Research Article

Effects of Neutrophil/Monocyte, Neutrophil/Lymphocyte, Neutrophil/Platelet Ratios and C-Reactive Protein Levels on the Mortality and Intensive Care Need of the Patients Diagnosed with Covid-19

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Abstract

Objectives: The Covid-19 has been spreading rapidly worldwide. We investigated the effects of some laboratory parameters of patients diagnosed with Covid-19 on admission to the intensive care unit and mortality rate. We aim to be a reference to other countries with demonstrating the effect of laboratory parameters to prognosis and mortality as a center from Turkey.

Methods: One hundred sixty patients diagnosed with Covid-19 that confirmed with PCR test included the study. The neutrophil/lymphocyte, neutrophil/monocyte neutrophil/platelet ratios, and C-reactive protein levels were evaluated. Patients were divided into 2 groups; who admitted to intensive care unit and who were treated in Covid-19 inpatient clinic without intensive care need. The groups were statistically compared. Mortality rates were examined to determine a cut-off value for each parameters.

Results: These parameters and C-reactive protein levels of the Covid-19 patients were found to be statistically significant in both admission to the intensive care and mortality. The upper limits of these determined cut-off values are predicted to be critical for admission to intensive care. The cut-off values for NLR, NMR, NPR and CRP for mortality rate were 9.5, 3.7, 0.022, 79.2. Among these parameters, it was seen that the best determinant for mortality rate was CRP (cut-off=79.2).

Conclusion: It was observed that NLR, NMR, NPR and CRP values were significant in determining the need for intensive care unit and mortality rate in patients diagnosed with Covid-19.

Keywords: Covid-19, intensive care unit and mortality rate, neutrophil/lymphocyte ratio (NLR), neutrophil/monocyte ratio (NMR), neutrophil/platelet ratio (NPR)

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A new type of coronavirus named SARS-CoV-2, firstly appeared in the city Wuhan of China, today the number of infected patients has reached above ten millions, and active patient numbers draw near one million. Considering that there is no universal consensus in treating this pandemic disease and that there is no effective drug, it is predicted that the factors affecting the prognosis of the disease will be critical. Especially in Covid-19 patients who received conventional treatment but transferred to intensive care units after a while, the need for ventilation arise due to acute respiratory disease (ARDS), and a significant portion of these patients die.[1–3] Determination of critical

patients in the early period can provide early intervention, so that the resources can be used more accurately by determining the need for intensive care and ventilation.[4,5]

Neutrophile/lymphocyte ratio (NLR) is a calculation commonly known as the biomarker of inflammation and used in routine hematology practice.[6–9] High values of NLR and platelet/lymphocyte ratio, have been shown to predict mortality and correlate with C-reactive protein (CRP), particularly in intensive care patients.[10] In a study conducted by Demir et al.,[11] the CRP and NLR levels of geriatric patients admitted to the intensive care unit were significantly higher in fatal cases. This can be interpreted as NLR, and CRP parameters can be used to predict mortality. In patients diagnosed with Covid-19, the duration of hospitalization, mortality rates, CRP, blood urea nitrogen, lactate dehydrogenase, and NLR levels were higher, especially in elders and clinical outcomes were observed to be more harmful in males.[12,13] Although the high rates of NLR are considered as a symptom of clinical deterioration and mortality, it is unknown whether the NLR has an importance on transportation to intensive care unit and mortality or not. Studies comparing the lymphocyte/monocyte ratio with platelet/lymphocyte ratio as well as NLR have been conducted before, and only the NLR was found to be significant.[14,15]

However, in our study, we studied the neutrophil/monocyte and neutrophil/platelet ratios in addition to the NLR. Furthermore determining these new cut-off values in Covid-19 cases may play a role for determining intensive care unit need and mortality rate.

Methods

Patients

This study was approved by the Bozyaka Hospital local ethics committee and written informed consent was obtained from recruited subjects. Between March 2020 and May 2020, a single-center case-cohort of one hundred sixty patients with laboratory-confirmed Covid-19 pneumonia was hospitalized to the University of Health Science Izmir Bozyaka Training and Research Hospital; these patients were all included in the present study. The probable and definite diagnosis of Covid-19 pneumonia was established according to the case definition established by the World Health Organization interim guidance.[16] Cases were diagnosed based on the World Health Organization (WHO) guidance and the diagnosis and treatment guidelines of Covid-19 in Turkey.[17] Patients met all following conditions: (1) Epidemiology history, (2) Fever or other respiratory symptoms, (3) Typical CT image abnormities of viral pneumonia, and (4) Positive result of RT-PCR for SARS-CoV-2 RNA. Sputum and throat swab specimens were col-

lected from all patients upon admission and tested by real-time polymerase chain reaction (RT-PCR) for SARS-CoV-2 RNA within three hours.

