Relationship of Blood Gas Measurements and Hematological Manifestations of COVID-19 Patients with Mortality: Retrospective Analysis

Covid-19 Hastalarının Kan Gazı Ölçümleri ve Hematolojik Manifestasyonlarının Mortalite ile İlişkisi: Retrospektif Analiz

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Özet

Amaç: Amacımız, COVİD-19'lu hastaların yoğun bakım ünitesine yatış ve sonrası dönemde kan gazı ve tam kan sayımı parametrelerinin mortalite ile ilişkilerini araştırmaktır.

Gereç ve Yöntemler: Hastalar grup yaşamayan ve grup yaşayan olarak iki gruba ayrıldı. Hematolojik parametreler 1, 3, 5. gün kaydedildi.

Bulgular: Yüz kırk iki hasta retrospektif olarak analiz edildi. Bunların 46'sı (%32) kadındı. 71 hasta (%50) yaşamayan gruptaydı. Yaşamayan grupta ortalama yaş 61, yaşayan grupta ortalama yaş 60'tı. Noninvaziv ventilasyon günü ve invaziv ventilasyon günü yaşamayan grupta daha yüksekti. Yaşamayan grupta yoğun bakıma yatışta, 3.günde ve 5.günde PO2/FiO2 (p<0.001), lenfosit sayısı (p<0.001), monosit sayısı (p<0.010) ve eozinofil yüzdesi (p<0.025) daha düşük iken nötrofil-lenfosit oranı daha yüksekti (p<0.001). Yoğun bakım yatışta ve üçüncü günde trombosit-lenfosit oranı yaşamayan grupta yaşayan grupta daha yüksekti (p<0.020). Yoğun bakıma yatışta, 3.gün ve 5.günde, sistemik immün-inflamasyon indeksi yaşamayan grupta yaşayan gruptan daha yüksekti (p<0.020). Yoğun bakıma yatışta, 3.gün ve 5.günde, sistemik immün-inflamasyon indeksi yaşamayan grupta yaşayan grupta daha yüksekti (p<0.011). PO2/FiO2, hematokrit, monosit yüzdesi, eozinofil sayısının mortalite üzerinde etkili olduğu bulundu. Monosit yüzdesindeki azalma, ölüm olasılığını 1.6 kat artırdı.

Sonuç: Kan gazı ve tam kan sayımı parametrelerindeki değişiklikler COVİD-19 hastalarında mortaliteyi etkiledi. Bu çalışma mortalite ile ilgili öngörü sağlayarak, daha etkin tedavi stratejisi geliştirilmesine yol açabilir.

Anahtar kelimeler: COVID-19, Hematolojik parametreler, Mortalite, Yoğun bakım ünitesi

Abstract

Objective: The aim was to investigate the relationship between blood gas and complete blood count parameters and mortality in patients with COVID-19 during and after in the intensive care unit (ICU).

Material and Methods: Patients were divided as group nonsurvivor and group survivor. Hematological parameters were registered on the day 1, 3, 5.

Results: A total of 142 patients were analyzed retrospectively in the study. Out of them, 46 were women (32%). Seventy-one patients were in group nonsurvivor (50%). The median age of group nonsurvivor patients was 61 years, and the median age of group survivor patients was 60 years. Noninvasive ventilation day and mechanical ventilation day were higher in group nonsurvivor. In group nonsurviver, at the admission to the ICU, in the third day and in the fifth day of ICU, PO2/FiO2 (p<0.001), the lymphocyte count (p<0.001), the monocyte count (p<0.010) and the eosinophil percentages (p<0.025) were lower while the neutrophil-lymphocyte ratio was higher (p<0.001) compared to group survivor. At the admission and in third day of ICU, platelet–lymphocyte ratio were higher in group nonsurvivor (p<0.020). At the admission, in the third and the fifth day of ICU, systemic immune-inflammation index were higher in group nonsurvivor than group survivor (p<0.011). The effects of PO2/FiO2, hematocrit, monocyte percentage, eosinophil count on mortality were found to be significant. The decrease in monocyte percentage increased the probability of mortality 1.6 times.

