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The role of alveolo-arterial oxygen gradient and pneumonia severity index in predicting mortality in patients with COVID-19 pneumonia

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Abstract

Purpose of the study is to determine the success rates of alveolo-arterial oxygen gradient (AaDO2) and the pneumonia severity index (PSI) in predicting mortality for the patients diagnosed with COVID-19 pneumonia. This retrospective study included patients who were treated with the diagnosis of COVID-19 pneumonia in the ICUs. Demographic characteristics, arterial blood gas values, radiological images and laboratory data of the patients were used through the hospital database and patient files. Group I patients consist of alive and Group II patients consist of deceased persons. 150 of 263 patients included in this study are in Group I and 113 are in Group II. RT-PCR test was positive in 20.9% of the patients. The most common symptom was dyspnea with 76.5% and the most common additional disease was hypertension with 58.1%.65% of patients had radiological involvement in both lungs, and the most common finding was the ground-glass opacity at 71.5%. In predicting mortality, PSI value was 135 in group I and 174 in group II ($p<0.001$);AaDO2 value was 154.88 mmHg in group I, 177.13 mmHg in group II ($p<0.001$), and this rate was different between the groups. Sensitivity is found at 84.1% and specificity at 67.3% for PSI, whereas sensitivity is found at 49.6% and specificity at 82.7% for the AaDO2 variable. It is important to estimate the mortality risk earlier for the patients with COVID-19 pneumonia who are also followed up in intensive care units. PSI is beneficial in detecting mortality risk whereas AaDO2 is valuable in determining the surviving patients.

Keywords: alveolo-arterial oxygen gradient, COVID-19, mortality, pneumonia severity index

1. Introduction

The new coronavirus disease-19 (COVID-19), also known as the new coronavirus pneumonia, first appeared in Wuhan Province of China during early December and spread almost all over the world within two months which also caused a pandemic. COVID-19 disease is caused by the virus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). 80% of COVID-19 patients have mild illness whereas 20% require hospitalization. Some of these cases need to be followed under the intensive care units (ICU). The cases that need to be followed up in intensive care refer to the patients with severe pneumonia and acute respiratory distress syndrome (ARDS) requiring invasive or non-invasive respiratory support. This rate is between 5% and 10% for the patients requiring hospitalization (1-3).

In general, pneumonia is ranked 6th among all causes of death in the United Kingdom and the USA. Pneumonia is also ranked 1st among the deaths caused by infections. The mortality rate ranges between 1-5% for the ambulatory patients diagnosed with pneumonia whereas it reaches up to 12% for the hospitalized patients and 40% for the patients in the ICUs. In our country, the mortality rate ranges between 30% and 87% for the hospital-acquired pneumonia (4). Several scoring systems are used to predict mortality in pneumonia. The most popular ones are the pneumonia severity index (PSI) and CURB-65. The patient's demographic data, concomitant diseases, physical examination findings and laboratory values are used in calculating PSI (5-7).

The fatal disease incidents appear as severe pneumonia and ARDS in COVID-19 patients. The PaO2/FiO2 (arterial oxygen pressure/fraction of inspired oxygen) and the alveolar-arterial oxygen gradient (AaDO2) are the indicators of oxygenation status in critical ill patients and stand as the diagnostic criteria for ARDS in adults. Low PaO2/FiO2 value has been associated with the increased mortality and hospitalization period for the patients admitted to the ICUs. The PaO2/FiO2 rate provides quick and easy data on the oxygenation status of critical ill

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patients and it is widely used in the ICUs (8). The AaDO2 refers to the difference between the alveolar oxygen pressure (PAO2) and arterial oxygen pressure (PaO2) whereas it enables the evaluation of ventilation/perfusion abnormalities in the lung and its calculation is fast, easy and practical on less variables in comparison to the PSI (5,9).

As end of December, the number of patients with positive COVID-19 real-time reverse transcriptase polymerase chain reaction (RT-PCR) tests in our country exceeded 2 million and the number of deaths exceeded 20.000. The purpose of this study conducted on the patients diagnosed with COVID-19 pneumonia and treated under the ICUs of Samsun Education and Research Hospital is to determine the success rate of alveolo-arterial oxygen gradient and the pneumonia severity index in predicting mortality.

2. Material and Methods

2.1. Ethics approval

Ethics approval was obtained through the Turkish Ministry of Health Scientific Research Platform with June 15, 2020 date and the ethics board of the Samsun Education and Research Hospital June 30, 2020 date and with 2020/10 number. The study adhered to Declaration of Helsinki.

2.2. Study Design and Patients

This single-center retrospective cohort study enrolled 263 patients with moderate to critical COVID-19 associated pneumonia hospitalized in Samsun Education and Research Hospital. The cohort was composed to include all patients who were admitted to the ICU during the period 01 April 2020-01 November 2020 with a primary admitting diagnosis of COVID-19 pneumonia and had both PSI and AaDO2 calculated at the time of admission. Patients were divided in to two groups based on the clinical outcomes: group I (discharge patients) and group II (deceased patients).

