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Which factors are predicting the mortality in patients with COVID-19 in the intensive care unit?

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ABSTRACT

Aims: COVID-19 infection is a global health problem; clinical and laboratory parameters have been developed to predict this disease-related mortality/morbidity. Some of these parameters are clinical parameters, while some are laboratory parameters. This study aims to determine whether Acute Physiology and Chronic Health Evaluation (APACHE) II, Glasgow Coma Scale (GCS), age, presence of comorbidity, and absolute lymphocyte count effectively predict mortality in patients admitted to intensive care unit (ICU) due to COVID-19.

Methods: We have included 108 PCR-positive COVID-19 patients admitted to the ICU between 1 October and 31 November 2020 in our research. Demographic characteristics of all patients, APACHE II values within the first 24 hours of admission to ICU, the GCS, the presence of comorbidity, lymphocyte count during ICU admission, duration of ICU stay, and the mortality rates were recorded.

Results: The average age of 108 individuals evaluated in the study was 67±13.61 years, and 56.5% of the patient group consisted of the geriatric age range. Seventy (64.8%) of the patients were female, eighty-nine (82.4%) patients had at least one comorbidity. In the multivariate analysis, it was determined that lymphocyte value, APACHE II score, and the presence of any comorbidity are independent prognostic factors for mortality when accepted to ICU.

Conclusion: In our study, we have determined that age, APACHE II value, presence of comorbidity, and baseline lymphocyte counts are independent predictors of mortality.

Keywords: Mortality, COVID-19, intensive care unit

INTRODUCTION

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) epidemic that emerged in Wuhan, China, is a member of the coronavirus family and has affected all world countries and caused a pandemic throughout 2020.[1] According to this infection spread table generated by the SARS-CoV-2 virus, 10-20% of the patients require intensive care unit (ICU).[2] While the disease-related hospital mortality rate is 4.3-11%, the mortality rate among the patients admitted to ICU varies between centers and is around 30-60%.[3,4] In COVID-19 patients admitted to ICU with respiratory failure, clinical deterioration may rapidly deteriorate. Patients are lost due to severe acute respiratory distress syndrome (ARDS) and subsequent multiple organ dysfunction.[5] COVID-19 infection is a global health problem, and an effective scoring system established with clinical and laboratory parameters to predict this disease-related mortality/morbidity has not been defined. Scoring systems developed to predict patients' prognosis during admission to ICU and evaluate the treatment's effectiveness is widely used in non-COVID patients. Acute Physiology and Chronic Health Evaluation (APACHE) II, one of the most commonly used scoring systems, is known to be a successful scoring system in terms of mortality prediction.[6] There is insufficient information that these scoring systems effectively predict mortality in COVID-19 patients, and research on this subject continues. Again, the decrease in the number of lymphocytes in COVID-19 associated viral infection is thought to be the result of direct binding of the virus with angiotensin converting enzyme 2 (ACE2) receptors on lymphocytes and apopytosis caused by a cytokine storm. In a recent meta-analysis published by Lui et al.[7] 35-75% of the patients developed lymphopenia, and it states that

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mortality increased significantly in these patients. Fan et al.[8] reported that a lymphocyte count of <0.6 x10^9/L was associated with a poor prognosis in an analysis of 67 COVID-19 patients during their admission to an ICU.[9]

In this study, we aim to determine which factors effectively predict mortality in patients admitted to ICU due to COVID-19.

METHODS

Study Design and Candidates

This study was conducted in 3rd level ICUs. These intensive care units, where the patients were followed and treated as the 3rd level ICUs, were separated as the COVID-19 ICU due to the pandemic. Patients admitted to the ICU between October 1 and November 31, 2020 were included in our study. After our hospital's ethics committee's approval (protocol number E1/1513/2021; dated 12/07/2023), all patient data were obtained from electronic medical records and patient follow-up forms. All procedures followed were in accordance with the ethical standards (institutional and national) of the committee responsible for human experiments and the 1975 Declaration of Helsinki, revised in 2008.

The demographic characteristics of all patients, APACHE II values within the first 24 hours of admission to ICU, Glasgow Coma Scale (GCS), presence of comorbidity, lymphocyte count during ICU admission, length of stay in ICU, and presence of mortality were recorded.

In this study, while 65 years and over were accepted as advanced age, the average APACHE value for APACHE II was obtained by univariate analysis. As a result of this analysis, it was planned to compare those with APACHE II values of 19 and above and those below. Again, patients with a value of 10 and below for the GCS were accepted as patients in the precoma state. The cut-off value for the baseline lymphocyte count was accepted as 0.8×10^9/L, based on the national COVID-19 science committee guidelines.

