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Factors Determining ARDS and Mortality in Covid-19 Pneumonia

Covid-19 Pnömonisinde ARDS ve Mortaliteyi Belirleyen Faktörler

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Abstract

Introduction: COVID-19 is caused by a newly discovered corona virus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 patients often present with fever, myalgia or fatigue and dry cough. Although most patients' prognosis is thought to be benign, it is known that poor results can be observed in elderly patients and those with chronic underlying diseases.

Our aim in this study is to investigate the factors that progress to ARDS and cause mortality in patients with COVID-19 pneumonia, based on symptoms, laboratory findings, Computed Tomography (CT) findings, chronic diseases and continuous medications they use.

Material and Method: Demographic characteristics of patients with Covid-19 pneumonia such as age, gender, complaints, vital signs, physical examination findings, smoking and other habits, chronic disease histories, laboratory and imaging examination results, treatment regimen applied in the hospital, hospitalization and intensive care durations were obtained and recorded in the hospital registration system. Clinical outcomes of all patients; Acute Respiratory Disitress (ARDS) has been recorded by classifying it as discharge or exitus. The definition of ARDS was made according to the Berlin criteria updated in 2012.

Result and Conclusion: In this study, low oxygen saturation at admission, chronic diuretic use, hypocalcemia, thrombocytopenia were found to be significant parameters that increase the risk for both ARDS and mortality in patients with Covid-19 pneumonia. In addition, high D-Dimer was found to be a significant risk factor for the development of ARDS, while advanced age was found to be a significant risk factor for mortality.

Keywords: Covid-19, ARDS, diuretic use, electrolyte disturbances

Öz

Giriş: COVID-19, şiddetli akut solunum sendromu koronavirüs 2 (SARS-CoV-2) adı verilen yeni keşfedilen bir korona virüsten kaynaklanır. COVID-19 hastaları genellikle ateş, miyalji, yorgunluk ve kuru öksürük ile başvurur. Çoğu hastanın prognozunun selim seyirli olacağı düşünülse de yaşlı hastalar ve kronik altta yatan rahatsızlıkları olanlar da kötü sonuçların gözlenebildiği bilinmektedir.

Bu çalışmada amacımız COVID-19 pnömonisi olan hastalarda ARDS'ye ilerleyen ve mortaliteye sebep olan faktörleri; semptomlar, laboratuvar bulguları, Bilgisayarlı Tomografi (BT) bulguları, kronik hastalıklar ve kullandıkları devamlı ilaçlardan yola çıkarak araştırmaktır.

Gereç ve Yöntem: Covid-19 pnomonisi olan hastaların yaş, cinsiyet gibi demografik özellikleri, şikayetleri, vital bulguları, fizik muayene bulguları, sigara kullanımı, kronik hastalık öyküleri kullandığı ilaçlar, laboratuvar, görüntüleme tetkik sonuçları, hastanede uygulanan tedavi rejimi, hastanede ve yoğun bakımda yatış süreleri hastane kayıt sisteminden elde edildi. Tüm hastaların klinik sonlanımları; Akut Respiratuvar Distres sendromu (ARDS) gelişip gelişmemesi, taburculuk veya exitus olarak sınıfladırılarak kayıt altına alınmıştır. ARDS tanımı 2012 yılında güncellenen Berlin kriterlerine göre yapılmıştır.

Bulgular ve Sonuç: Bu çalışmada Covid-19 pnomonisi olan hastalarda başvuru sırasındaki oksijen saturasyonu düşüklüğü, kronik diüretik kullanımı, hipokalsemi, trombositopeni hem ARDS hem de mortalite için riski artıran anlamlı parametreler olarak bulunmuştur. Ayrıca D-Dimer yüksekliği ARDS gelişimi için anlamlı risk faktörü olarak bulunurken, ileri yaş ise mortalite için anlamlı risk faktörü olarak bulunmuştur.