National Health Committee of the Republic of Turkey recommendations for diagnosis of COVID-19 associated pneumonia was used. Patients included in this study met the following criteria: confirmed COVID-19 infection based on RT-PCR testing from a throat swab sample; objective evidence of new-onset pneumonia from chest computed tomography (CT); typical symptoms of COVID-19 pneumonia, i.e., fever, cough, dyspnea (10).

Exclusion criteria

- Patients diagnosed with non-COVID-19 pneumonia
- Patients whose blood gas and laboratory values cannot be reached
- Patients without radiological images in the hospital database
- Patients who are not followed up in the ICU due to respiratory failure

2.3. Data collection

Demographic characteristics, comorbidities, presenting symptoms, vital signs (including fever, blood pressure, respiratory rate, oxygen saturation, heart rate), state of consciousness, initial laboratory parameters, and time to death were collected from electronic medical records. Clinical characteristics of all enrolled patients were recorded: gender, age, underlying disease, and smoking status. Baseline biochemical data, arterial blood gas, and complete blood count were also recorded. CRP, procalcitonin, troponin I and D-dimer tests were performed; radial arterial blood gases with arterial puncture were obtained in the first hour of hospital admission.

Calculation of alveolar–arterial oxygen gradient

Arterial blood gases, including arterial partial pressure of oxygen (PaO2), arterial partial pressure of carbon dioxide (PaCO2) and arterial oxygen saturation (SaO2), were measured on admission to the emergency room. The alveolar-arterial oxygen gradient was calculated as follows (9): AaDO2 [mmHg] = 150-1.25(PaCO2 – PaO2)

Calculation of pneumonia severity index

The PSI was calculated based on the description given by Fine et al. (7). Using the following parameters: age, gender, comorbidities (renal disease, liver disease, congestive heart failure, cerebrovascular disease and neoplasia), nursing home resident, physical examination (altered mental status, systolic blood pressure <90 mmHg, temperature <35 or ≥39.9°C, respiratory rate ≥30 breaths/min and heart rate ≥125 b.p.m.), laboratory data (pH <7.35, arterial oxygen tension <60 mmHg, serum Na <130 mEq/L, haematocrit <30%, serum glucose ≥250 mg/dL and blood urea nitrogen ≥30 mg/dL) and a radiological parameter, namely the presence of a pleural effusion. The normal value of PSI is between 8 and 90; 91-130 points indicate moderate risk, 130 points and above indicate high mortality risk. An on-line calculator is available to easily compute PSI: https://www.mdcalc.com/psi-port-score-pneumonia-severity-index-cap

2.4. Outcomes

The primary outcome was to compare the relationship between the AaDO2 and PSI outcome measures, namely LOS and survival. The secondary outcome was to assess the association between each of the two. The pneumonia diagnosis was determined by symptoms, physical examination findings, and radiological findings. After the first evaluation and radiological examination, arterial blood gases are derived from the patients.

2.5. Statistical Analysis

The compliance of relevant data with normal distribution was tested by the Shaphiro-Wilk test. The Student-test was used to compare normally distributed features in groups I and II, and the Mann-Whitney U test was used to compare non-normally distributed features in groups I and II. The relationship analysis of categorical variables observed in group I and II were analyzed by Exact or Pearson Chi-square tests. In this study, the age, gender and smoking variables as well as some clinical characteristics, laboratory and treatment methods were

analyzed firstly with the Univariate LR (Logistic Regression) method, and then the variables found as significant were analyzed with the Stepwise Multivariate Enter LR method. By means of the PSI, alveolar oxygen pressure, AaDO2, PaCO2 and PaO2 variables, the ROC graph was drawn over the mortality rate through the relevant cut-off rates. The minimum-maximum and median values are given as descriptive statistics for the numerical variables whereas the quantity and % rates are given for the categorical variables. SPSS Windows version 23.0 software was used for statistical analysis and $p<0.05$ was considered as statistically significant.

3. Results

Hundred fifty of 263 patients included in this study were evaluated in group I and 113 patients are evaluated in group II. The mortality rate was found at 42.9%. 55.9% (n=147) of the patients were male and 44.1% (n=116) were female, and the mean age was 72.05±12.2 (21-96) years. 75.7% of the patients were over 65 years old and 95.8% had comorbidity. The most common additional diseases in the patients are; hypertension at 58.1% (n=153), cardiac diseases at 50.2% (n=132), diabetes at 35% (n=92), neurological diseases at 24.3% (n=64), chronic obstructive pulmonary diseases at 23.9% (n=63) and chronic renal failure at 16.3% (n=43). The RT-PCR test was resulted positive only in 20.9% (n=55) of the patients included in this study. The remaining patients were diagnosed clinically and/or radiologically. The most common symptoms in the patients are dyspnea at 76.5% (n=202), fever at 28.8% (n=76) and cough at 26.1% (n=69). While the state of consciousness was normal in 31.9% of our patients who were under intensive care and 14.4% were in a state of coma (Table 1).

