure (CRF; Non-survivor: 4/34, Survivor: 12/363, $p=0.02$) Coronary Heart Disease (CHD; Non-survivor: 11/34, Survivor: 34/363, $p<0.0001$). Diabetes mellitus (DM) and hypertension (HT) showed no significant differences. When HS-mGPS scores were analyzed, there

was no patient with a score of 0 in non-survivors. More patients in non-survivors had score 2. However, in survivors there were more patients having score 0 or 1 than patients having score 2. There were statistically significant differences in baseline values of WBC, NEU, LYM and Albumin. But platelets and monocytes showed no difference (Table I).

Patients' data were rearranged according to two tertile values of d-NLR, NLR and PNI. Tertiles were defined according to median values. Tertile 1 of d-NLR, NLR and PNI were compared to tertile 2. Patients in tertile 1 was older than tertile 2 (d-NLR p=0.03, NLR p<0.0001). Although there were no significant differences in gender in d-NLR tertiles, for NLR there was a slight differ-

Table I. Demographics and baseline laboratory characteristic of the patients on admission, non-survivors, and survivors.

Variables		Total (n = 397)	Non-Survivors (n = 34)	Survivors (n = 363)	*p*-value
Age, M ± SD, years		57.1 ± 16.7	75.8 ± 8.9	55.4 ± 16.1	**< 0.0001***
Median (25%-75%)		55 (47-70)	77.5 (70-82)	54 (46-67)	
Sex, n (%)	Male	200 (50.4)	17 (50)	183 (50.4)	0.96**
	Female	197 (49.6)	17 (50)	180 (49.6)	
Co-morbidities n (%)	No	212 (53.4)	3 (8.8)	209 (57.6)	**< 0.0001****
	Yes	185 (46.6)	31 (91.2)	154 (42.4)	
Malignancy n (%)	No	384 (96.7)	26 (76.5)	358 (98.6)	**< 0.0001****
	Yes	13 (3.3)	8 (23.5)	5 (1.4)	
COPD n(%)	No	358 (90.2)	21 (61.8)	337 (92.8)	**< 0.0001***
	Yes	39 (9.8)	13 (38.2)	26 (7.2)	
CHD n(%)	No	352 (88.7)	23 (67.6)	329 (90.6)	**< 0.0001****
	Yes	45 (11.3)	11 (32.4)	34 (9.4)	
CRF n(%)	No	381 (96)	30 (88.2)	351 (96.7)	**0.02****
	Yes	16 (4)	4 (11.4)	12 (3.3)	
HT n(%)	No	286 (72)	20 (58.8)	266 (73.3)	0.07**
	Yes	111 (28)	14 (41.2)	97 (26.7)	
DM n(%)	No	300 (75.6)	23 (67.6)	277 (76.3)	0.26**
	Yes	97 (24.4)	11 (32.4)	86 (23.7)	
Symptoms at admission					
Dyspnea n (%)	No	306 (77.1)	9 (26.5)	297 (81.8)	**< 0.0001****
	Yes	91 (22.9)	25 (73.5)	66 (18.2)	
Fever n (%)	No	136 (34.3)	4 (11.8)	132 (36.4)	**0.004****
	Yes	261 (65.7)	30 (88.2)	231 (63.6)	
Cough n (%)	No	202 (50.9)	13 (38.2)	189 (52.1)	0.12**
	Yes	195 (49.1)	21 (61.8)	174 (47.9)	
Fatigue n (%)	No	265 (66.8)	28 (82.4)	237 (65.3)	**0.04****
	Yes	132 (33.2)	6 (17.6)	126 (34.7)	
GIS n (%)	No	292 (73.6)	31 (91.2)	261 (71.9)	**0.01****
	Yes	105 (26.4)	3 (8.8)	102 (28.1)	
HS-mGPS n (%)	0	40 (10.1)	-	40 (11)	**< 0.0001****
	1	263 (66.2)	10 (29.4)	253 (69.7)	
	2	94 (23.7)	24 (70.6)	70 (19.3)	
WBC, M ± SD, 10^9/L		6.71 ± 3.2	9.49 ± 4.5	6.2 ± 3	**< 0.0001***
Platelet, M ± SD, 10^9/L		213.88 ± 6.32	228.58 ± 71.9	208.6 ± 67.8	0.19*
Neutrophil, M ± SD, 10^9/L		7.99 ± 3.51	7.84 ± 4.42	4.37 ± 2.87	**< 0.0001***
Lymphocyte, M ± SD, 10^9/L		1.31 ± 0.59	0.96 ± 0.61	1.29 ± 0.59	**< 0.0001***
Monocyte, M ± SD, 10^9/L		0.63 ± 0.31	0.62 ± 0.35	0.64 ± 0.3	0.87
CRP, M ± SD, mg/L		56.52 ± 77.4	125.58 ± 87.17	55.04 ± 77.8	**< 0.0001***
Albumin, M ± SD, g/dL		3.75 ± 0.47	3.19 ± 0.45	3.78 ± 0.43	**< 0.0001***
NLR, M ± SD		5.02 ± 5.4	11.98 ± 10	4.42 ± 4.3	**< 0.0001***
SII, M ± SD		1139.46 ± 1442.47	2828.6 ± 2618	977.05 ± 1211.4	**< 0.0001***
PNI, M ± SD		44.152 ± 6.15	36.7 ± 5.64	44.47 ± 5.96	**< 0.0001***
d-NLR, M ± SD		2.79 ± 2.21	5.94 ± 4	2.55 ± 1.9	**< 0.0001***