Anahtar kelimeler: Covid-19, ARDS, diuretik kullanımı, elektrolit bozuklukları

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by a newly discovered corona virus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19, has spread globally.[1,2] According to World Health Organization (WHO) data, the number of confirmed COVID-19 cases as of January 1.2021 is 81 947 503 confirmed cases, with 1,808 041 deaths. [1] Due to the rapid spread of COVID-19, which has become a major global health problem and affects millions of people, the World Health Organization declared the "Internationally Significant Public Health Emergency" on January 30.2020 and the global "Pandemic statue" on March 11, 2020.[2-4]

COVID-19 patients often present with fever, myalgia or fatigue and dry cough. Although most patients' prognosis is thought to be benign, it is known that poor results can be observed in elderly patients and those with chronic underlying diseases.[2] Dyspnea and hypoxemia may develop in patients with severe disease within 1 week after the onset of the disease, and this situation can rapidly progress to acute respiratory distress syndrome (ARDS) or end organ failure.[3]

Although this disease has a wide spectrum, it is not fully known why it is asymptomatic in some people and symptomatic in some.[3] Major morbidity and mortality of hospitalized COVID-19 patients is due to acute viral pneumonia leading to acute respiratory distress syndrome (ARDS).[1,2,5] The average mortality among COVID-19 patients with ARDS in all countries is 39%.[4] Although it is said that the ARDS predisposing factors of COVID-19 are advanced age, neutrophilia, high D-dimer levels and comorbidities.[4] , studies have been analyzed on very new and few patients.

Our aim in this study is to investigate the factors that progress to ARDS and cause mortality in patients with COVID-19 pneumonia, based on symptoms, laboratory findings, Computed Tomography (CT) findings, chronic diseases and continuous medications they use.

MATERIAL AND METHOD

Study design and Setting

This study was carried out retrospectively observationally in the Covid-19 outpatient clinic of a tertiary education and research hospital. The study consists of patients who applied to the Covid outpatient clinic between March of 2020 and 2021 and were hospitalized after being diagnosed with Covid-19. Patient data were analyzed retrospectively. Before starting the study, consent was obtained from the hospital local ethics committee with the required number 711.

Study Population

All patients admitted to our hospital's COVID-19 outpatient clinic, diagnosed with COVID-19, confirmed by the RT-qPCR test result and detected pneumonia in imaging were included in the study. Patients who were younger than 18 years old, who had no respiratory symptoms, who did not have lung imaging, and who had no pneumonic infiltration in the thorax even if the RT-qPCR test was positive were excluded from the study.

Data Collection and processing

Demographic features such as age, gender, complaints, vital signs of patients with Covid-19 pneumonia, physical examination findings, smoking, other habits, chronic disease, drugs used, laboratory, imaging test results, the treatment regimen applied in the hospital, the length of stay in the hospital and intensive care unit were obtained and recorded in the hospital registry system. Clinical outcomes of all patients; acute respiratory distress syndrom (ARDS) has been recorded by classifying it as discharge or exitus.

Outcome Measures

The primary outcome of the study was the development of ARDS in patients with Covid-19 pneumonia. The definition of ARDS was made according to the Berlin criteria.[6] Updated in 2012 and stated below. It is aimed to determine the risk factors for the development of ARDS in patients with Covid-19 pneumonia. The secondary outcome of the study was the terms of survival and death. It was aimed to determine the factors affecting mortality in patients with Covid-19 pneumonia.

Berlin Criteria
1. Acute onset (over 1 week or less)
2. Bilateral opacities consistent with pulmonary edema must be present on CT or chest radiograph
3. PaO_2/FIO_2 ratio <300mmHg with a minimum of 5 cmH_20 PEEP (or CPAP)
4. "must not be fully explained by cardiac failure or fluid overload," in estimation using available information-an "objective assessment" (e.g. echocardiogram)

Statistical Analysis

Descriptive statistics were expressed as frequency, percentage, mean, standard deviation, median, minimum and maximum values. Number and percentage values were calculated for categorical variables. Mean, standard deviation, minimum and maximum values and interquartile range (IQR) were calculated for numerical variables. Histogram curves, kurtosis and skewness values and Shapiro-Wilk test were used to determine whether the data were normally distributed. Normally distributed parameters were expressed as mean and standard deviation, and non-normally distributed variables were expressed as median and minimum-maximum values.