Table 1. Demographic, clinical characteristics and comorbidities of patients

	Group I n=150		Group II n=113		Total n=263		
	n	%	n	%	n	%	p
RT-PCR test							**<0.001**
Positive	16	10.7	39	34.5	55	20.9	
Negative	134	89.3	74	65.5	208	79.1	
Age (year)							0.468
<65	39	26.0	25	22.1	64	24.3	
>65	111	74.0	88	77.9	199	75.7	
Gender							0.143
Female	72	48.0	44	38.9	116	44.1	
Male	78	52.0	69	61.1	147	55.9	
Smoking status							0.195
Yes	45	30.4	43	38.1	88	33.7	
No	103	69.6	70	61.9	173	66.3	
COVID-19 Diagnosis							**0.013**
RT-PCR	21	14.0	34	30.1	55	20.9	
Radiological	41	27.3	21	18.6	62	23.6	
Clinical	42	28.0	27	23.9	69	26.2	
Clinical/Radiological	46	30.7	31	27.4	77	29.3	
Comorbidity							0.428
Yes	145	96.7	107	94.7	252	95.8	
No	5	3.3	6	5.3	11	4.2	
Symptoms							
Dyspnea	113	75.3	89	78.7	202	76.5	0.484
Fever	49	32.7	27	23.9	76	28.8	0.121
Cough	38	25.3	31	27.4	69	26.1	0.707
Medical condition abnormality	15	10.0	14	12.4	29	11.0	0.541
Nausea/vomiting	10	6.7	8	7.1	18	6.2	0.896
Chest pain	11	7.3	5	4.4	16	6.1	0.329
Fatigue	8	5.3	8	7.1	16	6.1	0.557
Diarrhea	4	2.7	6	5.3	10	3.8	0.268
Consciousness							**<0.001**
Awake	59	39.4	25	22.1	84	31.9	
Confusion	45	30.0	24	21.2	69	26.3	
Delirium	12	8.0	9	8.0	21	8.0	
Stupor	23	15.3	28	24.8	51	19.4	
Coma	11	7.3	27	23.9	38	14.4	

It was observed that the rate of positive observation of COVID-19 RT-PCR test in group II (34.5%) was statistically significant and it is higher than the rate of positive observation of COVID-19 RT-PCR test (10.7%) in the individuals under group I ($p<0.001$). In group II, the rate of determining the diagnosis of COVID-19 by RT-PCR test (30.1%) was statistically significant and it is higher in comparison to the rate of diagnosis of COVID-19 observed with RT-PCR test (14%) in the individuals under group I ($p=0.013$). Furthermore, it was observed that the probability of the patients diagnosed

radiologically and clinically to be living individuals was significantly higher. When the groups were compared in terms of the level of consciousness, it was observed that the rate of awareness was significantly higher in group I patients (39.3%) compared to group II patients (22.1%) ($p<0.001$) (Table 1).

In the patients included in this study, systolic blood pressure and diastolic blood pressure in group I were found to be statistically significant and higher than the group II patients ($p<0.05$). On the other hand, respiratory rate and heart rate were significantly higher in group II patients ($p<0.05$). While BUN, creatine, lactate, CRP, procalcitonin, D-Dimer, PT, INR, AST, total bilirubin, CK-MB and troponin values were statistically higher in group II patients, it was observed that values such as lymphocyte percentage value, pH, oxygen saturation, PaCO2, PaO2, bicarbonate, base excess and albumin were statistically significantly lower in group II patients ($p<0.05$) (Table 2).