*Student's *t*/** Chi-square. Chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD), chronic renal failure (CRF), hypertension (HT), diabetes mellitus (DM), gastro-intestinal symptoms (GIS), high sensitivity modified Glasgow prognostic score (HS mGPS), white blood cell count (WBC), neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), systemic immune-inflammation index (SII), prognostic nutritional index (PNI), derived neutrophil-to-lymphocyte ratio (d-NLR).

ence for female dominance in tertile 2 (p=0.04). The most common symptoms on the admission of patients in tertile 2 were fever (significant in NLR, p=0.03) and dry cough (although no differences between tertiles for both d-NLR and NLR) followed by dyspnea and gastrointestinal symptoms. Furthermore, patients in tertile 2 were more likely to have COPD (d-NLR p=0.01, NLR p=0.004) and there was no significant difference for DM, HT, CHD, CRF and malignancy for both d-NLR and NLR tertiles. More patients with HS-mGPS scores 1 and 2 were located in tertile 2. Mortality in d-NLR and NLR tertile 2 was 30 (88%) and 31 (91.2%) respectively.

Same tertiles were performed for PNI. Different from d-NLR and NLR, patients in PNI tertile 1 were older (p=0.009). There was no difference for gender between tertiles. Dyspnea (p=0.004) was the most common symptom on the admission in tertile 1. For cough, fever, fatigue and gastrointestinal symptoms, there were no significant differences. Moreover, there were more patients with COPD (p<0.0001) and CHD (p=0.003). There was no significant difference for DM, HT, CRF and malignancy between tertiles. There were 32 (94.1%) mortality in tertile 1. More patients with HS-mGPS score 2 patients were in tertile 1. Since tertile 1 of PNI detected more mortality, it is decided to focus on PNI tertile results (Table II).

Univariate logistic regression models showing differences between baseline variables and in-hospital death were shown in Table III. Univariate analysis showed that age (OR: 1.1, 95% CI=1.07-1.14, p<0.05), having any comorbidity (OR: 14.02, 95% CI=4.21-46.71, p<0.05), CRF (OR: 3.9, 95% CI=1.19-12.84, p<0.05), COPD (OR: 8.02, 95% CI=3.61-17.83, p<0.05), CHD (OR: 4.63, 95% CI=2.08-10.3, p<0.05), from symptoms at admission fever (OR: 4.29, 95% CI=1.48-12.43, p<0.05), dyspnea (OR: 12,5, 95% CI=5.58-28.02, p<0.05), fatigue (OR: 0.4, 95% CI=0.16-0.99, p<0.05), gastrointestinal symptoms (OR: 0.25, 95% CI=0.07-0.83, p<0.05) were positively associated with in-hospital mortality. However there were no correlation between DM (OR: 0.72, 95% CI=3.61-17.83, p<0.05), HT (OR: 1.54, 95% CI=0.72-3.29 p>0.05), and cough at admission (OR: 1.75, 95% CI=0.85-3.61 p>0.05), SII (OR: 1.001, 95% CI=0.99-1.002, p>0.05) and in-hospital mortality.

