ORIGINAL RESEARCH

Is the prognostic nutritional index a predictor of Covid-19 related hospitalizations and mortality?

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Abstract

Introduction

Prognostic nutritional index (PNI) is a novel inflammation marker that useful in predicting prognosis of certain conditions. We aimed to study PNI of the outpatient and inpatient subjects with established Covid-19 and also aimed to compare PNI of deceased and survived Covid-19 patients.

Methods

The patients with Covid-19 whom presented to outpatient or inpatient clinics of Abant Izzet Baysal University Hospital were enrolled to the study. PNI levels of the inpatients and outpatients, deceased and survived were compared. PNI values of deceased and survived in inpatients were also compared.

Results

Study population was consisted of 4419 subjects (2907 outpatients and 1512 inpatients). PNI of the inpatient (41.55 (36.42-47.1)) group was significantly lower than the PNI of the outpatient (51.95 (47.95-55.75)) subjects ($p<0.001$). The sensitivity and specificity of PNI (≤46.2 level) in determination of requirement inpatient treatment were 71.2% and 83.5%, respectively. PNI of the deceased patients (37(33.39-40.86)) was lower than the PNI of the survivors (50.45(45.6-54.65)), ($p<0.001$). The sensitivity and specificity of PNI at ≤44.55 level in determining mortality were 89.22% and 78.87%, respectively.

Conclusion

We suggest that PNI could serve as a reliable prognostic index in covid-19 patients. Reduced level of PNI should alert physicians since it is associated with need for hospitalization and mortality in this population.

Keywords: Covid-19, prognostic nutritional index, mortality, inflammation

Introduction

The new type of coronavirus-induced Covid-19 disease, named as SARS-CoV-2, which started from Wuhan city of China in December 2019 and spread all over the world in a short time, has become an important threat by causing severe respiratory tract infections with a mortal course[1]. The novel coronavirus disease led to the emergence of the first global pandemic of coronavirus origin[2]. The infection could begin with flu-like symptoms[3]. However, unlike patients with other common infectious diseases, patients with COVID-19 have a wide range of clinical manifestations, including complex and mixed lung conditions and multi-organ failure that can lead to death.

Recent evidence suggests that malnutrition is a critical prognostic factor in many diseases, including autoimmune conditions[4], cardiovascular diseases[5], lung diseases[6], and malignancy[7]. A high degree of malnutrition is associated with high levels of inflammation[8]. Assessment of systemic immune nutritional status has been refined by adding the prognostic nutritional index (PNI) is a continuous variable based on serum albumin concentration and total lymphocyte count in peripheral blood[9]. PNI has been reported to be associated with poor survival and postoperative complications in patients with various conditions, but there are only limited reports regarding its role in Covid-19 course.

The aim of present study was to observe the association between PNI and length of hospital stay, necessity of intensive care unit admission, and mortality in patients with COVID-19.

Materials and Methods

Study Population

The patients with Covid-19 whom presented to outpatient or inpatient clinics of Abant Izzet Baysal University Hospital between March 2020 and October 2021 were enrolled to present cross sectional retrospective analysis after study protocol was approved by local ethics committee (date: 9th of November, 2021; decision no: 2021/266). All subjects have a positive RT- PCR throat swab result for covid-19. The patients with negative RT-PCR throat swab for Covid-19 were excluded from the study even if the clinical and radiological diagnosis of Covid-19 has been established. Indications for hospitalization of Covid-19 patients were as follows: dyspnea, reduced oxygen saturation (lower than

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92%), pulmonary involvement in chest radiology and severe symptoms in elderly with accompanied chronic conditions (i.e. congestive heart failure, diabetes mellitus, hypertension or chronic obstructive pulmonary disease). Patients under 18 years of age were also excluded. Flow chart summarizes the inclusion and exclusion criteria.

Age, gender, hospitalization duration, prognosis (deceased or survived), necessity of intensive care, laboratory parameters (albumin, c reactive protein [CRP], lactate dehydrogenase [LDH], D-Dimer, Ferritin, white blood cell count [WBC], lymphocyte count [LYM]) were recorded after obtaining from institutional database and patients' files. PNI was calculated with the following formula: (10×serum albumin [g/dL])+(0.005×lymphocytes/µL). Patients whom were hospitalized were grouped as inpatients and patients treated by usual homecare were grouped as outpatients. Data of the inpatients and outpatients were compared. We also compared the data of the subjects who survived and deceased. Patients were followed up for up to 30 days for survival analysis, if they discharged from hospital before 30 day.