Statistical Analysis

Statistical analyses were performed using Statistical Package for Social Sciences (IBM SPSS Inc, Chicago, IL, USA) version 20.0. Descriptive statistics were expressed as mean±standard deviation or median (min-max) for continuous variables and number/percentage for categorical variables. Chi-square test was used for the categorical parameters, and Anova Table Test was used for continuous parameters. Variables with a p-value <0.05 in the univariate analysis were included in the multivariate analysis after the correlation between the factors was determined for exitus. Multivariate Backward Stepwise Cox Proportional Hazard Regression Analysis was used to determine the effects of variables effective on mortality. P-value <0.05 was considered statistically significant for the results.

RESULTS

The average age of the 108 individuals evaluated in the study was 67±13.61 years, ranging from 27 to 89. The geriatric group comprised 56.5% of the patient group. Seventy (64.8%) of the patients were female, eighty-nine (82.4%) patients had at least one comorbidity. There were hypertension in 46 (42.6%) patients, diabetes mellitus in 39 (36.1%) patients, cardiovascular disease in 31 (28.7%) patients, chronic obstructive pulmonary disease in 18 (16.7%) patients, chronic renal failure in 9 (8.3%) patients, history of cerebrovascular disease 8 (7.4%) patients, 8 (7.4%) patients with a history of malignancy, and 4 (3.7%) asthma bronchiale (Table 1).

The study group's median APACHE II value was 19 (range; 1-50), and the median GCS score value was 13.5 (range; 3-15). GCS score value was 10 in 31 (28.7%) patients. When admitted to ICU, the median lymphocyte value was 605×10^9/L and varied between 80×10^9/L and 3910×10^9/L. It was observed that the patients stayed in the ICU for an average of 9.56±7.43 days, 46 (42.6%) patients were discharged from the ICU, and 62 (57.4%) patients died (Table 1).

Table 1. Demographic, clinical, characteristics of patients

Characteristics		Mean±SD	Median (range)
Age (year)		67±13.61	69 (27-89)
APACHE II		20.17±11.55	19 (1-50)
Glasgow coma scale score		11.78±4.14	13.5 (3-15)
ICU length of stay (day)		9.56±7.43	7 (1-39)
Lymphocyte count at ICU admission (x10^9/L)		774.5±589.28	605 (80-3910)
		n	**Percentage**
Geriatric patient	<65 years ≥65 years	47 61	43.5 56.5
Glasgow coma scale score	≤10 >10	31 77	28.7 71.3
Gender	Female Male	38 70	35.2 64.8
Any co-morbidity	Absent Present	19 89	17.6 82.4
Hypertension	Absent Present	62 46	57.4 42.6
Diabetes mellitus	Absent Present	69 39	63.9 36.1
Chronic obstructive pulmonary disease	Absent Present	90 18	83.3 16.7
Asthma bronchiale	Absent Present	104 4	96.3 3.7
Cardiovascular disease	Absent Present	77 31	71.3 28.7
History of malignity	Absent Present	100 8	92.6 7.4
Chronic renal failure	Absent Present	99 9	91.7 8.3
Cerebrovascular disease	Absent Present	100 8	92.6 7.4
Other co-morbidity	Absent Present	79 29	73.1 26.9
Mortality	No Yes	46 62	42.6 57.4

In the univariate analysis, it was seen that age, APACHE II score, GCS score, lymphocyte value when accepted to ICU, presence of any comorbidity determined mortality (Table 2).

Table 2. Factors predicting the mortality in patient with COVID 19 in intensive care unit, univariate analysis