Conclusion: Changes in blood gas and complete blood count parameters affected the mortality in COVID-19 patients. This study may lead to the development of a more effective treatment strategy by providing a prediction about mortality.

Keywords: COVID-19, Hematological parameters, Mortality, Intensive care unit

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, COVID 19), which originated in the city of Wuhan, China in December 2019, caused a pandemic. The World Health Organization announced that as of January 23, 2022, more than 346 million confirmed cases and more than 5.5 million deaths have been reported worldwide (1). Clinical observations have shown COVID-19 infection can vary from asymptomatic to a respiratory system disease with dry cough and sudden fever accompanied by a high rate of human-to-human transmission (2). The common symptoms of COVID-19 disease are ache, cough, fever, air hunger, hemoptysis, and diarrhea. Severe symptoms of COVID-19 are related to an increase in death rates (3). Epidemiologic and clinical features of COVID-19 have shown that this infection could cause severe respiratory illnesses leading to intensive care unit (ICU) admissions and high mortality rates (4).

Biomarkers are essential for this pandemic period to optimize patient care and source allocation, categorize patient risks and actively monitor the severity of the disease (5). Hematological markers such as, platelet–lymphocyte ratio (PLR), monocytes, platelets, lymphocytes, neutrophil–lymphocyte ratio (NLR), neutrophils help in risk categorization, diagnosis and early warning of disease (6). Recently, NLR, derived NLR (d-NLR), PLR, and systemic immune-inflammation index (neutrophils×platelets)/lymphocytes, SII) have been detected beneficial for diagnosis and evaluation of patients with COVID-19 (7,8). The relationship between hemogram parameters and clinical progress in patients with a diagnosis of COVID 19 may be important in terms of evaluating the prognosis (9).

The goal of this study was to analyze patients' laboratory parameters at to the intensive care unit admissions (ICUA) and in the third and fifth days and to investigate its connection with mortality. An important part of this study was to follow the change in these ratios on the ICUA and during the ICU stay.

MATERIALS AND METHODS

Bakırköy Dr. Sadi Konuk Training and Research Hospital Ethics Committee approved this study (Date: 24.08.2020, No: 2020-17-19). All procedures were performed according to the 1975 Declaration of Helsinki. Records of 194 patients in ICU of Istanbul Bahcelievler State Hospital, and their records in the hospital infor-

mation management system were retrospectively analyzed between March 14 and June 20, 2020. One hundred forty-two patients with COVID-19 symptoms, resulting positive in real-time reverse transcriptase-polymerase chain reaction (RT-PCR) test, and/or patients with signs of viral pneumonia in thoracic computed tomography (CT) were included in this study. Patients who were not diagnosed with COVID-19 were excluded from the study. The patients were divided into two groups as group nonsurvivors and the group survivor. Patients' sex, age, comorbidities, Acute Physiology and Chronic Health Evaluation II score (APACHE II), noninvasive ventilation day (NIVD), mechanical ventilation day (MVD), complete blood count and ratios: hematocrit (HCT), hemoglobin (HB), white blood cells (WBC), lymphocyte percentage (LYM %), platelet (PLT), the neutrophil percentage (NEU %), lymphocyte count (LYM #), absolute neutrophil count (NEU #), monocyte count (MONO #), monocyte percentage (MONO %), eosinophil percentage (EO %), eosinophil count (EO #), NLR, PLR, SII, blood gas counts; pH, PCO₂, PO₂, PO₂/FiO₂ were recorded at the time of hospitalization in ICU, in day 3 and 5 in ICU. In addition to these, blood types were also recorded. Comparison was made between the groups.

Statistical Analysis

The compatibility of the variables to the normal distribution was analyzed using the Shapiro–Wilk test. Statistical parameters were explained in median (interquartile range). Mann–Whitney U test was examined to compare and analyze the variables between the two groups that did not indicated normal distribution. Exact test and Chi-square test were utilized the frequency distribution between categorical variables. Logistic regression analysis was utilized to analyze the effects of variables on mortality. Statistical significance was acknowledged as p<0.05. The data were measured with IBM SPSS Statistics for Windows version 22 (IBM SPSS for Windows version 22, IBM Corporation, Armonk, New York, United States).