Clinical Characteristics and Laboratory Data

Epidemiological characteristics, including recent exposure history, clinical symptoms and signs, and laboratory findings, were obtained from electronic medical records. Laboratory assessments consisted of a complete blood count. The severity of Covid-19 was defined based on international guidelines for community-acquired pneumonia. The endpoint of the study was cure and discharge, or mortality within 28 days.

The study was approved by the University of Health Science Izmir Bozyaka Training and Research Hospital Ethics Commission (21.05.2020-222)

Statistical Analysis

Descriptive statistics included frequency analysis (percentages) for categorical variables and mean±SD or median and interquartile range for continuous variables. Comparisons were determined by t-test or Mann–Whitney U-test for continuous variables, as appropriate, and by the use of the Chi-squared test or Fisher exact test for categorical variables. Univariate and multivariate logistic regression was performed to explore the association of clinical characteristics and laboratory parameters and mortality.

The optimal cut-off values of the continuous NLR, neutrophil/monocyte (NMR), and neutrophil/platelet ratios (NPR), and CRP were calculated by applying the receiver operating curve (ROC) analysis.[15] Hazard risk (HR) and 95% confidence interval (CI) were used as common measures to assess relative risk. Enter elimination binary logistic regression analysis was conducted to determine the influence of age, gender, and all other significant factors. $P < 0.05$ was recognized as statistically significant. All these statistical calculations were performed using the SPSS 21.0 software (SPSS Inc, Chicago, USA).

Results

A total of 160 Covid-19 positive cases treated in in patient clinics and İCU (79 men, 81 women) included in the study. The mean age of the patients is 56.1±17.7. The average time of hospitalisation period was 8.4±8.1 days. The average time that the PCR test was made is 1.3±0.7 days. There is no statistically significant difference stated between men and women patients in terms of hospitalization duration and patients' ages. PCR tests were made almost the same days between genders and no statistically significant difference was stated (Table 1).

The cases included in the study were divided into two groups. First group was consisted of the patients who were admitted to intensive care unit, the other group was consisted of the patients who treated in inpatients clinics. While 125 patients were treated in inpatient clinics, 35 patients were treated in intensive care unit. Hemogram parameters and CRP values were compared between both groups. It was determined that NMR, NLR, NPL, CRP values are statistically significantly higher in patients who admitted to the intensive care unit and diagnosed with Covid-19 (Table 2).

When the parameters that will support and determine the inclusion criteria of patients diagnosed with COVID-19 are evaluated, CRP (cut-off=19.7 units) measurement stands out with its statistically significant and more precise expression power (AUC=0.882) than other hemogram rates

(Table 3). It is predicted that the upper limits of these determined cut-off values will be a critical value for admission to intensive care.

Hemogram rates and CRP evaluations at the admission and discharge time of the patients diagnosed with COVİD-19 compared (Table 4). Every parameter is found to be statistically significantly different from admission and discharge time from the hospital.

The cut-off values, sensitivity and specificity values of the hemogram rates and the CRP evaluated during discharge-ex and the parameters that may be an indicator due to ex status, were determined by ROC analysis. Besides, significance and values under the curve (AUC) are shown on the Table 5. Among these parameters best determining one is CRP (cut-off=79.2 mg/L).

Table 1. General condition of the COVID-19 patients

Parameters	General (n=160)				Man (n=79)				Woman (n=81)				
	Min	Max	Median	Mean±SD	Min	Max	Median	Mean±SD	Min	Max	Median	Mean±SD	p*
Age	18	96	55	56.1±17.7	19	92	53	54.7±17.6	18	96	56	57.1±19.6	0.330
Duration of hospitalization	0	44	6	8.4±8.1	0	40	5	7.7±7.7	0	44	7	9.0±8.5	0.198
How many days was PCR performed?	1	8	1	1.3±0.7	1	8	1	1.4±1.0	1	3	1	1.2±0.4	0.207

*Compare of between man and woman, p<0.05 was considered significant. Mann-Whitney U test were used.

Table 2. Comparison of parameters of the patients inpatient clinic and ICU.