Table 2. Vital signs and laboratory findings

	Group I		Group II		Total		
	min-max	median	min-max	median	min-max	median	p
Vital signs							
SBP, mmHg	60-214	127.5	50-194	110.0	50-214	120	**<0.001**
DBP, mmHg	40-130	74.0	18-127	66.0	18-130	70	**<0.001**
Respiratory rate, min^{-1}	14-47	23.0	10-52	25.0	10-52	24	**0.003**
Heart rate, min^{-1}	12-157	93.5	30-153	105.0	12-157	98	**<0.001**
Temperature, °C	36-40.1	36.6	34.5-39.6	36.6	34.5-40.1	36.6	0.284
GKS	5-15	14.0	3-15	12.0	3-15	13	**<0.001**
Laboratory findings							
Hemoglobin, g/l	4-18	12.1	5-16	11.5	4-18	11.7	0.212
Hematocrit, %	13-54	35.55	15-47	34.7	13-54	35.1	0.170
WBC count, 10^9/l	1-39	10.4	0-166	11.5	0-166	10.8	0.381
Lymphocyte count, 10^9/l	0-19	1.2	0-45	1.0	0-45	1.1	0.348
Lymphocyte, %	1-86	12.0	1-67	8.5	1-86	9.8	**0.004**
Neutrophil count, 10^9/l	2-21	8.8	0-30	9.8	0-30	9.45	0.155
Neutrophil, %	12-96	81.7	9-78	84.45	9-78	82.6	0.080
Patelet, 10^9/l	12-750	25.1	23-555	23.1	12-750	24.5	0.373
Glucose, mmol/l	56-593	150.0	40-435	148.0	40-593	149.0	0.760
Sodium, mmol/l	113-147	138.0	116-255	136.0	113-147	137.0	0.063
Potassium, mmol/l	3-8	4.3	3-8	4.5	3-8	4.36	0.056
Urea, mmol/l	3-290	52.5	12-407	95.0	3-407	68.0	**<0.001**
Creatine, mmol/l	0-7	1.0	0-10	1.7	0-10	1.2	**<0.001**
Arterial pH	7-8	7.38	7-8	7.36	7-8	7.37	**0.045**
Saturation, %	70-100	93.0	50-100	90.0	50-100	92.0	**<0.001**
$PaCO_2$, mmHg	23-98	43.0	24-99	39.5	23-99	41.6	**0.003**
PaO_2, mmHg	23-150	67.5	25-191	60.0	23-191	64.0	**0.006**
Arterial HCO_3, mmol/l	2-70	24.8	5-42	21.85	2-70	23.7	**<0.001**
Arterial lactate, mmol/l	0-11	1.65	1-12	2.2	0-12	1.9	**<0.001**
BE	-15-(-50)	0.7	-22-(-19)	-2.2	-22-(-50)	-0.4	**0.002**
CRP, mg/l	0-480	49.0	1-567	115.23	0-567	73.78	**<0.001**
Procalcitonin, µg/l	0-110	0.17	0-120	1.12	0-120	0.3	**<0.001**
D-Dimers, mg/dl	0-50	1.15	0-36	2.36	0-50	1.43	**<0.001**
PT, sec	0-81	12.8	11-146	14.1	0-146	13.35	**<0.001**
INR	1-11	1.14	1-11	1.23	1-11	1.17	**<0.001**
AST, u/l	9-1105	27.0	9-9551	41.0	9-9551	31.0	**<0.001**
ALT, u/l	2-515	17.0	4-3918	22.0	2-3918	19.0	0.051
Albumin, g/l	2-30	3.1	1-4	2.7	1-30	2.9	**<0.001**
Total bilirubin, µmol/l	0-2	0.5	0-11	0.7	0-11	0.6	**<0.001**
CK-MB, u/l	0-380	2.61	0-64	3.49	0-380	2.84	**0.014**
Troponin, ng/l	0-2500	0.10	0-25000	0.12	0-25000	0.1	**0.006**

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, BE: base excess, CK-MB: creatine kinase-MB, CRP: C-reactive protein, DBP: diastolic blood pressure, GKS: Glaskow Coma Score, HCO3: bicarbonate, INR: International Normalized Ratio, PT: Prothrombin time, PaO2: arterial oxygen pressure, PaCO2: arterial carbon dioxide pressure, SBP: systolic blood pressure, WBC: white blood cell.

The chest computed tomography was performed in all patients included in this study. Accordingly, the radiological findings were present in a total of 84.4%, bilateral in 65% and unilateral in 19.4%. While 71.5% of these findings were ground glass opacity (GGO), 43.7% were parenchymal consolidation. GGO was detected at 69.3% for the group I patients, at 74.3% for the group II patients. Parenchyma consolidation in group I patients is at 40.7% and group II patients is scored at 47.8%. There was no statistical difference between group I and II in terms of radiological findings (Table 3). Among the patients included in the study, 9.1% (n=24) required non-invasive mechanical ventilation (NIMV) and 37.2% (n=86) required invasive mechanical ventilation (MV) support. The duration of NIMV application was 0.4 (IQR 1-13)

days, while the duration of MV application was 3.4 (IQR 1-83) days. Complications developed in 38.2% of all patients (n=102), while this rate was significantly lower in group I (18%; n=27) than group II (66.4%; n=75) (p<0.001). The most common complications are; acute renal failure in 12.5% (n=33) of patients, sepsis in 11% (n=29), MODS in 9.8% (n=26) and cardiac dysfunction in 7.9% (n=21) of the patients. The length of stay was 6 (IQR 1-95) days in all patients included in the study, 7 (IQR 1-83) days in group I patients and 4 (IQR 1-95) days in group II patients, and this was statistically significant (p<0.001).