Patients with Covid-19 pneumonia were divided into two groups as patients with and without ARDS. Age, gender, vital signs, chronic diseases, and laboratory findings of these two groups were compared. In this comparison, the categorical variables were compared with the chi-square test and the Student-t test if the numerical variables provided the normal distribution, and the Mnnn-Whitney -u test if they did not. The areas under the curve and the cut-off values separating the two groups were determined by drawing the ROC curve separately for all parameters.

Regression analysis was used to analyze the power of all parameters found to be significant in these analyzes to predict the going to ARDS in Covid-19 pneumonia. First, all the parameters found to be significant were evaluated one by one in the univariate regression analysis, and all the parameters found to be statistically significant were included in the model in the multivariate logistic regression analysis, and their value in predicting ARDS access was calculated. Likewise, all patients were divided into two groups according to the clinical outcome of survival and death.

The power of all parameters, which showed a significant difference between the groups in the dual analysis, was drawn again by drawing the ROC curve, and the areas under the curve and cut-off values were calculated. All parameters that were successful in these analyzes were first tested in univariate regression alalysis.

A model was created from all significant parameters and the ability of this model to predict mortality in Covid-19 pneumonia was evaluated in multivariate logistic regression analysis. All statistical calculations were done on SPSS 23.0 (SPSS Inc., Chicago, IL, USA) for Windows software. All analyzes were done at a 95% confidence interval and p values of <0.05 were considered statistically significant.

RESULTS

Patients diagnosed with Covid pneumonia (434 patients), including 190 (44%) female and 244 (56%) male patients, were included in this study. The average age of all patients with Covid-19 pneumonia was 53±19. 164 (38%) of 434 patients had at least one chronic disease. 59 (14%) of 434 patients with Covid pneumonia had ARDS clinic and 48 (11%) died. The mean initial oxygen saturation of patients with COVID-19 pneumonia was 96±4, while the admission oxygen saturation of patients who progressed to ARDS was 84±7, and the admission oxygen saturation of the patients who died was 84±8. The demographic characteristics, complaints and vital signs and laboratory parameters of the patients are presented in **Table 1**.

ARDS developed in 59 of 434 patients with Covid pneumonia. Age, blood pressure at presentation and oxygen saturation were statistically significantly different between the group that developed ARDS and the group that did not. The comparison of the general characteristics, laboratory parameters and medical history of the group that developed ARDS and the groups that did not are presented in **Table 2**.

48 (11%) of the 434 patients with Covid-19 pneumonia died. All demographic data and laboratory parameters of patients with exitus and living patients were compared. Age, blood pressure, oxygen saturation at presentation, prodictive cough at presentation, myalgia and dyspnea were found to be statistically significantly different between the deceased and the surviving patients. In addition to these parameters, the comparison of laboratory findings and medical history data between the groups is presented in **Table 3**.

Table 1. General characteristics, vital signs and laboratuvar findings of subjects