RESULTS

One hundred forty-two patients were contained in the study. 46 were women (32%). The median age of group nonsurvivor was 61 years, also group survivor was 60 years. Seventy-one patients were sent from the ICU to the ward (50%). Seventy-one patients died. Comorbid diseases were similar in both groups. APACHE II score, NIVD and MVD were higher in group nonsurvivor (**Table 1**). In the third and fifth days, WBC value were increased significantly in group nonsurvivor compared to group survivor (p=0.010, p<0.001, respectively). PLT value in the fifth day was lower in group nonsurvivor than group survivor (p=0.001). At ICUA, in the third and fifth day NEU # and NEU % were increased significantly in group nonsurvivor compared to group survivor (p=0.001, p<0.001, At the ICUA, in the third and the fifth day LYM # and LYM % levels were lower in group nonsurvivor than group survivor (all, p<0.001). At the ICUA, in the third day and the fifth day MONO #, and MONO % were lower in group nonsurvivor than group survivor (p=0.005, p<0.001, p=0.010, p<0.001, p<0.001, p<0.001, p<0.001, respectively).

At the ICUA and in the third day EO # and, at the ICUA, in the third day and the fifth day EO % levels were lower in group nonsurvivor than group survivor (p=0.017, p<0.001, p=0.011, p<0.001, p=0.025, respectively). No was difference between the groups in terms

of ICUA, 3rd day and 5th day HB and HCT values. NLR was higher in group nonsurvivor than group survivor (all, p<0.001). At the ICUA and in the third day, PLR were higher in group nonsurvivor than group survivor (p=0.001, p=0.020, respectively). At the ICUA, in the third day and fifth day SII ratio was higher in group nonsurvivor than group survivor (p<0.001, p<0.001, p=0.001, p=0.011, respectively) (**Table 2**).

In blood gas evaluation, the fifth day PH, ICUA, PCO_2 and PO_2 , fifth day PO_2 values were lower in group nonsurvivor than group survivor (p<0.001, p=0.048, p=0.004, p<0.001, respectively). ICUA, third day and fifth day PO_2 /FiO₂ were lower in group nonsurvivor than group survivor (all, p<0.001) (**Table 3**).

The effects of PO_2/FiO_2 , HCT, MONO % and EO # variables on mortality were found to be statistically significant. The decrease in MONO % values increased the probability of mortality approximately 1.6 times (odds ratio [OR]: 1.608 95% confidence interval [CI]: 1.090–2.372) (**Table 4**).

Table 1. Comparison of demographic and clinical parameters in group nonsurvivor and group survivor				
		Groups		
		Group nonsurvivor (n=71)	Group survivor (n=71)	p-value
Age Median (Q1–Q3)		61.00 (50.00-72.00)	60.00 (49.00-76.00)	0.933
Sex n, (%)	Female	18.00 (39.13)	28.00 (60.87)	0.073
	Male	53.00 (55.21)	43.00 (44.79)	
Comorbidities n, (%)	None	34.00 (52.31)	31.00 (47.69)	0.617
	HT+DM	10.00 (58.82)	7.00 (41.18)	
	DM	7.00 (58.33)	5.00 (41.67)	
	HT	6.00 (42.86)	8.00 (57.14)	
	CVD	3.00 (37.50)	5.00 (62.50)	
	BPH	3.00 (75.00)	1.00 (25.00)	
	COPD	2.00 (33.33)	4.00 (66.67)	
	HT+DM+COPD	2.00 (40.00)	3.00 (60.00)	
	Hypothyroidism	2.00 (100.00)	0.00 (0.00)	
	HT+CAH	1.00 (33.33)	2.00 (66.67)	
	САН	1.00 (50.00)	1.00 (50.00)	
	HT+DM+CAH	0.00 (0.00)	2.00 (100.00)	
	Hyperthyroidism	0.00 (0.00)	2.00 (100.00)	
APACHE II	Median (Q1–Q3)	16.00 (14.00-20.00)	11.00 (8.00-14.00)	0.001*
NIVD	Median (Q1–Q3)	0.50 (0.00-3.00)	2.50 (1.00-5.00)	0.001*
MVD	Median (Q1-Q3)	5.00 (3.00-9.00)	0.00 (0.00-1.50)	0.001*