Table 3. Radiological findings

	Group I n=150		Group II n=113		Total n=263		p
	n	%	n	%	n	%	
Chest CT							0.232
Unilateral involvement	33	22.0	18	15.9	51	19.4	
Bilateral involvement	91	60.7	80	70.8	171	65.0	
None	26	17.3	15	13.3	41	15.6	
Ground glass opacity							0.399
Yes	104	69.3	84	74.3	188	71.5	
No	46	30.7	29	25.6	75	28.5	
GGO involvement							0.169
Unilateral	26	17.3	13	11.5	39	14.8	
Bilateral	78	52.0	71	62.8	149	56.7	
None	46	30.7	29	25.7	75	28.5	
Consolidation							0.249
Yes	61	40.7	54	47.8	115	43.7	
No	89	59.3	59	52.2	148	56.3	
Consolidation involvement							0.334
Unilateral	18	12.0	12	10.6	30	11.4	
Bilateral	43	28.7	42	37.2	85	32.3	
None	89	59.3	59	52.2	148	56.3	

Table 4. Comparison of the groups in terms of PSI, PaO_2/FiO_2, alveolar oxygen pressure, alveolo-arterial oxygen gradient

	Group I		Group II		Total		
	min-max	median	min-max	median	min-max	median	p
PSI	44-210	135.0	107-242	174.0	44-242	150.0	**<0.001**
PaO_2/FiO_2	68-402	168.75	53-412	150.0	53-412	162.0	**<0.001**
PAO_2	59-350	221.19	62-385	235.88	59-385	226.25	**<0.001**
$AaDO_2$	28-300	154.88	60-343	177.13	28-342	161.63	**<0.001**

AaDO2: alveolar arterial oxygen gradient, FiO_2: fraction of inspired oxygen, PSI: pneumonia severity index, PaO_2: arterial oxygen pressure, PAO_2: alveolar oxygen pressure.

While PSI, alveolar oxygen pressure, alveolo-arterial oxygen gradient were significantly higher in group II patients, PaO2/FiO2 rate was statistically significantly higher in group I patients (p<0.05) (Table 4).

According to Stepwise logistic regression results; patients diagnosed with COVID-19 radiologically were more protective against mortality compared to those diagnosed with the RT-PCR test (OR: 0.103: p=0.014), in other words, it was observed that the mortality rate was lower in patients diagnosed with COVID-19 by radiological or clinical methods. Again, the patients with high albumin levels are more protective against mortality (OR: 0.053: p<0.001), but the patients with high total bilirubin levels are at a 3.72 times under the risk of mortality in each unit in comparison to the patients with lower levels (OR: 3.722: p<0.001). It was found that the patients who had complications during COVID-19 treatment were at 39.3 times under the risk of mortality in comparison to other patients (OR: 39.370: p<0.001) (Table 5).

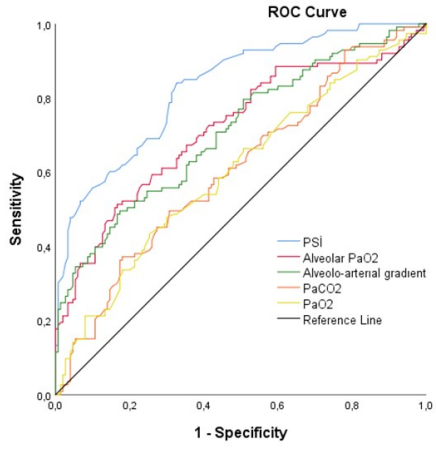

Fig 1. Mortality ROC curve

Table 5. Univariate and Stepwise Multivariate LR Analysis of Prediction of COVID-19 mortality