Features		Mortality		P value
		No n (%)	Yes n (%)	
Age [1]	<65 years ≥65 years	30 (63.8) 16 (26.2)	17 (36.2) 45 (73.8)	<0.001
APACHE II [2]	≤19 >19	43 (79.6) 3 (5.6)	11 (20.4) 51 (94.4)	<0.001
Glasgow coma scale score [3]	≤10 >10	3 (9.7) 43 (55.8)	28 (90.3) 34 (44.2)	<0.001
Gender	Female Male	14 (36.8) 32 (45.7)	24 (63.2) 38 (54.3)	0.373
Lymphocyte count at ICU admission (10^9/L) [4]	≤800 >800	24 (32.4) 22 (64.7)	50 (67.6) 12 (35.3)	0.002
Any co-morbidity	Absent Present	13 (68.4) 33 (37.1)	6 (31.6) 56 (62.9)	0.012
Hypertension	Absent Present	31 (50) 15 (32.6)	31 (50) 31 (67.4)	0.071
Diabetes mellitus	Absent Present	35 (50.7) 11 (28.2)	34 (49.3) 28 (71.8)	0.023
Chronic obstructive pulmonary disease	Absent Present	42 (46.7) 4 (22.2)	48 (53.3) 14 (77.8)	0.056
Asthma bronchiale	Absent Present	44 (42.3) 2 (50)	60 (57.7) 2 (50)	0.760
Cardiovascular disease	Absent Present	35 (45.5) 11 (35.5)	42 (54.5) 20 (64.5)	0.343
History of malignity	Absent Present	43 (43) 3 (37.5)	57 (57) 5 (62.5)	0.762
Chronic renal failure	Absent Present	43 (43.4) 3 (33.3)	56 (56.6) 6 (66.7)	0.557
Cerebrovascular disease	Absent Present	43 (43) 3 (37.5)	57 (57) 5 (62.5)	0.762
Other co-morbidity	Absent Present	36 (45.6) 10 (34.5)	43 (54.4) 19 (65.5)	0.302

1: Geriatric age, 2: Median value, 3: The cut-off value for Glasgow Coma Scale Score was selected 10 which is defined comatose patient , 4: The cut-off value for the baseline lymphocyte count was accepted as 0.8×10^9/L, based on the national COVID -19 science committee guidelines. ICU: Intensive Care Unit

Factors associated with mortality were evaluated by correlation in univariate analysis, and it was found that there was only a correlation between the presence of any comorbidity and diabetes mellitus. Therefore, excluding diabetes mellitus, age (≤65 years vs. <65 years), lymphocyte value (≤800×10^9/L vs. >800×10^9/L), APACHE II score (> 19 vs. ≤19, when admitted to ICU), the presence of any comorbidity (present vs. absent), and the GCS score (≤10 vs. >10) for multivariate analysis to determine death. In the multivariate analysis, it was determined that lymphocyte value, APACHE II score, and the presence of any comorbidity are independent prognostic factors for mortality when accepted to ICU. Death increased 76 times in those with APACHE II score >19 (95% Confidence Interval: 10.851-533.783; p <0.001). This ratio was 7 (95% Confidence Interval: 1.520-33.827; p=0.013) for those with a lymphocyte count of ≤800×10^9/L and 8 for those with any comorbidity (95% Confidence Interval: 1.015- 64.151; p=0.048) (Table 3).

Table 3. Factors predicting exitus, multivariate analysis

Factors	Odds ratio	95% confidence interval	P value
Age (≥65 years vs. <65 years) [1]	2.4	0.625-9.212	0.202
Lymphocyte count (≤800×10^9/L vs.>800×10^9/L) [2]	7.171	1.520-33.827	0.013
APACHE II (>19 vs. ≤19) [3]	76.105	10.851-533.783	<0.001
Co-morbidity (present vs. absent)	8.068	1.015-64.151	0.048
Glasgow coma scale score (≤10 vs. >10) [4]	1.487	0.154-14.374	0.732

1: Geriatric age was selected for analysis, 2: The cut-off value for the baseline lymphocyte count was accepted as 0.8×10^9/L, based on the national COVID -19 science committee guidelines. 3: Median value, 4: The cut-off value for Glasgow Coma Scale Score was selected 10 which is defined comatose patient

DISCUSSION

Our primary aim in this study was to evaluate whether age, APACHE II value, presence of comorbidity, GCS, and baseline lymphocyte count were successful in predicting mortality in COVID-19 patients. Our study determined that the baseline lymphocyte value, APACHE II score, and the presence of any comorbidity are independent prognostic factors for mortality.

For many years, many scoring systems have been used in ICUs to predict mortality and morbidity.[10] Among these systems, APACHE II is accepted as the most successful scoring system in predicting mortality in all ICU types and different patient groups.[11,12] In some articles, it has been reported to be successful in COVID-19 patients.[13,14] A study conducted by Zou et al.[15] they stated that the APACHE II value of 17 or above in COVID-19 patients was an independent predictor for hospital mortality. Our study determined that the APACHE II value of >19 and above is an independent risk factor, and death is 76 times more common in these cases. APACHE II scoring, which is calculated by taking the worst values during admission to ICU, acts as an early warning system for physicians' high scores following these cases. These scoring systems are widely used in centers where intensive patient admissions are made during the pandemic, and they are instrumental in planning the treatment process of cases with high APACHE II values.

