Title: Predictors of Intensive Care Unit Admission or Death in Patients with Coronavirus Disease 2019 Pneumonia in Istanbul, Turkey

Running Head: Prognostic Indicators in Patients with COVID-19

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Summary

We aimed to determine the predictors of intensive care unit (ICU) admission or death in patients with Coronavirus Disease 2019 (COVID-19) pneumonia. This retrospective and single-center study includes patients aged ≥18 years who were diagnosed with COVID-19 pneumonia (laboratory and radiologically confirmed) between March 9 and April 8, 2020. Our composite endpoint was ICU admission or in-hospital death. To evaluate the factors in the composite endpoint, univariate and multivariate logistic regression analyses were performed. A total of 336 patients with COVID-19 pneumonia were recorded. The median age was 54 years [interquartile range (IQR): 21] and 187 (55.7%) were male. Fifty-one (15.2%) patients were admitted to the ICU. In-hospital death occurred in 33 (9.8%) patients. In univariate analysis, 17 parameters were associated with the composite endpoint and procalcitonin had the highest ODDs ratio (OR=36.568 CI=5.145-259.915). Our results revealed that body temperature (OR=1.489 CI=1.023-2.167, p=0.037), peripheral capillary oxygen saturation (SpO2) (OR=0.835 CI=0.773-0.901, p<0.001), and consolidation (>25%) in chest computed tomography (OR=3.170 CI=1.218-8.252, p=0.018) at admission were independent predictors. As a result, increased body temperature, decreased SpO2, a high level of procalcitonin, and degree of consolidation in chest computed tomography may predict a poor prognosis and have utility in the management of patients.

INTRODUCTION

At the end of 2019, an outbreak of pneumonia with unknown etiology originated in China. With gratitude to Chinese scientists' awareness, a pathogen was successfully identified and isolated (1). The disease was named Coronavirus Disease 2019 (COVID-19) which is caused by Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (previously known as "2019 novel coronavirus"). Despite all efforts, COVID-19 spread rapidly and evolved into a pandemic (2).

SARS-CoV-2 can cause mild, moderate, severe, or critical COVID-19. Although most infections are not severe, patients with severe or critical diseases are more common among hospitalized patients. COVID-19 has caused hospitalization, readmission and mortality particularly among older adults, and has become a major public health issue (3-5). In this study, we aimed to determine the predictors of intensive care unit (ICU) admission or death in patients with COVID-19 pneumonia. We evaluated the epidemiological, clinical characteristics, laboratory test results, and radiological findings, treatment regimens and clinical outcomes of the patients admitted to a tertiary hospital in Istanbul, Turkey. To our knowledge, this is the first comprehensive study to evaluate outcomes of laboratory and radiologically confirmed COVID-19 pneumonia in Turkey.

MATERIALS AND METHODS

Study Design and Patients

This retrospective and single-center study includes patients aged ≥18 years who were diagnosed with COVID-19 pneumonia by the Department of Infectious Diseases and Clinical Microbiology between March 9 and April 8, 2020. SARS-CoV-2 testing was performed by real-time reverse transcription-polymerase chain reaction (RT-PCR) of samples collected by nasopharyngeal and/or oropharyngeal swabs.

Chest computed tomography (CT) confirmed patients with COVID-19 pneumonia requiring hospitalization were included in the study. Outpatients, asymptomatic patients, and radiologically unconfirmed patients were excluded. Also, we excluded patients if oropharyngeal or nasopharyngeal swab samples were repeatedly negative for SARS-CoV-2 by RT-PCR. The mortality was defined as all-cause in-hospital death. Our composite endpoint was ICU admission or in-hospital death.

Data collection

The demographic data, underlying diseases, immunosuppressive conditions, symptoms and physical examination findings, laboratory test results and radiological findings, the treatments and responses were recorded via a follow-up datasheet. We recorded body temperature, respiratory rate, heart rate, arterial blood pressure, oxygen saturations at the time of first presentation to hospital. Laboratory results and radiological examinations were included if performed within 24 hours of admission. The degree of consolidation in chest CT was visually assessed and classified as mild (0–25%), moderate (25–50%), and severe (>50%).

Statistical analysis

Frequencies (n) and percentages (%) were used to present the descriptive characteristics of the data. Numerical variables were represented through median and interquartile range (IQR). The Kolmogorov–Smirnov test was used for normal distribution analysis. The Mann–Whitney U test and Independent Sample t-Test were used to compare the two groups in terms of the continuous variables. Categorical data were compared with Chi-Square test or Fischer's Exact test. To evaluate the factors in the composite endpoint including ICU admission and in-hospital death, univariate and multivariate logistic regression analyses were performed. Confounders with less than 10 events per variable were not included in the multivariate model to mitigate overfitting. Additionally, when there was a strong correlation between continuous

and categorical variables, continuous variables were preferred to reduce multicollinearity effect which may cause bias errors. Receiver operating characteristic (ROC) curve analyses were performed to determine the optimal cut-off values of predictors. The analyses were performed using IBM SPSS-22 (Statistical Package for Social Sciences, Chicago, IL, USA). A p-value <0.05 was considered as statistically significant.