Univariate logistic regression model results analyzing the relations of NLR, d-NLR, PNI and in-hospital mortality were demonstrated in Table IV. In unadjusted models, ORs of in-hospital mortality significantly augmented as NLR and d-NLR increased. There was negative correlation for PNI and OR of mortality significantly augmented as PNR tertile decreased. There were 1.16-fold, 1.57-fold increases in risk of in-hospital death for per unit increase in NLR (OR: 1.16, 95% CI=1.11-1.23, p<0.05) and d-NLR (OR: 1.57, 95% CI=1.37-1.80, p<0.05). ORs for tertile 2 were significantly higher than OR for tertile 1 of NLR (OR: 12.26, 95% CI=3.68-40.83, p<0.05) and d-NLR (OR: 8.7, 95% CI=3.0-25.21, p<0.05). There was reverse correlation for PNI and 0.79-fold decrease in-hospital mortality risk (OR: 0.79, 95% CI=0.73-0.84, p<0.05) and OR of tertile 1 was higher than tertile 2 (OR: 18.57, 95% CI=4.39-78.65, p<0.05).

When performance statistics of prediction scoring method were analyzed, the negative predictive value (NPV) of criterion 1 was 57% and it was not significant. However positive predictive value (PPV) was 98% to detect in-hospital mortality and this value was significant. Accuracy of this criterion was 97%. For criteria 2 NPV was 74% and it was significant. PPV was 90% and accuracy was %86, and both were significant. Diagnostic odd ration for criteria 1 was 55.57 and 25.9 for criteria 2 and both were significant (Table V).

Discussion

Total in-hospital mortality number was 34/397 (8.56%, 95% CI=0.06-0.11). Higher NLR, d-NLR and lower PNI values were significantly associated with an increased risk of in-hospital mortality. Being in older age, having any comorbidity, fever and dyspnea on admission were significant factors affecting in-hospital mortality. Although having DM and HT have been shown as a risk factor for mortality in previous studies, there was no difference for these comorbidities between survivors and non-survivors in this study[15-17]. Furthermore, there was no difference in genders for mortality.

In the present study, lymphocyte counts in survivor patients was significantly lower, while neutrophil counts and CRP of survivors was significantly higher. Decrease in number of lymphocytes, and level of albumin were the mostly evident. NLR, d-NLR, SII and HS-mGPS of patients increased and PNI decreased signifi-

Table II. Baseline characteristics of COVID-19 patients and all-cause death during hospital according to the tertiles of prognostic nutritional index (n= 397).