HT: Hypertension; DM: Diabetes mellitus; CVD: Cardiovascular disease; BPH: Benign prostatic hyperplasia; COPD: Chronic obstructive pulmonary disease; CAH: Congenital adrenal hyperplasia; APACHE: Acute Physiology And Chronic Health Evaluation; NIVD:, Noninvasive ventilation day; MVD: Mechanical ventilation day. *p<0.05

Table 2. Comparison of com	plete blood count parameters betweer	group nonsurvivor and group survi	vor
	Groups		
	Group nonsurvivor Median (Q1–Q3)	Group survivor Median (Q1–Q3)	p-value
ICUA WBC	8.72 (6.21–11.0)	7.64 (6.16–10.4)	0.301
3rd day WBC	10.7 (7.77–13.5)	8.4 (6.43–11)	0.010*
5th day WBC	11.9 (9.15–15.47)	7.91 (6.51–10.55)	0.001*
ICUA PLT	238.0 (173–307)	263 (197–385)	0.228
3rd day PLT	261.0 (192–366)	302 (242–415)	0.054
5th day PLT	271.5 (180.50-373.50)	333 (268–466)	0.001*
ICUA NEU #	7.65 (5.01–10.43)	5.63 (3.97-7.99)	0.001*
3rd day NEU #	9.33 (6.76–11.6)	6.19 (4.28-8.8)	0.001*
5th day NEU #	9.92 (7.24–13.25)	5.99 (4.34-8.9)	0.001*
ICUA NEU %	85.0 (79.8-89)	75.5 (65.7–82)	0.001*
3rd day NEU %	86.0 (82–90)	74.4 (66–81.6)	0.001*
5th day NEU %	87.35 (81.45-90.58)	73.7 (65–80.3)	0.001*
ICUA LYM #	0.75 (0.53–1.05)	1.04 (0.76–1.6)	0.001*
3rd day LYM #	0.65 (0.53–0.85)	1.15 (0.77–1.5)	0.001*
5th day LYM #	0.78 (0.52–1.04)	1.18 (0.88–1.41)	0.001*
ICUA LYM %	8.5 (5.6–12.1)	13.1 (9.5–22.5)	0.001*
3rd day LYM %	6.7 (5.1–9.4)	13.55 (9.4–22)	0.001*
5th day LYM %	7.95 (5.20–11.05)	14.9 (9.50–20.2)	0.001*
ICUA MONO #	0.48 (0.26-0.69)	0.63 (0.36–1.1)	0.005*
3rd day MONO #	0.5 (0.34–0.72)	0.74 (0.51–1.14)	0.001*
5th day MONO #	0.58 (0.31-0.79)	0.79 (0.58–1.03)	0.010*
ICUA MONO %	5.1 (3.7–7.8)	7.6 (5.10–11.1)	0.001*
3rd day MONO %	5.1 (3.3–7)	9.35 (5.8–12)	0.001*
5th day MONO %	4.3 (2.85-6.35)	10.00 (7.3–12.9)	0.001*
ICUA EO #	0.01 (0-0.05)	0.03 (0-0.1)	0.017*
3rd day EO #	0.01 (0-0.04)	0.07 (0.01–0.16)	0.001*
5th day EO #	0.05 (0.01–0.14)	0.08 (0.03-0.14)	0.101
ICUA EO %	0.1 (0-0.5)	0.3 (0.00–1.4)	0.011*
3rd day EO %	0.2 (0-0.3)	0.9 (0.10-2)	0.001*
5th day EO %	0.3 (0.10–1.4)	1 (0.20–1.8)	0.025*
ICUA NLR	9.75 (6.60–16.56)	6.15 (3.35–7.78)	0.001*
3rd day NLR	13.52 (10.20–17.58)	5.78 (3.01-8.73)	0.001*
5th day NLR	11.98 (9.15–19.49)	5.42 (3.42-8.29)	0.001*
ICUA PLR	355 (244.68-486.08)	234.88 (173.08-362.20)	0.001*
3th day PLR	392.21 (262.71–566.67)	324.62 (171.58-420.75)	0.020*
5th day PLR	339.38 (198.45–514.15)	330.50 (204.76-462.50)	0.769
ICUA SII	2296.8 (1546.12-4386.50)	1379.38 (717.74–2477.21)	0.001*
3rd day SII	3521.4 (2240.00-5072.73)	1673.72 (1050.00-2820.45)	0.001*
5th day SII	2898.08 (1974.23-5348.8)	1710.11 (1069.50-398.09)	0.011*