Ethical statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of National Research Committee and the Declaration of Helsinki. This study was approved by the Ethics Committee of Haseki Training and Resarch Hospital (approval number: 2020-151, date: 19/08/2020). Written informed consent was waived, given the retrospective nature of this study.

RESULTS

Demographic characteristics and comorbidities

A total of 336 patients with COVID-19 pneumonia were recorded. The median age was 54 years [interquartile range (IQR): 21] and 187 (55.7%) were male. Fifty-one patients (15.2%) were admitted to the ICU. In-hospital death occurred in 33 (9.8%) patients. A total of 3.6% (n=12) were health care workers, and a travel history was reported in 3.9% (n=13); 102 patients (30.4%) had a close contact with a confirmed or probable case. Among 336 patients, 56.5% had at least one or more underlying diseases. Hypertension (31.3%) and diabetes mellitus (30.1%) were the most common chronic conditions. Chronic obstructive pulmonary disease (COPD) (p=0.003) and chronic renal failure (p=0.004) were more common in the presence of ICU admission or in-hospital death. The demographic characteristics of COVID-19 patients with pneumonia are shown in Table 1. Whereas ICU admission or in-hospital

death was not associated with the presence of underlying diseases (at least one or more comorbidities) (p=0.360), in-hospital mortality was two times higher among patients with underlying diseases than patients with none (12.6% vs. 6.2%, p=0.048).

Signs and symptoms at presentation

Cough (n=267, 79.5%) and fever (n=200, 59.5%) were the most common symptoms. Dyspnea (p<0.001), body temperature (p<0.001), respiratory rate (p<0.001), heart rate (p=0.016) and oxygen saturation (p<0.001) were associated with ICU admission or in-hospital death (Table 2).

Radiological findings

Bilateral lung involvement was detected 72.1% and 94.9% in chest radiograph and CT, respectively. Ground glass opasity (n=301, 89.6%) was the most common finding, followed by consolidation (n=100, 29.8%) and small patch (n=77, 22.9%). Consolidation in chest CT (p=0.018) was associated with ICU admission or in-hospital death (Table 3). Clinical deterioration was more frequent in patients with consolidation >25% (moderate or severe consolidation) than without (n=16, 45.7% vs. n=37, 12.7%).

Laboratory parameters

Fourteen laboratory parameters were associated with ICU admission or in-hospital death (Table 4). Neutrophil count (p<0.001), lymphocyte count (p<0.001), neutrophil/ lymphocyte ratio (p<0.001), %monocyte (p=0.003), glucose (p=0.049), urea (p<0.001), creatinine (p<0.001), triglyceride (p=0.019), alanine aminotransferase (p=0.017), lactate dehydrogenase (p<0.001), sodium (p=0.003), C-reactive protein (p<0.001), troponin (p<0.001), and procalcitonin (p<0.001) were associated with the composite end-point. However, leukocyte count, platelet, hemoglobin, hematocrit, aspartate aminotransferase, creatine kinase, albumin, potasium, ferritin, fibrinogen, and d-dimer were not associated with the composite end-point.

Univariate analysis for the composite endpoint

ICU admission or in-hospital death occurred in 53 patients (15.8%). In univariate analysis, 23 parameters were associated with the composite endpoint including ICU admission and in-hospital death. Procalcitonin had the highest ODDs ratio (OR=36.568 CI=5.145-259.915, p<0.001). Age, COPD, chronic renal failure, dyspnea, body temperature, respiratory rate, heart rate, SpO2, degree of consolidation in chest CT, neutrophile, lymphocyte, neutrophile/lymphocyte ratio, %monocyte, creatinine, sodium, CRP, and procalcitonin were associated with the composite end-point (Table 5).

Multivariate analysis for the composite endpoint

Body temperature, SpO2, creatinine, and consolidation in chest CT were included in our multivariate model, after excluding highly correlated candidate predictors and confounders with less than 10 events per variable. Our results revealed that body temperature (OR=1.489 CI=1.023-2.67, p=0.037), SpO2 (OR=0.835 CI=0.773-0.901, p<0.001), and degreee of consolidation (>25%) in chest CT (OR=3.170 CI=1.218-8.252, p=0.018) at admission were independent predictors for ICU admission or in-hospital death in patients with COVID-19 pneumonia (Table 6). ROC analyses revealed that the optimal cut-off value of body temperature to predict the composite end-point was 37.0 °C, with sensitivity and specificity were 71.1% and 67.0%, respectively. The optimal cut-off value of SpO2 was 93%, with sensitivity and specificity were 70.6% and 62.3%, respectively. The optimal cut-off value of procalcitonin was 0.1 μg/L, with sensitivity and specificity were 80.0% and 75.6%, respectively.