Parameters	Total Patients (with Covid-19 pneumonia)	Patients with ARDS	Dying patients
General characteristics &Vital signs			
No.	434	59	48
Age y (mean±SD)	53±19	68±18	71±17
Male n (%)	56	58	63
Female n (%)	44	42	38
Siistolik BP (mm Hg)	122±18	111±17	110±17
Diastolik BP (mm Hg)	74±13	68±12	67±12
Admission oxygen saturation (%)	96±4	84±7	84±8
Admission symptoms			
Fever (C)	38± 0.6	37±08	36.9±0.9
Throat ache (%)	17.3	15.3	14.6
Myalgia (%)	29.5	20,3	47.9
Diarrhea (%)	6.9	3.2	8.3
Runny nose (%)	4.8	5.1	2.1
Dry cough (%)	49.5	76.3	72.9
Productive cough (%)	8.1	11.9	20.8
Dyspnea (%)	25.8	93.2	93.8
Laboratory analysis			
WBC (*10^9/L wbc/mcL)	6.6±3	9±6	9.5±6.6
Neutrophil (*10^3 neut/mcL)	4.6±5	7.4±5	7.8±5.4
Lymphocyte(*10^3 lym/mcL)	1.7±1.1	1.6±2.4	1.6±1
Platelet (*10^3 plt/mcL)	227±89	148±64	153±64
K+(mmol/l)	4.1±0.5	4.3±0.9	4.3±0.9
Ca+(mg/dL)	8.5±0.7	7.5±0.5	9±7,4
Na+(mEq/L)	137.3±4	136±5.6	136±6
AST (IU/L)	40±117	132.6±44	154±52
ALT (IU/L)	45±217	136±30	161±38
BUN (mg/dL)	17±13	32±27	35.3±24
Lactate (mmol/L)	1.7±17.3	2.3±1.6	2.5±2.7
Troponin (ng/ml)	0.69±0.55	0.36±0.02	0.44±0.29
D-Dimer (mcg/mL)	502±997	2077±1874	2080±1167
Ferritin (ng/mL)	350±469	999±88	1020±790
Medical history			
CHF n (%)	3.9	5.1	6.3
DM n (%)	17.1	20.3	25
CRF n (%)	3.7	5.1	6.3
COPD (%)	11.1	18.6	16.7
HT (%)	17.1	33.9	41.7
CAD (%)	9	15.3	16.7
Cancer (%)	3	11.9	10.4
Alzheimer and dementia (%)	2.3	8.5	10.4
Medication			
ACEI inhibitors (%)	13.6	22	27.1
Diuretic (%)	9	30.5	33.3
Anticoagulant (%)	14.7	28.8	33.3
Ca Channel Blocker (%)	12.2	6.8	8.3

WBC: White blood cell, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, BUN: Blood urea nitrogen, CHF: Chronic heart failure, DM : Diabetes mellitus, CRF : Chronic renal failure, COPD: Chornic obstructive pulmonary disease, HT: Hypertension, CAD: Coronary artery disease, ACEI: Angiotensin-converting enzyme (ACE) inhibitors

Table 2. Comparison of data of patients with Covid-19 pneumonia with and without ARDS

Parameters	Patients with ARDS n:58	Patients without ARDS n:373	p
General characteristics &Vital signs			
Age y (mean±SD)	68±18	51±18	<0.001
Gender F n (%)	25 (13%)	165 (87%)	0.815
M n (%)	34 (14%)	210 (86%)	
Systolic BP (mm Hg)	111±17	123±15	<0.001
Diastolic BP (mm Hg)	68±12	75±9.8	<0.001
Admission oxygen saturation (%)	85±7	97±2.3	<0.001
Admission symptoms			
Fever (C)	36.8±0.8	36.7±0.7	0.487
Throat ache (%)	9 (15.5%)	66 (17.7%)	0.684
Myalgia (%)	29	99	<0.001
Diarrhea (%)	7 (12%)	23 (6%)	0.10
Runny nose (%)	3 (3.2%)	18 (4.8%)	0.909
Dry cough (%)	45 (76%)	174 (47%)	<0.001
Productive cough (%)	12 (21%)	23 (6%)	<0.001
Dyspnea (%)	55 (93%)	80 (22%)	<0.001
Laboratory analysis			
WBC (*10^9/L wbc/mcL)	9.1±5.9	6.3±2.4	0.002
Neutrophil (*10^3 neut/mcL)	7.4±5.8	4.3±4.8	<0.001
Lymphocyte(*10^3 lym/mcL)	1.6±2.4	1.7±0.7	<0.001
Platelet (*10^3 plt/mcL)	148±64	239±86	<0.001
K+(mmol/l)	4.3±0.9	4.1±0.39	0.016
Ca+(mg/dL)	7.5±0.4	8.9±3.8	<0.001
Na+(mEq/L)	136±5.6	138±3.6	0.010
AST (IU/L)	133±510	28±22	<0.001
ALT (IU/L)	137±614	33±47	0.046
BUN (mg/dL)	32±27	15 ±7.6	<0.001
Lactate (mmol/L)	2.3±2.2	1.4±0.6	0.138
Troponin (ng/ml)	0.36±1.4	0.018±0.058	<0.001
D-Dimer (mcg/mL)	2078±1875	357±628	<0.001
Ferritin (ng/mL)	999±851	262±300	<0.001
Medical history			
CHF n (%)	3 (7%)	14 (4%)	0.374
DM n (%)	12 (27%)	62 (17%)	0.100
CRF n (%)	3 (7%)	13 (4%)	0.317
COPD (%)	11 (25%)	37 (10%)	0.030
HT (%)	20 (44%)	96 (26%)	0.012
CAD (%)	9 (20%)	30 (8%)	0.012
Cancer (%)	7 (15%)	6 (2%)	<0.001
Alzheimer and dementia (%)	5 (11%)	5 (1%)	<0.001
Medication			
ACEI inhibitors (%)	13 (28%)	46 (13%)	0.004
Diuretic (%)	21 (36%)	24 (7%)	<0.001
Anticoagulant (%)	10 (17%)	12 (3%)	<0.001
Ca Channel Blocker (%)	4 (9%)	49 (13%)	0.380