Statistical Analyses

IBM SPSS 16.0 software was used for statistical evaluation of the data. Compliance with the normal distribution was examined by the Kolmogorov-Smirnov test. Independent Sample t test for comparing two independent groups by comparing the arithmetic mean of the groups with normal distribution; One-Way ANOVA test for comparison of more than two independent groups; The Mann-Whitney U test was used to compare two independent groups by comparing the medians of the groups that did not show normal distribution, and the Kruskal-Wallis test was used to compare more than two independent groups. The relationship between categorical variables was compared with chi-square test. Survival results were obtained by Kaplan-Meier method, log-rank test was used in univariate analyzes and cox regression method was used in multivariate analyses. A $p<0.05$ was considered significant.

Results

Study population was consisted of 4419 subjects; 2907 in outpatient group and 1512 patients in inpatient group. 2429 (55%) of the study population were female and 1990 (45%) were male. Mean age of the study population was 48.2±23 years. PNI of the inpatient (41.55 (36.42-47.1)) group was significantly lower than the PNI of the outpatient (51.95 (47.95-55.75)) subjects ($p<0.001$). Table 1 summarizes the characteristics of outpatients and inpatients. The sensitivity and specificity of PNI (≤46.2 level) in determination of requirement inpatient treatment were 71.2% and 83.5%, respectively (AUC: 0.837, $p<0.001$, 95% CI: 0.825-0.847). Table 2 shows the ROC analysis data of the study variables in determining requirement inpatient treatment. Serum albumin and PNI were best variables in determining inpatient treatment in Covid-19 subjects (figure 2).

The data and characteristics of the survived and deceased patients were also compared. Deceased (n=538) subjects were significantly older than survived (n=3881) subjects (75 (66-82) years versus 44 (29-61) years; $p<0.001$). PNI of the deceased patients (37(33.39-40.86)) was lower than the PNI of the survivors (50.45(45.6-54.65)). The difference was statistically significant ($p<0.001$). Table 3 summarizes the characteristics and laboratory data of the survived and deceased subjects. The sensitivity and specificity of PNI at ≤44.55 level in determining mortality were 89.22% and 78.87%, respectively (AUC: 0.902, $p<0.001$, 95%CI: 0.893-0.910). Table 4 shows the ROC analysis data of the study variables in determining mortality. Figure 3 shows the ROC curves of study variables in predicting mortality. Univariate and multivariate analyses of the study variables in determining survival were summarized in table 5. Figure 4 shows Kaplan-Meier survival curves the study variables in determining overall survival in patients with Covid-19. Finally, inpatients sub-grouped into two according to mortality as deceased and survived. PNI of deceased and survived inpatients were 37(33.39-40.81) and 44.5(39.65-49.31), respectively ($p<0.001$). Table 6 shows data of the deceased and survived subgroups of inpatient subjects.

Of those inpatient subjects PNI (at ≤41.75 level) had 80.71% sensitivity and 64.83% specificity in predicting mortality (AUC: 0.779, $p<0.001$, 95%CI: 758 to 0.8). Table 7 shows

Table 1. Data of the inpatients and outpatients

	Outpatient (n=2907)	Inpatient (n=1512)	p value
Age; years	40(26-55)	67(54-78)	<0.001
Female Gender; n (%)	1708 (58.8%)	721 (47.7%)	<0.001
Needs For ICU; n (%)		830 (54.9%)	
Total hospitalization, days		11(6-21)	
Mortalite; n(%)	4(0.1%)	534(35.3%)	<0.001
CRP; mg/L	5.2(0.6-15.3)	47.4(11.2-110.78)	<0.001
Albumin; g/L	44(41.2-46.3)	35.9(31.6-40.5)	<0.001
LDH; U/L	246(205-311)	310(234-415)	<0.001
D-Dimer,; µg/mL	0.37(0.23-0.68)	0.63(0.32-1.39)	<0.001
Ferritin; µg/L	53.46(22.78-120.15)	187.7(75.11-462.88)	<0.001
WBC; 10^9/L	5.92(4.73-7.51)	6.4(4.89-8.55)	<0.001
LYM; 10^9/L	1.5(1.07-2.08)	1.07(0.7-1.5)	<0.001
PNI	51.95 (47.95-55.75)	41.55 (36.42-47.1)	<0.001