Variables		Tertile 1 (28.3-44.7 n = 200)	Tertile 2 (44.7-60.1 n = 197)	*p*-value
Age, M ± SD, years		59.29 ± 17.98	54.95 ± 14.96	**0.009****
Sex, n (%)	Male	100 (50)	100 (50)	0.88*
	Female	100 (50)	97 (49.2)	
Co-morbidities, n (%)	No	101 (50.5)	111 (56.3)	0.24*
	Yes	99 (49.5)	86 (43.7)	
Malignancy, n (%)	No	191 (95.5)	193 (98)	0.17*
	Yes	9 (4.5)	4 (2)	
COPD, n (%)	No	170 (85)	188 (95.4)	**< 0.0001***
	Yes	30 (15)	9 (4.6)	
CHD, n (%)	No	168 (84)	184 (93.4)	0.003*
	Yes	32 (16)	13 (6.6)	
CRF, n (%)	No	193 (96.5)	188 (95.4)	0.59*
	Yes	7 (3.5)	9 (4.6)	
Hypertension, n (%)	No	145 (72.5)	141 (71.6)	0.84*
	Yes	55 (27.5)	56 (28.4)	
Diabetes mellitus, n (%)	No	154 (77)	146 (74.1)	0.5*
	Yes	46 (23)	51 (25.9)	
Dyspnea, n (%)	No	142 (71)	164 (83.2)	**0.004***
	Yes	58 (29)	33 (16.8)	
Fever, n (%)	No	60 (30)	76 (38.7)	0.07*
	Yes	140 (70)	121 (61.4)	
Cough, n (%)	No	103 (51.5)	99 (50.3)	0.8*
	Yes	97 (48.7)	98 (49.7)	
Fatigue, n (%)	No	140 (70)	125 (63.3)	0.17*
	Yes	60 (30)	72 (36.5)	
GIS, n (%)	No	154 (77)	138 (70.1)	0.12*
	Yes	46 (23)	59 (29.9)	
Mortality, n (%)	No	168 (84)	195 (99)	**< 0.0001***
	Yes	32 (16)	2 (1)	
HS-mGPS, n (%)	0	7 (3.5)	33 (16.8)	
	1	101 (50.5)	162 (82.2)	**< 0.0001***
	2	92 (46)	2 (1)	
WBC, M±SD, 10^9/L		7.19 ± 3.79	6.22 ± 2.41	**0.002****
Platelet, M±SD, 10^9/L		215.82 ± 84.98	211.9 ± 48.67	0.57**
Neutrophil, M±SD, 10^9/L		5.79 ± 3.77	4.17 ± 3.01	**< 0.0001****
Lymphocyte, M±SD, 10^9/L		1 ± 0,4	1.64 ± 0.59	**< 0.0001****
Monocyte, M±SD, 10^9/L		0.62 ±0.32	0.63 ± 0.28	0.65**
CRP, M±SD, mg/L		89.41 ± 90.61	23.13 ± 39.57	**< 0.0001****
Albumin, M±SD, g/dL		3.43 ± 0.41	4.08 ± 0.26	**< 0.0001****
NLR, M±SD		7.18 ± 6.56	2.82 ± 2.37	**< 0.0001****
SII, M±SD		1635.82 ± 1758.6	635.54 ± 746.37	**< 0.0001****
d-NLR M±SD		3.77 ± 2.60	1.79 ± 0.80	**< 0.0001****

*Chi-square/**Student's *t*-test. Chronic renal failure (CRF), chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD), gastro-intestinal symptoms (GIS), high sensitivity modified Glasgow prognostic score (HS mGPS), white blood cell count (WBC), neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), systemic immune-inflammation index (SII).

cantly. It has been reported that "progression and prognosis of COVID-19 are related to the body's immune status and excessive inflammatory response"[18,19].

When unadjusted ORs were analyzed being in tertile 2 of NLR, d-NLR; 12.26 and 8.7-fold increased risk of mortality respectively. For PNI in the current study, being in tertile 1, 18.57-fold increases the risk of in-hospital mortality. Qin et al[20] showed that "there was a correlation between higher neutrophil count but lower lymphocyte count and severe disease situation". Liu et al[3] "demonstrated that increased NLR had a higher risk of mortality during hospitalization". Yang et al[5] also showed that "NLR, d-NLR have prognostic possibility of clinical symptoms to change

Table III. The unadjusted association between baseline variables and all-cause death during hospitalization (n = 397).