WBC: White blood cell; PLT: Platelet; NEU #: Neutrophil count; NEU %: Neutrophil percentage; LYM #: Lymphocyte count; LYM %: Lymphocyte percentage; MONO #: Monocyte count; MONO %: Monocyte percentage; EO #: Eosinophil count; EO %: Eosinophil percentage; ICUA: Intensive care unit admission; NLR: Neutrophil–lymphocyte ratio; PLR: Platelet- lymphocyte ratio; SII: Systemic immune-inflammation index; *p<0.05

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Table 3. Comparison of blood gas parameters between group nonsurvivor and group survivor				
	Groups			
	Group nonsurvivor	Group survivor	p-value	
	Median (Q1–Q3)	Median (Q1-Q3)		
ICUA pH	7.41 (7.34–7.49)	7.4 (7.32–7.47)	0.107	
3rd day pH	7.4 (7.35–7.44)	7.41 (7.35–7.45)	0.455	
5th day pH	7.36 (7.32–7.4)	7.4 (7.38–7.43)	0.001*	
ICUA PCO ₂	32 (2.2-41)	34 (30-44)	0.048*	
3rd day PCO ₂	38 (33–45.)	40 (35–45)	0.223	
5th day PCO ₂	40 (36.5–48.5)	41 (38–46)	0.505	
ICUA PO ₂	49 (44–56)	55 (49–59)	0.004*	
3rd day PO ₂	56 (52–62)	59.5 (52–65)	0.107	
5th day PO ₂	58.5 (51–63)	65(60–78)	0.001*	
ICUA PO ₂ /FiO ₂	51 (44–59)	65 (50-80)	0.001*	
3rd day PO ₂ /FiO ₂	57 (51–68)	69 (56–112)	0.001*	
5th day PO_2/FiO_2	58.5 (50.5–66.5)	120 (65–160)	0.001*	

ICUA, intensive care unit admission, *p<0.05

Table 4. Comparison of intensive care admission values and the fifth day values between group nonsurvivor and group survivor				
	OR (95% CI)	p-value		
PO ₂ /FiO ₂	1.094 (1.031–1.160)	0.003*		
НСТ	0.471 (0.254–0.872)	0.017*		
MONO %	1.608 (1.090-2.372)	0.017*		
EO #	0.000 (0.000-0.002)	0.004*		

Logistic regression; α: 0.05; Nagelkerke R2: 0.656; *p<0.05; HCT: Hematocrit; MONO %: Monocyte percentage; EO #: Eosinophil count.

Blood type (A) was found to be the most common blood type among COVID-19 patients (53.53%). It was followed by blood type (O) (34.50%).

DISCUSSION

The current study revealed that, laboratory results can be used as parameters associated with mortality in COVID-19 patients. APACHE II scores, NIVD and MVD were detected higher in group nonsurvivor. NLR, PLR, and SII values were higher in group nonsurvivor. The change in PO_2/FiO_2 , HCT, MONO % and EO # values affected the mortality status.

In a study including 52 patients, 32 (61.5%) patients died within 28 days (10). In another study 54 (28%) of 191 patients died (3). A study including 119 COVID-19 patients, While 90 patients (75.6%) were discharged, the resudiary 29 patients (24.4%) died (8). The median age of group nonsurvivor patients was 61. Seventy-one of 142 patients (50%) died in the present study.