Values were given as the median (1st-3rd quartile), and significance was evaluated with the Mann Whitney-U test. The gender variable was shown as n(%) and compared with the Pearson chi square test. CRP: C-reactive protein, WBC: white blood count, LYM: lymphocyte, PNI: prognostic nutritional index, ICU: Intensive care unit

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Table 2: Receiver operating characteristic (ROC) curve analysis to distinguish between hospitalized and non-hospitalized patients in COVID-19 patients by the markers studied

	AUC (95% CI)	Cut-off	Sensitivity (95% CI)	Specificity (95% CI)	+LR	-LR	Accuracy	p
CRP; mg/L	0.790 (0.777- 0.802)	>18.2	66.7 (64.3-69.1)	78.7 (77.1 - 80.1)	3.1	0.42	74.6	<0.001
Albumin; g/L	0.848 (0.837-0.858)	≤40.1	74.2 (71.9-76.4)	82.2 (80.7- 83.5)	4.16	0.31	79.4	<0.001
LDH, U/L	0.662 (0.648-0.676)	>308	50.7 (48.2-53.3)	74.5(72.6-75.9)	1.97	0.66	66.4	<0.001
D-Dimer, μg/mL	0.637 (0.623-0.651)	>0.76	43.7 (41.1-46.2)	79.8 (78.3-81.3)	2.16	0.71	67.4	<0.001
Ferritin; μg/L	0.750 (0.737-0.762)	>114.5	64.2 (61.7-66.6)	73.7 (72.1-75.3)	2.44	0.49	70.5	<0.001
WBC, 10^9/L	0.563 (0.548-0.577)	>9.38	20.4 (18.4-22.5)	92.1 (91.0-93.0)	2.56	0.87	67.5	<0.001
LYM, 10^9/L	0.680 (0.666-0.694)	≤1.1	54.6 (52.0-57.1)	73.2 (71.5-74.8)	2.03	0.62	66.8	<0.001
PNI	0.837 (0.825-0.847)	≤46.2	71.2 (68.9-73.5)	83.5 (82.1-84.8)	4.31	0.34	79.3	<0.001

AUC: area under curve, 95% CI: 95% confidence intervals, +LR: positive likelihood ratio, -LR: negative likelihood ratio, CRP: C-reactive protein, WBC: white blood count, LYM: lymphocyte, PNI: prognostic nutritional index

Table 3: Comparison of study variables in deceased and survived patients

	survived (n=3881)	deceased (n=538)	P value
Age; years	44 (29-61)	75 (66-82)	<0.001
Female Gender; n (%)	2197 (56.6%)	232 (43.1%)	<0.001
Needs For ICU; n (%)	311 (8.0%)	519 (96.5%)	<0.001
Day of admitted to ICU	0(0-0)	4(1-9)	<0.001
Needs for ICU, days	0(0-0)	9(4-17)	<0.001
Total hospitalization, days	0(0-1)	16(9-25)	<0.001
CRP; mg/L	7.6(1.2-26.25)	84.76(24.8-126.06)	<0.001
Albumin; g/L	43(39.3-45.7)	32.35(28.9-35.61)	<0.001
LDH, U/L	253(209-327)	359.5(262.75-505.25)	<0.001
D-Dimer, μg/mL	0.4(0.24-0.76)	0.86(0.42-1.77)	<0.001
Ferritin; μg/L	67.68(27.04-161.89)	293.22(119.97-736.85)	<0.001
WBC, 10^9/L	5.98(4.73-7.6)	7.1(5.21-9.94)	<0.001
LYM, 10^9/L	1.42(1-1.99)	0.86(0.58-1.2)	<0.001
PNI	50.45(45.6-54.65)	37(33.39-40.86)	<0.001

Values were given as the median (1st-3rd quartile), and significance was evaluated with the Mann Whitney-U test. The gender variable was shown as n(%) and compared with the Pearson chi square test. CRP: C-reactive protein, WBC: white blood count, LYM: lymphocyte, PNI: prognostic nutritional index, ICU: Intensive care unit

Table 4: Receiver operating characteristic (ROC) curve analysis to distinguish between patients with and without mortality in all COVID-19 patients with the markers studied.