Variables	Odds Ratio	Lower (95% CIs)	Upper (95% CIs)	*p*-value
Age	1.1	1.07	1.14	**< 0.05**
Co-morbidities	14.02	4.21	46.71	**< 0.05**
Malignancy	22.03	6.73	72.14	**< 0.05**
COPD	8.02	3.61	17.83	**< 0.05**
CHD	4.63	2.08	10.3	**< 0.05**
CRF	3.9	1.19	12.84	**< 0.05**
Hypertension	1.92	0.93	3.95	> 0.05
Diabetes mellitus	1.54	0.72	3.29	> 0.05
Dyspnea	12.5	5.58	28.02	**< 0.05**
Fever	4.29	1.48	12.43	**< 0.05**
Cough	1.75	0.85	3.61	> 0.05
Fatigue	0.4	0.16	0.99	**< 0.05**
GIS	0.25	0.07	0.83	**< 0.05**
WBC	1.24	1.13	1.35	**< 0.05**
Platelet	1.003	0.99	1.008	> 0.05
Neutrophil	1.17	1.09	1.26	**< 0.05**
Lymphocyte	0.23	0.1	0.52	**< 0.05**
Monocyte	0.89	0.28	2.89	> 0.05
Albumin	0.08	0.04	0.17	**< 0.05**
CRP	1.008	1.005	1.1	**< 0.05**
SII	1.001	0.99	1.002	> 0.05
PNI	0.79	0.73	0.84	**< 0.05**
d-NLR	1.57	1.37	1.80	**< 0.05**
NLR	1.16	1.11	1.23	**< 0.05**

Chronic renal failure (CRF), chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD), gastro-intestinal symptoms (GIS), white blood cell count (WBC), neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), systemic immune-inflammation index (SII), prognostic nutritional index (PNI), derived neutrophil-to-lymphocyte ratio (d-NLR).

from mild to severe". To show this possibility NLR was superior to d-NLR. In the current study, NLR was similarly superior in predicting mortality.

Zhong et al[21] reported that there was a poor association with elevated SII and poor overall survival or progression-free survival of patient with cancer[22-24]. In this study, although there was significant difference between tertile 1 and tertile 2 of PNI levels, there was no significant difference according to unadjusted ORs for SII and mortality.

Glasgow prognostic score is considered to reflect both inflammation and nutrition status[25]. It has been revealed that a high level of the GPS is significantly correlated with poor survival outcome in multiple types of cancers. Proctor et al[26] showed HS-mGPS as a more sensitive prognostic predictor in patients with and malignancy. Takeno et al[27] reported that HS-mGPS was superior to mGPS as a prognostic predictor. Therefore, to the best of our knowledge, prognostic predictive value HS-mGPS was tested in COVID-19 patients for the first time. All non-survivor patients get

Table IV. Risk association between baseline NLR, d-NLR, PNI and in-hospital death.

Variables	Unadjusted Odds Ratio (%95 CIs)	*p*-value
NLR	1.16 (1.11-1.23)	**< 0.05**
NLR Tertile 2 (3.2-38.8)	12.26 (3.68-40.83)	**< 0.05**
d-NLR	1.57 (1.37-1.80)	**< 0.05**
d-NLR Tertile 2 (2.06-16.86)	8.7 (3.006-25.21)	**< 0.05**
PNI	0.79 (0.73-0.84)	**< 0.05**
PNI Tertile 1 (28.3-44.7)	18.57 (4.39-78.65)	**< 0.05**

CI: confidence interval, neutrophil-to-lymphocyte ratio (NLR), derived neutrophil-to-lymphocyte ratio (d-NLR), prognostic nutritional index (PNI).

Table V. Performance statistics of prediction scoring method for prediction of in-hospital mortality.

	Criteria 1	*p*-value	Criteria 2	*p*-value
NPV	0.57	NS	0.74	**< 0.05**
Lower (% 95 CI)	0.20		0.56	
Upper (%95 CI)	0.96		0.92	
PPV	0.98	**< 0.05**	0.90	**< 0.05**
Lower (% 95 CI)	0.96		0.83	
Upper (% 95 CI)	0.99		0.97	
Accuracy	0.97	**< 0.05**	0.86	**< 0.05**
Lower (% 95 CI)	0.94		0.79	
Upper (% 95 CI)	0.99		0.93	
Diagnostic Odds Ratio	55.57	**< 0.05**	25.9	**< 0.05**
Lower (% 95 CI)	10.2		7.69	
Upper (% 95 CI)	304.6		87.26	

NPV: negative predictive value, PPV: positive predictive value, CI: Confidence interval, NS: not significant. Criteria 1: HS-mGPS score 1, Criteria 2: HS-mGPS score 2.

of score 1 (10 of 34) or 2 (24 of 34). Although 32 of 34 non-survivor patients were in this tertile 1, there were 193 patients tertile 1 having score 1 and 2 too. Since there are many survivors having score 1 and 2, it is not a good predictive score by itself in COVID-19.