WBC: White Blood Cell, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, BUN: Blood Urea Nitrogen, CHF: Chronic Heart Failure, DM : Diabetes Mellitus, CRF : Chronic Renal Failure, COPD: Chornic Obstructive Pulmonary Disease, HT: Hypertension, CAD: Coronary artery disease, ACEI: Angiotensin-converting enzyme (ACE) inhibitors

Table 3. Comparison of data of patients with Covid pneumonia by clinical outcome in terms of survival and death

Parameters	Dying patients n:48	Surviving patients n:387	p
General characteristics &Vital signs			
Age y (mean±SD)	71±17	51±18	<0.001
Gender F n (%)	18 (10 %)	172 (90 %)	0.353
M n (%)	30 (12%)	214 (88 %)	
Systolic BP (mm Hg)	110±17	123±15	<0.001
Diastolic BP (mm Hg)	67±12	75±10	<0.001
Admission oxygen saturation (%)	84±8	97±3	<0.001
Admission symptoms			
Fever (C)	36.9±0.9	36.7±0.7	0.511
Throat ache n (%)	7 (14 %)	68 (18 %)	0.631
Myalgia n (%)	23 (27 %)	105 (49 %)	0.002
Diarrhea n (%)	4 (9 %)	26 (7 %)	0.658
Runny nose n (%)	1 (2 %)	20 (5 %)	0.354
Dry cough n (%)	35 (%)	184 (%)	0.001
Productive cough n (%)	10 (21 %)	25 (8 %)	<0.001
Dyspnea n (%)	45 (94 %)	90 (24 %)	<0.001
Laboratory analysis			
WBC (*10^9/L wbc/mcL)	9.5±6.3	6.3±2.4	0.006
Neutrophil (*10^3 neut/mcL)	7.8±6.2	4.3±4.7	<0.001
Lymphocyte(*10^3 lym/mcL)	1.6±2.7	1.7±0.8	<0.001
Platelet (*10^3 plt/mcL)	153±65	237±88	<0.001
K+(mmol/l)	4.3±0.9	4.1±0.4	0.52
Ca+(mg/dL)	9±2	8.6±0.6	<0.001
Na+(mEq/L)	136±6	137±4	0.112
AST (IU/L)	155±561	28±21	<0.001
ALT (IU/L)	161±675	32±46	0.02
BUN (mg/dL)	35±29	15±8	<0.001
Lactate (mmol/L)	2.5±2.3	1.4±0.6	0.035
Troponin (ng/ml)	0.4±1.5	0.01±0.05	<0.001
D-Dimer (mcg/mL)	2081±2038	406±698	<0.001
Ferritin (ng/mL)	1021±880	273±322	<0.001
Medical history			
CHF n (%)	3 (8 %)	14 (4 %)	0.212
DM n (%)	12 (25 %)	62 (16 %)	0.015
CRF n (%)	3 (8 %)	13 (3 %)	0.173
COPD n (%)	8 (17 %)	40 (10 %)	0.036
HT n (%)	20 (53 %)	96 (25 %)	<0.001
CAD n (%)	8 (21 %)	31 (8 %)	0.009
Cancer n (%)	5 (13 %)	8 (2 %)	<0.001
Alzheimer and dementia (%)	5 (13 %)	5 (1%)	<0.001
Medication			
ACEI inhibitors (%)	13 (34 %)	26 (12 %)	<0.001
Diuretic (%)	19 (40 %)	46 (7 %)	<0.001
Anticoagulant (%)	16 (41 %)	48 (12 %)	<0.001
Ca Channel Blocker (%)	4 (11 %)	49 (13 %)	0.665