Although there is not enough information about using the GCS, which is frequently preferred in neurological examination in ICU, in COVID-19 cases, the GCS data can be based on studies using APACHE II since it is a parameter of APACHE II scoring.[16] Our study showed

that GCS being 10 or less has a significant relationship with mortality. In 28.7% of the cases, the GCS was 10 or less, and the mortality was 90.3%.

In the COVID-19 outbreak, it was observed that mortality rates were different in different age groups.[17] It is observed that pulmonary physiology, pathology, and functions change in the presence of lung infection with aging. Therefore, in elderly individuals, response to the disease and tolerability deteriorate, and the mortality rate increases.[18] Studies on advanced age COVID-19 patients have shown an increased risk of death.[19-22] In our study, 56.5% of the cases were 65 years old and above, and the mortality rate in these cases was significantly higher compared to patients aged 65 years or younger.

The presence of concomitant diseases in COVID-19 cases complicates the clinical picture. In their study by Chen et al.[23] in which they evaluated the epidemiological and clinical characteristics of the cases they followed up with COVID-19 viral infection, they determined the presence of chronic disease in 51% of the cases and stated that cardiovascular, cerebrovascular disease, and diabetes mellitus were the most common accompanying diseases. They indicate in their research that mortality is higher in cases with comorbidity.[24] In our research, we observed that 82.4% of our cases had at least one concomitant disease. The most common accompanying disease was hypertension (42.6%), followed by diabetes mellitus (36.1%). In our study, unlike Chen et al., the accompanying cardiovascular disease rate was in the 3rd rank with 28.7%. While any comorbidity's presence increased the risk of death eight times, mortality was found to be statistically significantly higher in patients with diabetes mellitus compared to those without diabetes mellitus.

The absolute value of lymphocytes decreases in COVID-19 associated viral infection. The reason for this decrease is related to the effect of 2019-nCoV on SARS-CoV lymphocytes, especially T lymphocytes. Virus particles spread to the respiratory mucosa and initiate a cytokine storm in the body. This situation stimulates the immune system and causes changes in peripheral white blood cells and immune cells such as lymphocytes. Some patients progress rapidly and pass away by developing ARDS, septic shock, and multiple organ failure. For this reason, early detection and timely treatment of critical cases are vital. The decrease in the absolute lymphocyte count during admission to ICU is a laboratory parameter that supports clinicians' diagnosis during the diagnosis of COVID-19. In comparison, Huang et al.[25] stated that their absolute lymphocyte count was $<1.0\times10^9$/L in 63% of their patients, Fan et al. showed that absolute lymphocyte count $<0.6\times10^9$/L had a significant correlation with mortality.[8] In our study, when we evaluated the mortality relation of absolute lymphocyte count $<0.8\times10^9$/L, we determined that lymphocyte count $<0.8\times10^9$/L was an independent predictor for mortality. Absolute lymphocyte count $<0.8\times10^9$/L increased the risk of death seven times.

Frater et al.[26] state that there is some geographic variation in the percentage of COVID-19 patients presenting with lymphopenia in their article evaluating COVID-19 and clinical, hematological laboratory findings. For example, an article from Singapore reporting several COVID-19 patients describes a much lower percentage of lymphopenia patients, as in a retrospective analysis of COVID-19 patients from Zhejiang Province, located ~450 miles from Wuhan.[8,27] In contrast, in studies reported from Italy, lymphopenia is common in most patients admitted to the emergency room.[28] The reasons for these and similar discrepancies are unclear, although they are probably multifactorial. Due to viral genomic mutations, it is possible that the immunological response to the virus will change as the pandemic spreads to other countries. Another possibility is that testing patients is not uniform, and the degree of lymphopenia can vary depending on the time of admittance. In our study, we have observed that 74 of 108 patients had an absolute lymphocyte value $<0.8\times10^9$/L.

There were some limitations in our study. The first is that it is a retrospective study, and the second is that there is no long-term (28 days or 6 months) data when determining ICU and hospital mortality. Besides, we think that further studies should be conducted that comparative studies of baseline absolute lymphocyte count with data from different countries may help determine the cut-off value for lymphopenia.

CONCLUSION

In our study, we determined that age, APACHE II value, presence of comorbidity, and initial lymphocyte count are independent predictors of mortality. We concluded that studies with more patients and other clinical / laboratory data related to COVID-19 would be beneficial.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the University of Health Sciences, Ankara City Hospital Ethics Committee (Date: 12/07/2023, Decision No: E1/1513/2021).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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