Different from previous studies related with COVID-19, in this study PNI was focused on for predicting in-hospital mortality. Serum albumin could play a role in stimulating or moderating immune activation according to pathophysiological situation. PNI shows immune-nutritional status of human body and might predict prognosis in COVID-19[28].

To the best of our knowledge, this is the first study investigating predictive value of PNI in COVID-19 patients. Although the relationship of hypoalbuminemia and severity of COVID-19 has been studied in literature[29-34], predictive value of albumin and underlying factors for hypoalbuminemia in COVID-19 patients have not been rigorously examined. A decrease in serum albumin level cannot be explained by hepatocellular dysfunction alone. Since patients' median admission time to hospitals was shorter than serum albumin half-life, "hypoalbuminemia was less likely to be a result of decreased albumin synthesis in severe COVID-19"[33]. It suggests that some different underlying factors other than a hepatocellular damage may be responsible. Increased capillary permeability in many inflammatory diseases may cause hypoalbuminemia due to escape of albumin to interstitial space[35,36]. In the present study severe COVID-19 patients showed significantly lower albumin levels than mild cases. Inverse relationship observed between albumin level and in-hospital mortality risk in COVID-19 patients was one important result of this study which revealed that serum albumin level <35 g/L on admission increased mortality risk.

PNI is an index that contemplate chronic inflammation, immune system and nutritional status, and has a prognostic significance[37]. Several meta-analyses indicated that, high PNI was associated with longer overall survival in cancer patients[38,39]. However the importance of PNI in COVID-19 patients are still not clear. In our study, patients with higher PNI (>44.7) were in survivor group. Univariate analyses also confirmed that PNI was prognostic for overall survival. In addition to all these findings, the highest unadjusted odds ratio was 18.57 for PNI, indicating superiority of this index relative to NLR, d-NLR, and SII.

Secondary endpoint of this current study, a prediction model for detecting in-hospital mortality was constituted to be a baseline for a further scoring systems. To the best of our knowledge, in many previous articles several ratios have been tested to predict mortality, however, none of them tested as a combination of several parameters to form a scoring system detecting in-hospital mortality. Although NPV of criteria 1 was not significant (57%), PPV value was 98% and accuracy was 97%, which indicated that this prediction model was effective to predict mortality. Currently, there is no optimal inflammatory biomarker for as-

sessing a COVID-19 patient's inflammatory status. Several studies have shown importance of neutrophil, lymphocyte, CRP, albumin and NLR on progression of severity of COVID-19. Although all these values are important, it is difficult to draw a definite conclusion by using any of them as a single parameter. However, as a general approach to evaluate any disease and patient, both laboratory and clinical findings have high and equal importance to draw a conclusion. Therefore, we tried to integrate a prediction score system comprising NLR, HS-mGPS, and PNI, with having any comorbid disease, fever and dyspnea as symptoms at admission. These clinical parameters were decided according to the higher ORs of univariate analyzes. This study shows that combination of biomarkers and clinical parameter had stronger discriminative power than any of biomarkers alone to reveal in-hospital mortality.

This study has some limitations as well. First of all, it was a retrospective single center cohort study to show results of patients treated in very limited time period. Second the suggested prediction score is performed over a small group of non-survivor patients. Therefore, it should be validated by larger prospective studies.

Conclusions

Being able to make risk stratification is crucial for giving timely and correct management. PNI was a good marker to show prognosis. The suggested prediction scoring method with a 98% PPV to show in-hospital mortality, may guide healthcare professional to discriminate severe COVID-19 patients and provide prompt intensive therapies which is highly important due to rapid progression leading to mortality. Therefore, risky patients should receive more attention, should be monitored more closely, and treated promptly to improve prognosis.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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