	Univariate LR		*Stepwise LR*	
RT-PCR (ref: positive)	***Odds Ratio (95% CI)***	***p***	***Odds Ratio (95% CI)***	***p***
Age (>65)	1.237 (0.696 2.197)	0.469		
Male	1.448 (0.882 2.376)	0.144		
Smoking status	1.406 (0.839 2.357)	0.196		
COVID-19 diagnosis (ref: test)		**0.001**	0.069	
Radiological	0.295 (0.134 0.652)	**0.003**	**0.103 (0.017 0.626)**	**0.014**
Clinical	0.351 (0.162 0.760)	**0.008**	0.739 (0.129 4.219)	0.734
Clinical/Radiological	0.387 (0.182 0.825)	**0.014**	1.007 (0.976 1.039)	0.671
Comorbity	1.626 (0.484 5.469)	0.432		
SBP	0.981 (0.972 0.992)	**<0.001**	1.007 (0.976 1.039)	0.671
DBP	0.975 (0.960 0.989)	**<0.001**	0.964 (0.916 1.014)	0.157
Respiratory rate	1.056 (1.020 1.093)	**0.002**	1.051 (0.960 1.150)	0.285
Heart rate	1.019 (1.007 1.031)	**0.001**	1.008 (0.977 1.039)	0.633
Temperature	0.867 (0.568 1.322)	0.507		
GKS	0.996 (0.970 1.023)	0.783		
Consciousness (ref: awake)		**0.001**	0.287	
Confusion	1.259 (0.637 2.488)	0.508	0.878 (0.154 4.996)	0.883
Delirium	1.770 (0.663 4.729)	0.255	1.703 (0.212 13.645)	0.616
Stupor	2.873 (1.394 5.921)	**0.004**	0.454 (0.071 2.900)	0.404
Coma	5.793 (2.494 13.455)	**<0.001**	4.559 (0.798 26.039)	0.088
Laboratory				
Hemoglobin	0.935 (0.840 1.039)	0.212		
Hematocrit	0.975 (0.939 1.011)	0.171		
Leukocyte	1.026 (0.993 1.060)	0.119		
Lymphocyte	1.077 (0.986 1.117)	0.100		
Neutrophil	1.057 (0.995 1.122)	0.071		
Platelet	1.000 (0.999 1.000)	0.205		
Glucose	0.999 (0.996 1.002)	0.999		
Sodium	0.997 (0.983 1.011)	0.625		
Potassium	1.371 (1.017 1.848)	**0.038**	1.041 (0.463 2.341)	0.923
Urea	1.011 (1.006 1.016)	**<0.001**	1.005 (0.990 1.020)	0.515
Creatine	1.446 (1.196 1.750)	**<0.001**	0.716 (0.368 1.396)	0.327
pH	0.110 (0.014 0.893)	**0.039**	326.025(0.019 550.100)	0.244
Saturation	0.923 (0.891 0.957)	**<0.001**	1.004 (0.885 1.139)	0.952
$PaCO_2$	0.967 (0.944 0.990)	**0.005**	1.049 (0.964 1.140)	0.266
PaO_2	0.990 (0.980 0.999)	**0.043**	0.998 (0.969 1.028)	0.873
Bicarbonate	0.920 (0.881 0.961)	**<0.001**	0.992 (0.857 1.148)	0.917
Lactate	1.384 (1.176 1.629)	**<0.001**	1.311 (0.821 2.092)	0.256
BE	0.940 (0.907 0.975)	**0.001**	0.971 (0.853 1.105)	0.653
CRP	1.004 (1.002 1.006)	**0.001**	1.001 (0.996 1.007)	0.652
Procalcitonin	1.024 (1.004 1.045)	**0.020**	1.001 (0,956 1.048)	0.966
D-dimer	1.058 (1.008 1.110)	**0.021**	0.991 (0.913 1.076)	0.833
PT	1.033 (0.999 1.068)	0.061		
INR	1.132 (0.891 1.439)	0.311		
AST	1.001 (0.999 1.003)	0.227		
ALT	1.002 (0.999 1.006)	0.173		
Albumin	0.164 (0.088 0.306)	**<0.001**	0.053 (0.012 0.242)	**<0.001**
Total Bilirubin	3.180 (1.667 6.067)	**<0.001**	3.722 (1.120 12.376)	**<0.001**
CK-MB	0.997 (0.988 1.006)	0.527		
Troponin	1.000 (0.999 1.000)	0.478		
Radiological involvement (ref: none)		0.756		
Unilateral	0.945 (0.401 2.227)	0.898		
Bilateral	1.524 (0.755 3.078)	0.240		
Ground glass opacity	1.262 (0.734 2.170)	0.399		
Ground glass opacity (ref: none)		0.145		
Unilateral	0.793 (0.352 1.786)	0.576		
Bilateral	1.463 (0.831 2.575)	0.188		
Consolidation	0.749 (0.458 1.225)	0.250		
Consolidation localization (ref: none)		0.645		
Unilateral	1.108 (0.505 2.433)	0.798		
Bilateral	1.499 (0.875 2.569)	0.141		
Complication	1.332 (1.167 1.522)	**<0.001**	39.370 (7.504 206.557)	**<0.001**
LOS	0.986 (0.964 1.009)	0.227		

Table 6. ROC analyses for mortality

	Cut-off	AUC	Std Eror	Sensitivity	Specificity	p
$PaCO_2$	<36.15	0.607	0.035	0.373	0.820	**0.003**
PaO_2	<56.85	0.601	0.036	0.434	0.747	**0.006**
PSI	>144.50	0.830	0.025	0.841	0.673	**<0.001**
PAO_2	>234.75	0.717	0.033	0.513	0.833	**<0.001**
$AaDO_2$	>177.89	0.710	0.032	0.496	0.827	**<0.001**

According to the arterial blood gas analysis in our study; the PaCO2 level below 36.15 mmHg posed a risk for mortality and similarly the PaO2 value below 56.85 mmHg posed a significant risk to mortality by ROC analysis. Observation of PSI value above 144.50, alveolar oxygen pressure above 234.75 mmHg and AaDO2 above 177.89 mmHg emerges as a significant risk factor for mortality. A statistical significance was observed in terms of AUC values of all these variables ($p < 0.05$). In predicting mortality, the sensitivity for the PSI variable was 84.1%, specificity 67.3%, and 49.6% specificity 82.7% for the AaDO2 variable (Table 6, Figure 1).