WBC: White Blood Cell, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, BUN: Blood Urea Nitrogen, CHF: Chronic Heart Failure, DM : Diabetes Mellitus, CRF : Chronic Renal Failure, COPD: Chornic Obstructive Pulmonary Disease, HT: Hypertension, CAD: Coronary artery disease, ACEI: Angiotensin-converting enzyme (ACE) inhibitors

First of all, all parameters in Table 2, which were found to be statistically significantly different between the group with ARDS and the group without ARDS, were tested in the univariate logistic regression analysis. The age of the patients, the oxygen saturation value obtained from the patients at the time of admission, blood calcium value, platelet value, D-Dimer value and the data of chronic diuretic use of the patients were found to be statistically significant ($p<0.005$) in the univariate logistic regression analysis. The sensitivity and specificity of these parameters to detect ARDS and the results of the logistic regression model created from these parameters are presented in **Table 4**. In the regression analysis, it was seen that the age parameter was a confounding factor. The model consisting of oxygen saturation, calcium, platelet, d-dimer and diuretic use was strong enough to detect 50% of all ARDS events according to Cox & Snell R Square, and the overall percentage of success of the model for predicting all events was found to be 86.2%.

Factors determining the course of mortality in patients were tested using logistic regression analysis. First of all, all parameters in **Table 3** that were found to be statistically significantly different between patients who died and those who survived were tested in the univariate logistic regression analysis. The age of the patients, the oxygen saturation value, blood calcium value, platelet value, D-Dimer value and the chronic diuretic use of the patients were found to be statistically significant ($p<0.005$) in univariate logistic regression analysis. The sensitivity and specificity of these parameters calculated to determine mortality and the results of the logistic regression model created from these parameters are presented in **Table 5**. After making age related corrections D-Dimer was found to be a confounding factor in the regression analysis. According to the Cox & Snell R Square, the model consisting of oxygen saturation, calcium, platelet, d-dimer and diuretic use was strong enough to explain 38% of all cases resulting in mortality, and the overall percentage of success of the model in predicting all events was found to be 94%.

DISCUSSION

434 patients diagnosed with Covid pneumonia, including 190 (44%) female and 244 (56%) male patients, were included in this study, 59 of these patients (14%) developed ARDS clinic and 48 (11%) died. The 22 parameters shown in Table 2 were found to be statistically significant between patients who developed ARDS and those who did not. However, in regression analysis, low oxygen saturation at admission, chronic diuretic use, low laboratory calcium level, low platelet level and high D-dimer value were found to be significant risk factors in the development of ARDS in patients with covid pneumonia. Among these parameters, the highest risk was found in relation to the use of diuretics. Diuretic use was found to be associated with an approximately 13-times increased risk of developing ARDS. However, in the analyzes we conducted to determine the factors determining mortality in Covid-19 patients, the 24 parameters seen in table 3 were statistically significant between the patients who died and survived. However, among these parameters, elderly patients, low oxygen saturation at the time of admission, chronic diuretic use, laboratory calcium, and low platelet levels were found among significant risk factors for mortality in Covid-19 pneumonia. Among these parameters, the use of diuretics was found to be the most significant parameter, creating approximately 6 times (Exb: 1/0.154) risk for mortality.