DISCUSSION

In this study, we present detailed clinical characteristics and outcomes of 336 laboratory and radiologically confirmed patients with COVID-19 pneumonia admitted to a tertiary hospital during the first month of the pandemic in Istanbul, Turkey. Our results include a comprehensive data report and provide evidence that increased body temperature and decreased SpO2, and degree of consolidation in chest CT at the time of presentation are independent predictors for ICU admission or in-hospital death in patients with COVID-19 pneumonia. Additionally, among 17 predictors in the univariate analysis, procalcitonin had the highest ODDs ratio. However, procalcitonin was not included in the multivariate model because of strong correlation between significant variables.

An increasing number of studies has been published analyzing COVID-19 patients and related factors (6-9). Some studies show that comorbidities and other conditions have been associated with the severity and poor outcomes (5,10-14). There are also some studies suggesting that particular laboratory parameters (15-19) and radiological findings (20-21) may predict worse outcomes. However, the strength of evidence informing the associations varies and universal predictive parameters have not yet been explored with a robust evidence. Most of these reports have a lack of multivariable model and do not represent independent predictors (5,22). Also, they do not exclude the patients who had COVID-19 without pneumonia from their study (6-19).

Among older adults and people with comorbid conditions, COVID-19 is frequently severe and has resulted in worse prognosis (23-27). In a nationwide study conducted by Stokes et al. (27), among 287,320 laboratory-confirmed COVID-19 patients individually reported to the Centers for Disease Control and Prevention the United States, the most common were cardiovascular disease (32%), diabetes (30%), and chronic lung disease (18%). Overall, 184,673 (14%) patients were hospitalized, 29,837 (2%) were admitted to ICU, and 71,116 (5%) died. Stokes et al. (27) reported that the case fatality rate was 12 times as high among

patients with reported underlying conditions (19.5%) compared with those without reported underlying conditions (1.6%). In our study, in-hospital mortality rate was two times higher among patients with underlying diseases (12.6%) than patients with none (6.2%) (p=0.048). However, ICU addmission was not associated with the presence of underlying diseases (at least one or more comorbidities) (p=0.360) (Table 1). Therefore, patients without underlying diseases are also prone to be admitted to the ICU, but intensive care implementations are more efficient for this group.

In our study, ICU admission (n=51, 15.2%) or in-hospital death (n=33, 9.8%) occurred in 53 patients (15.8%). In the first detailed study included 1099 hospitalized COVID-19 patients in China, of whom 5.0% were admitted to the ICU, 1.4% died, and the composite endpoint occured in 67 (6.1%) patients (28). In another report of 1590 laboratory confirmed hospitalized patients with COVID-19, the composite endpoint including the admission to ICU, invasive ventilation or death occurred in 131 (8.2%) patients (13). These results were not consistent with our findings. However, this could be due to the fact that they included the patients without pneumonia in their analyses. Guan et al. (13) reported that after adjusting for age and smoking status, COPD, diabetes, hypertension, and malignancy were risk factors for the composite endpoints. In contrast, Petrilli et al. (10) reported that 990 (36.1%) patients had critical illness (intensive care, mechanical ventilation, discharge to hospice care, or death) and comorbidities were less strongly associated with critical illness in hospitalized patients with COVID-19. They showed that age and comorbidities were powerful predictors of hospital admission, however, impairment of oxygenation on admission and laboratory parameters such as troponin, C-reactive protein, and D-dimer were more strongly associated with critical illness than age or comorbidities. Similarly, in a report of 99 hospitalized patients with COVID-19 in Switzerland, a higher lactate, C-reactive protein, procalcitonin levels and compromised oxygenation were significant predictors for ICU admission or in-hospital death,

whereas age and comorbidities provided little prognostic information (29). In our study, age and comorbid conditions were detected as risk factors in univariate analysis. COPD and chronic renal failure were associated with the primary composite endpoint.