Deng et al. in their study found a significantly higher level of WBC at admission, while patients who died had a low lymphocyte count and lymphocyte percentage. In patients who died, the percentage of lymphocytes continued to decrease during hospitalization (11). In a study including 452 patients (286 severe patients and 266 nonsevere patients), severe patients had higher leukocytes (4.9 109/L vs. 5.6 109/L) and neutrophils (4.3 10⁹/L vs. 3.2 10⁹/L). In severe patients, lower percentages of, eosinophils (0.0% vs. 0.2%), and monocytes (6.6% vs. 8.4%), basophils (0.1% vs. 0.2%) were observed (12). In the study of Guan et al., at the time of application, 83.2% of the patients had lymphocytopenia, 36.2% had thrombocytopenia, and 33.7% had leukopenia (13). In another trial, out of 45 patients in the severe type group, 21 patients (46.7%) were diagnosed with lymphopenia, and 16 patients (35.6%) were diagnosed with eosinopenia. It has been stated that lymphopenia and eosinopenia can be used as markers in disease severity and follow-up in COVID-19 patients (14). In another study, the baseline

lymphocyte count was significantly lower in those who died than those who survived. The lymphocyte count returned to normal during the hospital stay in survivors. Severe lymphopenia was observed until death in those who died (3). In the study of Wang et al., 70.3% of patients had lymphopenia (15). Wu et al. in their study compared those who developed acute respiratory distress syndrome (ARDS) with those who did not. Of 197, 126 (64%) had lymphocytopenia, 68 (34.5%) had neutrophilia, and 46 (23.4%) had leukocytosis. Platelet counts did not differ between patients with ARDS and patients without ARDS (16). In the study of Zhang et al., WBC, NEU %, and absolute NEU # were higher in the critically ill group than noncritical ones. LYM #, LYM %, MONO %, and lymphocyte-monocyte ratio (LMR) were lower than those in the critically ill group (17).

Evaluation of the NLR can help detect severe cases early and initiate timely and effective treatment, which can reduce the overall mortality of COVID-19 (18). Platelets are important immune cells that play an important role in hemostasis, angiogenesis innate immunity, coagulation, inflammatory response, maintenance of vascular integrity (19). The platelet counts recorded in those who died were 191 (63) and 164 (74) in survivors; a statistical test was not presented (10). A low platelet count is incorporated with a rised risk of death and serious illnessin COVID-19 patients and should therefore be considered as a clinical indicator of disease worsening during hospital stay (5). In the present study, at the time of the ICUA and in the third day, no was significant difference between group nonsurvivor and group survivor in platelet counts. However, platelet counts were significantly decreased in the fifth day in group nonsurvivor. PLR is more valuable than platelet or lymphocyte counts alone, as it reflects both clustering and inflammatory pathways and predicts various inflammations (20). Yang et al. detected a specificity of 0.636 and a sensitivity of 0.88 for the NLR in defining the prognosis of severely sick COVID-19 patients. Severe patients' PLR, NLR, and LMR were found to be significantly higher than those of nonsevere patients (21). SII has been recommended as a prognostic indicator in the pursiting of patients with sepsis as an index that defines the instability in the inflammatory response (22). In another study, patients who died had significantly higher NLR

and SII values compared to survivors. SII independently predicts in-hospital mortality in COVID-19 patients at admission, and it can help early risk stratification in this group (8). In the present study, except PLR on the fifth day, NLR, PLR, and SII values were higher in group nonsurvivor than group survivor at the ICU admission and in the third and the fifth days.

In the study of Deng et al, PO_2/FiO_2 ratio was significantly lower in patients who died (10). Another study showed that, patients who died had lower blood oxygen saturation (11). In this study, at the time of to the ICUA, both groups' PO_2 value was under 60 mmHg. It was lower in group nonsurvivor than group survivor. At the time of ICUA, and in the third and fifth days, PO_2/FiO_2 values were lower in group nonsurvivor compared to group survivor. It is known that progressive hypoxemia generally suggests poor prognosis in lung diseases, and hypoxemia indicators are used to evaluate the severity of COVID-19 (23).

There were some potential limitations to this study. This was a retrospective, single-center study with a small sample. The reason for the patients' application to the hospital and the acute treatment of patients could not be obtained from the patient files.

As a conclusion, in light of these data, evaluating the prognosis of the disease at an early stage and applying treatment can effectively decrease the mortality rate.

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