4. Discussion

This study evaluated the risk factors and the PSI and AaDO2 rates for mortality for the patients with moderate to severe COVID-19 pneumonia and it also provides information about the success of predicting mortality. In compliance with previous reports, the available data confirm that some biochemical markers, the presence of complications during treatment, and higher PSI rate are associated with mortality. It is also found that the AaDO2 rate stands as the valuable data in detecting the living patients as a result of this study. PSI and AaDO2 in the patients with critical COVID-19 pneumonia treated in the ICU should be used together.

Most of the patients with COVID-19 that spread from the Wuhan Province of China and caused a worldwide pandemic have been recovered within two weeks. The pneumonia occurs 15% to 20% of such patients (11). In the literature, it has been reported that 5-20% of patients diagnosed with COVID-19 had critical disease, especially acute respiratory distress syndrome, and the mortality rate is reported as 16-78% for the patients with ARDS and requiring invasive mechanical ventilation support in ICUs (12-15). Singer et al. concluded that 9 out of every 100 individuals admitted to the hospital would require ICU, invasive mechanical ventilation, or both whereas 12 out of 100 people would require ICU admission or invasive mechanical ventilation within 2 to 3 days and they reported that the duration of median mechanical ventilation is 1 week (16).

Pneumonia is an inflammatory disease of the lung alveoli caused by viruses, bacteria, and fungi. Guidelines, algorithms and scoring systems are the mechanisms that facilitate and support physicians' decision making and have the impact in reducing variability among the physicians. Many scoring systems are used to predict mortality risk in pneumonia, but the most popular ones are PSI and CURB65 (6,7,17). The PSI is the most sensitive test, with a low false negative rate, thus giving clinicians' confidence in identifying patients who do not require hospitalization. PSI includes a detailed history, physical examination, venous blood sampling, arterial blood gas measurements, and chest X-ray, so it is calculated by summing up a total of 12 parameters from history and examination and 7 parameters from further studies (7,17).

The most important pathophysiology of pneumonia is ventilation-perfusion mismatch. AaDO2 shows the integrity of the alveolocapillary membrane and is used as a gas exchange index. The affecting factors are diffusion gradient, ventilation-perfusion imbalance, and true shunt (9). AaDO2 can distinguish whether hypoxemia is caused by alveolar hypoventilation or ventilation/perfusion mismatch, but this parameter can be misleading when the patient receives additional oxygen support (18). In our study, the arterial blood gas values obtained during admission to the emergency room were taken into account. However, some patients received oxygen therapy because their oxygen saturation values were below 90% during admission and the arterial blood gas study was conducted accordingly. Therefore, the success of PSI, which is also among the aims of our study, in predicting mortality was investigated.

The most common diagnostic tool for COVID-19 disease is RT-PCR, which is considered the reference gold standard. Recent studies have emphasized the importance of chest CT in COVID-19 pneumonia with false negative RT-PCR results and reported CT sensitivity as 98% (19-22). In the diagnosis of COVID-19 when RT-PCR is accepted as the reference standard, the specificity, PPV, NPV and accuracy rates of chest CT are reported as 21.6%, 61.9%, 73.3%, and 63.3%, respectively. The most common and typical CT findings of COVID-19 are bilateral multi-lobe involvement, peripheral localized, irregular shape and ground-glass opacity (19,20). In our study, it was found that the diagnosis of COVID-19 pneumonia both radiologically and clinically in the patients with negative RT-PCR test was reliable. The most common radiological finding was the GGO observed in both lungs. We believe that the parenchymal consolidation was detected less frequently because the patients were admitted to the hospital as soon as relevant symptoms began.

Although the initial chest CT is normal in some COVID-19 patients, new lung lesions may develop during treatment. This period is reported as an average of 5.8 days. Therefore, a new chest CT is recommended especially for the patients who worsen or develop new symptoms during treatment even if the initial chest CT is negative (23). In our study, chest CT imaging was performed in all patients during admission, and no

radiological involvement caused by COVID-19 pneumonia was detected in only 15.6%. Fever with a rate of 85% and cough with a rate of 70% are the most common major symptoms in COVID-19 pneumonia (2,3). In our study, the most common presenting symptom was dyspnea at 76.5%. We attribute this case to the reason that our patients had a moderate-severe course of COVID-19 pneumonia and were in need of intensive care.