	AUC (95% CI)	Cut-off	Sensitivity (95% CI)	Specificity (95% CI)	+LR	-LR	Accuracy	p value
CRP; mg/L	0.824 (0.812 to 0.835)	>40.4	70.45 (66.4 - 74.3)	81.22 (80.0 - 82.4)	3.75	0.36	79.9	<0.001
Albumin; g/L	0.904 (0.895 to 0.912)	≤38.8	90.71 (87.9 - 93.0)	77.38 (76.0 - 78.7)	4.01	0.12	79.0	<0.001
LDH, U/L	0.714 (0.700 to 0.727)	>314	62.45 (58.2 - 66.6))	71.45 (70.0 - 72.9)	2.19	0.53	70.4	<0.001
D-Dimer, μg/mL	0.683 (0.669 to 0.697)	>0.76	54.83 (50.5 - 59.1)	75.47 (74.1 - 76.8)	2.24	0.60	73.0	<0.001
Ferritin; μg/L	0.781 (0.768 to 0.793)	>155.06	69.89 (65.8 - 73.7)	74.21 (72.8 - 75.6)	2.71	0.41	73.7	<0.001
WBC, 10^9/L	0.615 (0.601 to 0.630)	>8.69	34.76 (30.7 - 39.0)	85.85 (84.7 - 86.9)	2.46	0.76	79.6	<0.001
LYM, 10^9/L	0.752 (0.739 to 0.765)	≤1.1	71.93 (67.9 - 75.7)	68.62 (67.1 - 70.1)	2.29	0.41	69.0	<0.001
PNI	0.902 (0.893 to 0.910)	≤44.55	89.22 (86.3 - 91.7)	78.87 (77.6 - 80.1)	4.22	0.14	80.1	<0.001

AUC: area under curve, 95% CI: 95% confidence intervals, +LR: positive likelihood ratio, -LR: negative likelihood ratio, CRP: C-reactive protein, WBC: white blood count, LYM: lymphocyte, PNI: prognostic nutritional index

Table 5: Univariate and Multivariate Cox proportional hazard model for survival

Variable	Univariate analysis		Multivariate analysis	
	HR (95%)	P value	HR (95%)	P value
Age, years	1.064 (1.058-1.070)	<0.001	1.03 (1.03-1.04)	<0.001
Female Gender	0.60 (0.50-0.71)	<0.001	0.84 (0.71-1)	0.055
CRP, >40.4 vs ≤40.4	6.87 (5.68-8.30)	<0.001	1.16 (0.92-1.46)	0.205
Albumin; ≤38.8 vs >38.8	20.93 (15.60-28.08)	<0.001	3.61 (2.36-5.52)	<0.001
LDH, >314 vs ≤314	3.35 (2.81-3.99)	<0.001	1.24 (1.01-1.51)	0.037
D-Dimer, >0.76 vs ≤0.76	2.93 (2.46-3.48)	<0.001	0.99 (0.82-1.19)	0.908
Ferritin; >155.06 vs ≤155.06	4.91 (4.08-5.92)	<0.001	1.43 (1.16-1.75)	0.001
WBC, >8.69 vs ≤8.69	2.59 (2.17-3.10)	<0.001	1.61 (1.33-1.95)	<0.001
LYM, ≤1.1 vs >1.1	4.04 (3.34-4.90)	<0.001	1.42 (1.15-1.76)	0.001
PNI, ≤44.55 vs >44.55	19.05 (14.46-25.10)	<0.001	2.23 (1.47-3.38)	<0.001

HR: Hazard ratio, 95% CI: 95% confidence intervals, CRP: C-reactive protein, WBC: white blood count, LYM: lymphocyte, PNI: prognostic nutritional index