ARDS is one of the major complications of Covid-19. Among the application complaints of patients with severe Covid-19 pneumonia and ARDS, dyspnea was stated as the most common complaint.[7] In our study, 55 (93%) of 59 patients who developed ARDS had dyspnea at presentation. In their study with patients with Covid-19 pneumonia, Hu et al. [8] reported that 20% of patients developed ARDS and 12% needed a mechanical ventilator. In our study, it was observed that 59 (13.4%) of 434 patients with Covid-19 pneumonia developed ARDS and our data were found to be compatible with the reports of Hu et al. ARDS is a clinical syndrome with a mortality rate of more than 50% and characterized by hypoxia and

Table 4. Multivariate Logistic Regression analysis to predict ARDS in patients with Covid-19 Pneumonia

ARDS	B	Exb (ods r)	CI(%95)Upper bound	CI(%95) Lower bound	P	Cut-off	Sensitivity	Specificity	AUC
Sat O_2	-0.822	0.44	0.304	0.637	<0.001	88.5	0.458	0.011	0.019
Ca^{++}	-1.051	0.35	0.146	0.836	0.018	7.45	0.508	0.019	0.049
Plt	-0.028	0.973	0.958	0.987	<0.001	152500	0.458	0.125	0.172
D-dimer	0.001	1.001	1	1.001	0.034	351	0.915	0.709	0.899
Age	0.001	1.001	0.96	1.043	0.979	56.5	0.746	0.635	0.753
Diuretic use	2.585	13.265	1.898	92.707	0.009	0.5	0.356	0.062	0.647

AUC: Area under the curve, ARDS: Acute respiratory distress syndrome, Ca++ : Calcium, Sat O2 : Saturation of Oxygen, Plt: Platelet

Table 5. Multivariate Logistic Regression analysis to predict mortality in patients with Covid-19 pneumonia

Mortality	B	Exb (ods r)	CI (%95) Lower bound	CI (%95) Upper bound	P	Cut-off	Sensitivity	Specificity	AUC
Plt	-0.01	0.99	0.985	0.996	0.001	152500	0.511	0.142	0.213
Age	0.037	1.038	1.006	1.072	0.021	64.5	0.73	0.761	0.788
Diuretic use	-1.87	0.154	0.046	0.512	0.002	0.5	0.356	0.068	0.644
D-dimer	0	1	1	1.001	0.333	334.5	0.991	0.682	0.863
Sat O_2	-0.408	0.665	0.579	0.764	0.001	81	0.644	0.008	0.024
Ca^{++}	-2.728	0.065	0.034	0.127	0.001	7.94	0.21	0.101	0.054

AUC: Area under the curve, ARDS: Acute respiratory distress syndrome, Ca++ : Calcium, Sat O2 : Saturation of Oxygen, Plt: Platelet

pulmonary damage.[8] In this syndrome, the pulmonary barrier is disrupted; permeability, inflammation, cellular infiltration and exudation are increased; necrosis occurs; as a result, ventilation and perfusion are impaired.[3] It is known that lung damage and ARDS are the main factors that cause death in patients with Covid-19 disease. In our population, only one of 48 patients who died did not develop ARDS. It was observed that 47 (79%) of 59 patients with ARDS died. According to the results of our study, the mortality of patients who developed ARDS due to Covid-19 pneumonia was found to be 79%. This shows us that ARDS developing due to Covid-19 may have a more mortal course than ARDS caused by other reasons.