Parameters	Inpatient clinics (n=125)		ICU (n=35)		
	Mean±SD	Median (IQR) Min-Max	Mean±SD	Median (IQR) Min-Max	p
NEU/MON Ratio	7.0±4.6	6.0 (3.0) 0.2-32.3	19.8±16.9	15.5 (24.8) 0.3-75.2	<0.001
NEU/LYM Ratio	2.7±4.2	1.9 (1.7) 0.1-38.1	19.9±50.4	7.7 (12.6) 0.1-290.7	<0.001
NEU/PLT Ratio	0.015±0.01	0.013 (0.006) 0.001-0.074	0.053±0.09	0.032 (0.04) 0.004-0.55	<0.001
CRP	18.5±33.5	6.8 (14.0) 0-221	187.3±171.0	160.0 (197.0) 2-723	<0.001

p<0.05 was considered significant. Mann-Whitney U test was used. ICU: Intensive care unit; NEU: Nutrophil; MON: Monocyt; LYM: Lymphocyt; PLT: Platelet; CRP: C-reactive protein.

Table 3. The parameters during transition to intensive care unit

Parameters	Cut-off Value	AUC	p	CI (min-max)		Sensitivity (%)	Specificity (%)
NEU/MON Ratio	8.9	0.777	<0.001	0.664	0.891	73.5	82.4
NEU/LYM Ratio	2.9	0.787	<0.001	0.680	0.895	73.5	76.0
NEU/PLT Ratio	0.018	0.796	<0.001	0.695	0.896	70.6	79.2
CRP	19.70	0.882	<0.001	0.809	0.954	82.4	79.2

AUC: Area under curve, CI: Confidence interval (95%), NEU: Nutrophil; MON: Monocyt; LYM: Lymphocyt; PLT: Platelet; CRP: C-reactive protein; p<0.05 was considered significant.

Table 4. Compare of parameters between entrance and discharge Covid-19 patients

Parameters	Entrance		Exit		
	Mean±SD	Median (IQR) Min-Max	Mean±SD	Median (IQR) Min-Max	p*
NEU/MON	10.9±12.5	7.3 (6.8) 0.4-99.2	9.8±10.2	6.7 (4.9) 0.2-75.2	0.001
NEU/LYM	4.9±7.6	2.7 (3.3) 0.3-75.0	6.4±24.4	2.0 (2.2) 0.1-290.7	0.020
NEU/PLT	0.027±0.04	0.02 (0.02) 0.002-0.36	0.023±0.05	0.014 (0.011) 0.001-0.6	<0.0001
CRP	276.7±508.9	111.0 (201.0) 1.0-3685.0	55.4±109.7	10.0 (45.0) 0.0-723.0	<0.0001

*Wilcoxon Sign Rank test was used. p<0.05 was considered significant. NEU: Nutrophil; MON: Monocyt; LYM: Lymphocyt; PLT: Platelet; CRP: C-reactive protein.

Table 5. Compare of parameters during exit (mortality) for hospitalization.

| Parameters	Cut-off Value	AUC	p	CI [min-max]		Sensitivity (%)	Specificity (%)
NEU/MON Ratio	9.5	0.845	<0.001	0.720	0.970	87.5	83.7
NEU/LYM Ratio	3.7	0.854	<0.001	0.736	0.972	83.3	87.4
NEU/PLT Ratio	0.022	0.890	<0.001	0.795	0.984	87.5	87.4
CRP (mg/L)	79.2	0.953	<0.001	0.916	0.990	87.5	93.3

AUC: Area under curve; CI: Confidence interval (95%); Nutrophil; MON: Monocyt; LYM: Lymphocyt; PLT: Platelet; CRP: C-reactive protein; p<0.05 was considered significant.

The ratio of neutrophil monocyte, neutrophil lymphocyte, neutrophil platelet and CRP values were shown in Figure 1 by ROC analysis while the patients were transferred to intensive care. In Figure 2, the differences in the same parameters were shown by ROC analysis while being followed in the normal clinic.