Table 6: Comparison of the data of deceased and survived inpatients

	Survived (n=978)	Deceased (n=534)	P value
Age; years	61(46-73)	75(66-82)	<0.001
Female Gender; n (%)	491 (50.2%)	230 (43.1%)	<0.001
Needs For ICU; n (%)	311 (31.8%)	519(97.2%)	<0.001
Day of admitted to ICU	0(0-0)	4(1-9)	<0.001
Needs for ICU, days	0(0-3)	9(4-17)	<0.001
Total hospitalization, days	9(4-16)	16(10-25)	<0.001
CRP; mg/L	29.78(7.2-92.34)	84.76(24.95-125.93)	<0.001
Albumin; g/L	38(34-42)	32.3(28.9-35.6)	<0.001
LDH, U/L	287(226-377)	358(262.75-505.25)	<0.001
D-Dimer, µg/mL	0.55(0.28-1.12)	0.86(0.41-1.77)	<0.001
Ferritin; µg/L	144.25(58.63-337.61)	294.55(121.5-736.85)	<0.001
WBC, 10^9/L	6.15(4.75-7.82)	7.1(5.22-9.94)	<0.001
LYM, 10^9/L	1.2(0.83-1.69)	0.87(0.58-1.2)	<0.001
PNI	44.5(39.65-49.31)	37(33.39-40.81)	<0.001

Values were given as the median (1st-3rd quartile), and significance was evaluated with the Mann Whitney-U test. The gender variable was shown as n(%) and compared with the Pearson chi square test. CRP: C-reactive protein, WBC: white blood count, LYM: lymphocyte, PNI: prognostic nutritional index, ICU: Intensive care unit

Table 7: Receiver operating characteristic (ROC) curve analysis to distinguish between patients with and without mortality in hospitalized COVID-19 patients with the markers studied

	AUC (95% CI)	Cut-off	Sensitivity (95% CI)	Specificity (95% CI)	+LR	-LR	Accuracy	p value
CRP; mg/L	0.666 (0.641 to 0.689)	>40.7	70.41 (66.3 - 74.3)	56.54 (53.4 - 59.7)	1.62	0.52	61.4	<0.001
Albumin; g/L	0.766 (0.744 to 0.787)	≤35.64	75.47 (71.6 - 79.1)	65.34 (62.3 - 68.3)	2.18	0.38	68.9	<0.001
LDH, U/L	0.635 (0.610 to 0.659)	>392	43.63 (39.4 - 48.0)	78.43 (75.7 - 81.0)	2.02	0.72	66.1	<0.001
D-Dimer, µg/mL	0.607 (0.582 to 0.632)	>0.8	53.00 (48.7 - 57.3)	64.83 (61.7 - 67.8)	1.51	0.73	60.7	<0.001
Ferritin; µg/L	0.652 (0.628 to 0.676)	>237.82	57.30 (53.0 - 61.5)	65.75 (62.7 - 68.7)	1.67	0.65	62.8	<0.001
WBC, 10^9/L	0.592 (0.567 to 0.617)	>7.79	42.13 (37.9 - 46.5)	74.54 (71.7 - 77.2)	1.65	0.78	63.1	<0.001
LYM, 10^9/L	0.671 (0.647 to 0.695)	≤1.1	71.72 (67.7 - 75.5)	54.81 (51.6 - 58.0)	1.59	0.52	60.8	<0.001
PNI	0.779 (0.758 to 0.800)	≤41.75	80.71 (77.1 - 84.0)	64.83 (61.7 - 67.8)	2.29	0.30	70.4	<0.001

AUC: area under curve, 95% CI: 95% confidence intervals, +LR: positive likelihood ratio, -LR: negative likelihood ratio, CRP: C-reactive protein, WBC: white blood count, LYM: lymphocyte, PNI: prognostic nutritional index