Pan et al. stated that the average time between the onset of symptoms and the admission to hospital was 11 days, and that 73.4% of patients developed ARDS within a median of 7 (IQR 4-11) days after admission to the hospital. Again, in the evaluation made during the application was reported that detection of oxygen saturation ≤89%, lymphocyte ≤0.64×109/L, CRP > 77.35 mg/L, procalcitonin >0.20 μg/L and LDH >481 U/L is a risk factor for mortality, and these values should be closely monitored in critical COVID-19 patients (11). Most of the data reported in the literature in our patients were followed closely, and it was observed that blood gas values, CRP, procalcitonin, D-dimer, albumin and total protein, especially in univariate analysis, and albumin and total bilirubin in multivariate analysis were found to be associated with high mortality. The complication rate seen in the deceased patient group was found to be significant with 66% in multivariate analysis.

In a multi-center cohort study conducted in the USA, the mortality rate of a 28-day intensive care was reported at 35.4% for the patients with critical COVID-19 disease. Again, in this study, it was reported that the risk of mortality increased in the presence of advanced age, male gender, high BMI, hypoxemia at the time of admission to hospital, and comorbidities such as malignancy, coronary artery disease and renal failure. In this study, they reported the most common cause of death in patients followed up in the ICUs as respiratory failure with 92.7%, septic shock with 39.7% and renal failure with 36.7%. They also reported that 37.2% of patients treated in ICUs could be discharged, the average length of stay in the intensive care unit was 9 (IQR, 5-14) days, and the average hospital stay was 16 (IQR, 11-22) days (13). Similarly Cummings et al. reported that the intensive care mortality rate was 39% and 37% of the patients were still treated in the hospital. Similar to previous data, advanced age, cardiopulmonary comorbidities, and high D-dimer concentration were reported as poor prognostic factors (14). Graselli et al. stated that the length of stay in the ICU was 10 (IQR, 5-16) days in the patients who were deceased, and 15 (IQR, 8-24) days in the patients who were discharged, and that the presence of hypertension as a comorbidity was associated with short survival (15).

The mortality rate in our study was 42.9%, and the most common cause of death was found to be renal failure with 12.5%. According to the multivariate analysis, it was seen that low albumin and high total bilirubin levels and the development of complications posed a risk for mortality. The length of stay was shorter in deceased patients, which means that patients with critical COVID-19 pneumonia were lost in the early period, and the study starting from the pandemic period when the treatment methods to be applied fail to settle properly.

Garcia et al. reported lack of oxygenation, renal and microvascular dysfunction, and coagulation activation as risk factors for mortality in critically ill patients, and they recommended that they be followed creatine, D-dimer, lactate, potassium and AaDO2 closely (3). Esteve et al. low PaO2/FiO2 rate was associated with increased mortality and prolonged length of stay in the patients admitted to the ICU (8).

One of the main findings of our study is that in group II patients, PaO2/FiO2 rate, i.e. low PaO2/FiO2 rate was associated with high mortality. Again, AaDO2 as an indicator of bad oxygenation and it was significantly higher in the deceased patients. Although it is calculated in patients receiving oxygen therapy in our study, it was observed that the specificity value of AaDO2 was high. In other words, it was valuable in determining the surviving patients. We attribute the low sensitivity to the arterial blood gas values obtained while the patients are under oxygen therapy. We found that PSI, which evaluates more than one data, was more powerful in predicting mortality with a sensitivity value of 84.1%.

In conclusion, early estimation of mortality risk and taking precautions accordingly are important for hospitalization and close follow-up of patients with critical COVID-19 pneumonia. We think that pneumonia severity index is reliable in predicting mortality and alveolo-arterial oxygen gradient in determining the surviving patient, especially in the patients receiving oxygen therapy under intensive care units. We recommend that both rates should be used together in the follow-up of patients with critical COVID-19 pneumonia in intensive care units.

The main limitation on our study is that it is conducted as a retrospective and a single center study with a relatively limited number of patients. The results should be confirmed with the studies involving more patients. Secondly, the number of patients diagnosed with COVID-19 pneumonia based on clinical and radiological evaluation is higher than the number of RT-PCR positive patients. Since the rate of unconfirmed cases is consistent with the reported sensitivity data of the RT-PCR test for COVID-19, we assume these are misleading negative tests.

Conflict of interest

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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Authors' contributions

Concept: H.K.Ç., Design: H.K.Ç., Z.D., Data Collection or Processing: H.K.Ç., T.S.A., Analysis or Interpretation: H.K.Ç., M.K., Literature Search: H.K.Ç., Z.D., T.S.A., Writing: H.K.Ç.

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