While COVID-19 may progress with an asymptomatic or mild clinical course in some patients,[9,10] it may cause severe respiratory failure and death in some patients.[11,12] The reason for the different severity of the disease among individuals has not been fully elucidated yet. However, it has been previously reported that comorbidities,[11,13] advanced age,[14] and male gender[15] may be factors indicating that the disease may progress to a severe course. In later studies, it was reported that high D-Dimer levels,[16] hypocalcemia,[17] and low platelets,[18] may be associated with the severity and mortality of the disease. In our study, among these parameters, thrombocytopenia and hypocalcemia were found to be risk factors for both ARDS and mortality. In addition, D-dimer level was found to be associated with the development of ARDS in parallel with these studies, while advanced age was also found to be associated with mortality, similar to other studies. In our study, the severe course of the disease and the factors affecting mortality are largely similar to the literature. Unlike the literature, chronic diuretic use has been found to be an important risk factor for both mortality and ARDS. There are previous studies claiming that the use of angitensin converting enzyme inhibitors (ACEIs) may be associated with poor outcome in Covid-19 patients,[19] as well as studies claiming to be unrelated.[20] There are rare studies evaluating the effect of diuretic use on Covid-19. In these studies, it is reported that the use of in-hospital diuretics is associated with poor outcome in Covid-19.[21] Covid-19 pneumonia is a disease that can progress with taste disturbance, fever, and loss of appetite. Therefore, it is possible that the tendency to dehydration will increase in these patients with a decrease in oral intake and an increase in insensible losses with possible fever. Especially in elderly patients with comorbidities and who have a high tendency to be complicated, the tendency to dehydration is likely to increase with Covid-19 pneumonia. Presence of additional diuretic use in these patients may increase diuresis and the resulting dehydration may lead to circulatory disturbance and shock. Therefore, as in our population, the use of diuretics in patients with Covid-19 pneumonia may be associated with mortality, albeit indirectly.

The relationship between hypocalcemia and Covid-19 disease has been evaluated in many studies. Hypocalcemia has been recently identified as one of the major biochemical features of COVID-19 patients.[3,4,25] Until now, both low ionized and low total calcium levels have frequently been reported in emergency rooms (ED) and hospitalized patients.[4,25] Moreover, a strong association between lower calcium and higher inflammatory parameters and increased disease severity has also been reported.[4] In addition, some authors defined hypocalcemia as a relevant and independent risk factor for worse clinical outcome, including hospitalization rate, intensive care unit admission, and mortality.[4,22,23] Calcium is an essential ion for the survival of pathogens and virulence and plays a role in regulating the inflammatory response, and hypocalcemia is a common laboratory finding in critically ill patients.[24] In our study, in accordance with the literature, hypocalcemia was found to be associated with mortality and ARDS.

It is known that the coagulation system is affected in COVID-19, while the D-dimer and prothrombin time increase, the platelet value decreases. D-Dimer is one of the most studied prognostic factors on this subject. Numerous studies have reported a high number of venous thromboembolism (VTE), especially in patients with severe COVID-19.[26] Coagulopathy caused by COVID-19 manifests itself with an increase in D-dimer and fibrin/fibrinogen levels and a decrease in platelet count.[26] In our study, while high D-dimer levels were found to be associated with ARDS, thrombocytopenia was found to be closely related to both ARDS and mortality. These data we obtained in our study are consistent with the present findings in the literature.

Limitation

The most important limitation of this study is that it was conducted with a relatively low number of patients in a global epidemic such as a pandemic, and as in all retrospective studies, it was conducted through patient records.

CONCLUSION

In this study, low oxygen saturation, chronic diuretic use, hypocalcemia and thrombocytopenia were found to be significant parameters that increase the risk for both ARDS and mortality in patients with Covid-19 pneumonia. In addition, high D-Dimer was found to be a significant risk factor for the development of ARDS, while advanced age was found to be a significant risk factor for mortality.

ETHICAL DECLARATIONS

Ethics Committee Approval: İzmir Katip Çelebi University Non-Interventional Clinical Studys Institutional Review Board (date: 12.05.2020 number: 711).

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 author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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