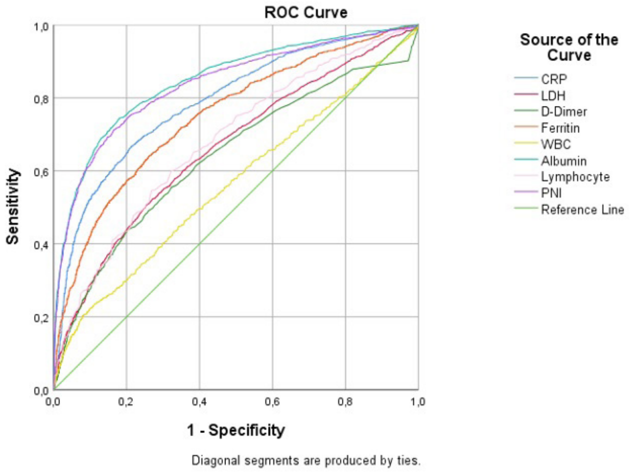

Figure 1: Serum albumin and PNI inpatient treatment in Covid-19 subjects

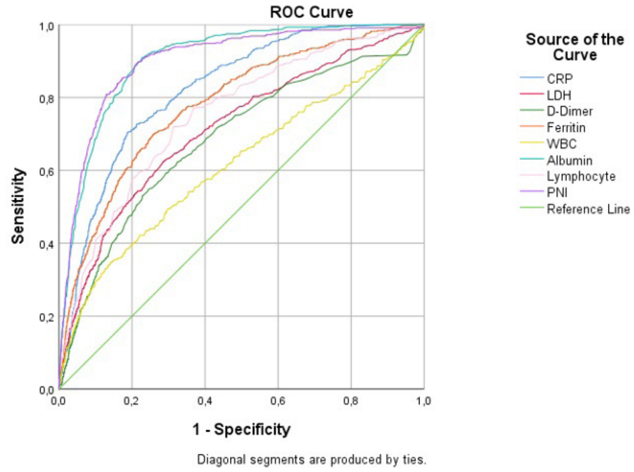

Figure 2 shows the ROC curves of study variables in predicting mortality

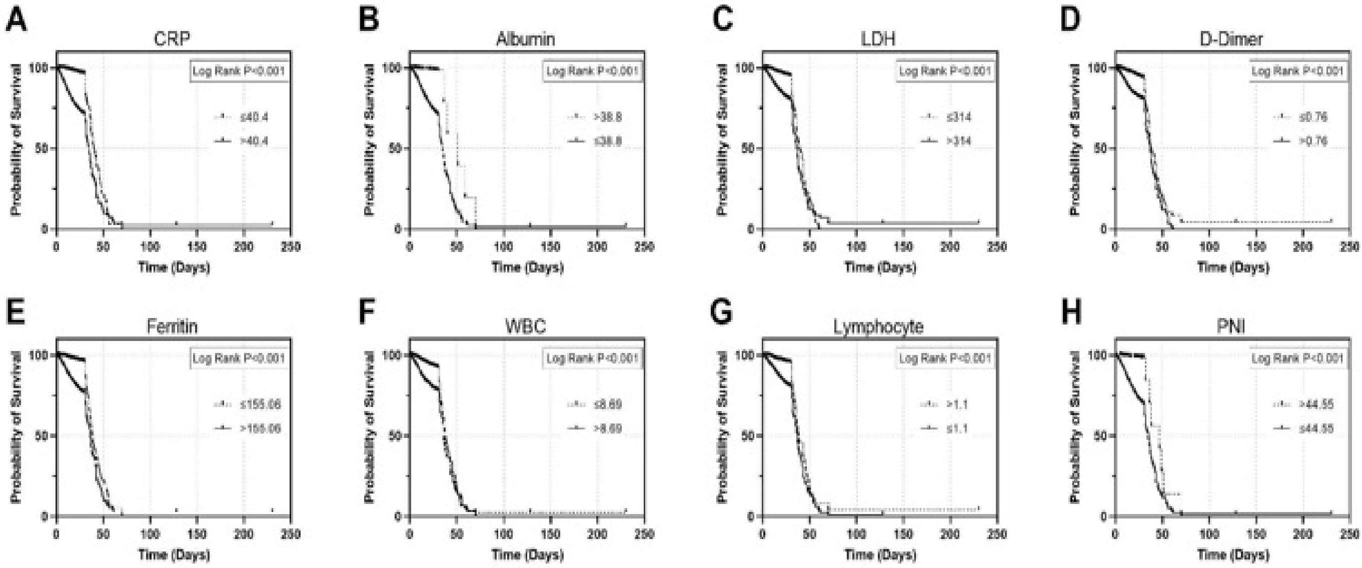

Figure 3: Kaplan-Meier survival curves the study variables in determining overall survival