Discussion

Covid-19 infection has caused a rapidly progressing viral pandemic that spreads from human to human. While the number of cases is increasing rapidly, the total case number has reached above 10 million while death rates reached a million. In this study, the effects of NLR, NMR, NPR, and CRP values on the patients' transmission to the intensive care unit and the mortality rates are determined. As known, the reason for the vast majority of the cases taken into intensive care is respiratory insufficiency. Respiratory support with ventilators are used forhelping some of the patients in intensive care unit and the majority of them die. Early diagnosis, early treatment may be a live saving issue. Considering the cut-off values of laboratory tests for both intensive care unit need and mortality rates will help clinicians for early treatment. NLR rates cut-off value of admitting to the intensive care was 2.9 while the mortal-
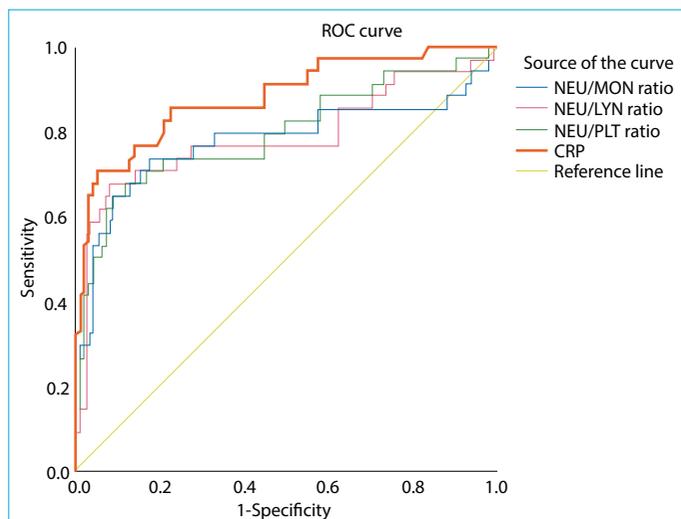
Figure 1. ROC analysis during transition to intensive care.
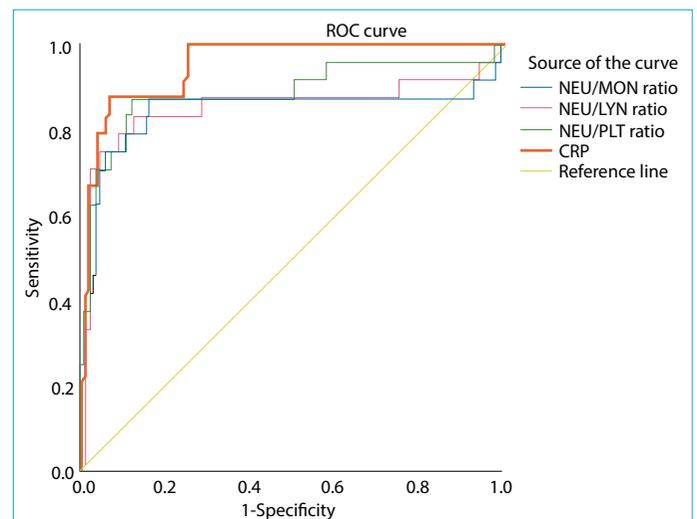
Figure 2. ROC analysis for blood cell ratio and CRP parameters.

ity cut-off value was 3.7. İn previous studies treatability of cases has been suggested with cut off point 3.3.[18,19] In addition to NLR, NMR and NPR values found to be significant in this study. The NMR ratio found to be 8.9 in patients who needed intensive care, and 9.5 in patients that died. This result has not been observed in other studies. It was also determined that although the NPR value has found 0.018 in patients who will be admitted to the intensive careunitlater, it found 0.022 in patients that die and this value has not found in other studies.

CRP is a non-specific acute phase protein sysnthesis induced by IL-6. It is a sensitive indicator that reflects inflammation, infection and tissue damage. CRP level rises rapidly in acute inflammatory conditions. In a study evaluating patients with Covid-19, a CRP above 41.8 mg/L was accepted as the possibility of developing severe disease.[20] In our study, the cut off value of CRP was found to be 19.70 in patients followed up in the intensive care unit and 79.2 in exitus patients. Wang L and et al.[21] stated that pulmonary involvement and CRP values increased in parallel. They found that the CRP value was 1.52±1.56 in cases with mild lung involvement, 16.76±18.38 in the middle group, 54.15±1.06 in the severe group and 105.00±12.73 in critical cases. In another study, it is claimed that the average CRP value was 40 mg/L in survivor cases and 125 mg/L in exitus cases.[22] Shang W and et al.[23] reported that average CRP value 43.15 (9.78-97.27) in severe cases and 10.05 (2.92-27.11) in mild Covid -19 cases.

In conclusion; this study shows that, if the NLR, NMR, NPR, and CRP values that are determined above certain cut-off values in these patients may precede the intensive care need and mortality, the prognosis is usually not good and considering high risk of mortality, these values are significant in terms of planning the necessary treatment.

Disclosures

Ethics Committee Approval: The study protocol was approved by University of Health Science Izmir Bozyaka Training and Research Hospital Ethics Committee with 21/05/2020 dated and 222 numbered decision.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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