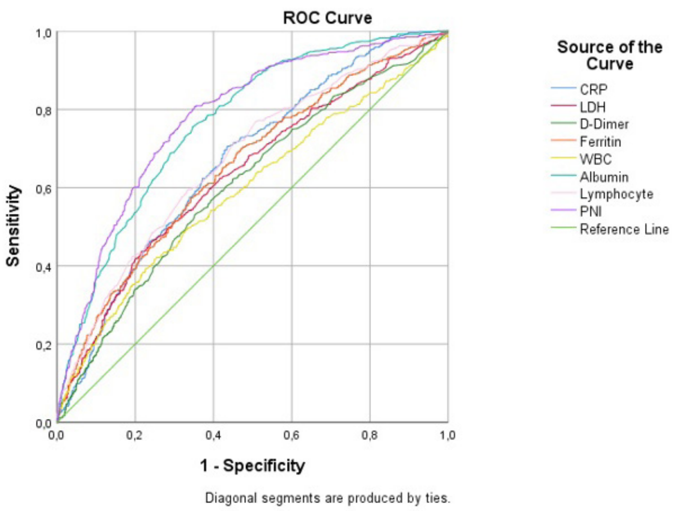

Figure 4: ROC curves study variables in predicting mortality in inpatients

ROC analysis data of the study variables in determining mortality in inpatients. Figure 5 shows the ROC curves study variables in predicting mortality in inpatients

Discussion

The results of present study confirmed that PNI was a useful marker of inpatient treatment requirement and mortality in Covid-19 population. Moreover, PNI was also useful in predicting mortality in Covid-19 patients whom required treatment in hospital.

Calculation of PNI is dependent to two variables, serum albumin and blood lymphocyte count. Serum albumin is a negative acute phase marker meaning its serum level is reduced during inflammatory conditions[10,11]. On the other hand, reduced lymphocyte count has been found to be associated with poor prognosis in several conditions[12-14]. Thus, serum albumin and blood lymphocyte count together pose a better predictor of outcome in inflammatory conditions. Accordingly, we reported reduced PNI in subjects required treatment as inpatients compared to outpatients and in deceased patients compared to the survivors. These data suggest that PNI could be a reliable marker of prognosis in Covid-19.

The prognostic role of PNI has been well established in medical literature. Authors studied the role of PNI in patients received gastrointestinal surgery and reported that PNI was useful in estimation of the risk of surgery and in estimation of the subjects that require preoperative nutritional support[15]. Nozoe et al. investigated the efficacy of PNI in determination of the prognosis in subjects with colorectal carcinoma and claimed that preoperative PNI could be a reliable predictor of patient outcome in these subjects[16]. In addition, authors introduced PNI as a marker of poor overall survival in subjects with hepatocellular carcinoma[17]. These studies were followed by another study which reported PNI was a useful indicator of prognosis in breast cancer patients[18]. Subsequently, Okada et al.'s study showed that PNI was a useful predictor of postoperative complications and mortality in patients with non-small cell lung cancer[19]. PNI was also suggested as a novel prognostic index in subjects with malignant mesothelioma[20]. In a recent meta-analysis, PNI has been suggested as an effective indicator of outcome in patients with malignant conditions, especially gastrointestinal cancers[21]. Cancer is associated with continuous, low grade inflammatory burden as Covid-19 infection do. In accordance with the literature knowledge, in present study, we reported reduced PNI levels in inpatients compared to outpatients, in deceased compared to survived subjects and in deceased inpatients compared to survived inpatient subjects.

Not only malignant diseases but also other chronic conditions were associated with PNI. Authors suggested that PNI was a prognostic predictor in patients with cirrhosis[22]. Cheng et al. studied the association between PNI and survival in patients hospitalized for acute heart failure and found that PNI was an independent predictor of long term survival in this population[23]. Furthermore, PNI was associated with long-term cardiovascular outcomes in patients with stable coronary arterial disease[24]. Recently, authors studied PNI in subjects with aortic dissection and found that reduced PNI was associated with increased mortality[25]. Moreover, decreased levels of PNI has been found to be associated with development of contrast agent associated acute kidney injury in patients with acute myocardial infarction[26]. Cirrhosis, heart failure, aortic dissection and coronary artery disease are associated with some level of inflammation. Therefore, similar association between prognosis and PNI reported in present work is a result which consistent with literature data. Retrospective design, which make impossible to control other variables, is a limitation of our study. Single center nature is another limitation of present work. However, this is the first study in literature that reported decreased PNI in deceased Covid-19 subjects compared to survived patients.

Conclusion

We suggest that PNI could serve as a reliable prognostic index in covid-19 patients. Reduced level of PNI should alert physicians since it is associated with need for hospitalization and mortality in this population.

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Declaration of financial/other relationships

The authors have no conflicts of interest.

Ethical Approval

This study was approved by ethics committee of Abant Izzet Baysal University (date: 9th of November, 2021; decision no: 2021/266).

Availability of data and materials

Data are available by corresponding author upon reasonable requests

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