In the study of Singer et al, they evaluated 4,404 patients under investigation for COVID-19 and found that testing positive for SARS-CoV-2 and lower oxygen saturations were associated with need for ICU and invasive mechanical ventilation, and with death (30). Zhao et al. reported that lactate dehydrogenase, procalcitonin, pulse oxygen saturation, smoking history, and lymphocyte count were significant variables predicting ICU admission (31). By contrast, lactate dehydrogenase and smoking history were not associated with critical illness neither in multivariate nor in univariate analyses in our study. Additionally, Liu et al. (32) found that fasting plasma glucose, cardiac troponin, serum ferritin, and IL-6 were also associated with ICU admission. As a result, different factors from different studies have been identified for ICU admission and/or mortality. In the present study, elevations of body temperature and procalcitonin were limited. Similarly, Xu et al. demonstrated a limited increase in procalcitonin levels and suggested that the limited increase could be associated with increased interferon-gamma levels (33). Also, Tharakan et al. reported that a significant increase was observed in mortality for every 0.5 °C increase in body temperature (34). In consistent with our study, Grodecki et al. showed that consolidation in chest CT was associated with 3.4-fold increased risk for clinical deterioration (35).

This study has several strengths. First, multiple comorbidities and different types of variables such as vital signs, laboratory parameters and radiological findings were included in the multivariate regression analysis. Second, our case exclusion criteria was strict. We excluded patients without laboratory and radiologically confirmed COVID-19 pneumonia. Our study has also several limitations. First, it was retrospectively conducted in a single-center. Second, this study had a small sample size and a control group was not included. The generalizability

of our results may be limited. Thus, we need new large scale studies providing important information to better understand COVID-19 pandemic. In addition, we did not perform multiplex RT-PCR to determine co-infections with other respiratory pathogens such as influenza virus, parainfluenza virus, respiratory syncytial virus, and adenovirus.

In conclusion, COVID-19 pneumonia is a significant threat to both older and younger adults. Increased body temperature, decreased SpO2, a high level of procalcitonin, and degree of consolidation in chest CT at the time of presentation may predict a poor prognosis and have utility in the management of patients. Our results justify the need for comprehensive evaluation of patients with COVID-19 pneumonia at the time of first presentation to hospital.

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Conflict of Interest

This research did not receive any specific grant. No funding was used. The authors declare that they have no competing interests.

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Table 1. The demographic characteristics of COVID-19 patients with pneumonia

			ICU admission/Death				
	In total		Absence		Presence		
	n	%	n	%	n	%	p
Number of patients	336	100	283	84.2	53	15.8	
Age (years)							**0.016**
Median	54		54		57		
IQR	21		21		25.5		
Age							**0.002**
<65 years	263	78.3	230	81.3	33	62.3	
≥65 years	73	21.7	53	18.7	20	37.7	
Gender							**0.050**
Male	187	55.7	151	53.3	36	67.9	
Female	149	44.3	132	46.7	17	32.1	
Epidemiological history							
Healthcare workers	12	3.6	8	2.8	4	7.5	0.103
Close contact with a confirmed or probable case	102	30.4	88	31.1	14	26.4	0.626
Underlying diseases	190	56.5	157	55.5	33	62.3	0.360
COPD	11	3.3	5	1.8	6	11.3	**0.003**
Diabetes mellitus	101	30.1	82	29.0	19	35.8	0.330
Hypertension	105	31.3	86	30.4	19	35.8	0.431
Chronic artery disease	36	10.7	27	9.5	9	17.0	0.108
Chronic renal failure	15	4.5	8	2.8	7	13.2	**0.004**

Malignancy	8	2.4	6	2.1	2	3.8	0.617
Asthma	22	6.5	18	6.4	4	7.5	0.762
Chronic steroid use	4	1.2	3	1.1	1	1.9	0.498
Smoking history	77	22.9	61	21.6	16	30.2	0.170

IQR= interquartile range; COPD= Chronic obstructive pulmonary disease

Table 2. The distribution of clinical signs and symptoms

			ICU admission/Death				
	In total		Absence		Presence		
	n	%	n	%	n	%	p
Fever	200	59.5	170	60.1	30	56.6	0.637
Cough	267	79.5	228	80.6	39	73.6	0.248
Dyspnea	127	37.8	92	32.5	35	66.0	**<0.001**
Chest pain	11	3.3	8	2.8	3	5.7	0.390
Myalgia	45	13.4	40	14.1	5	9.4	0.356
Arthralgia	13	3.9	12	4.2	1	1.9	0.701
Fatigue	132	39.3	115	40.6	17	32.1	0.242
Sore throat	25	7.4	24	8.5	1	1.9	0.149
Nausea	22	6.5	20	7.1	2	3.8	0.549
Vomiting	13	3.9	12	4.2	1	1.9	0.701
Systolic BP (mmHg)							
median (IQR)	120 (15)		120 (13.75)		120 (20)		0.540
Diastolic BP (mmHg)							
median (IQR)	70 (10)		70 (10)		70 (30)		0.662
Body temperature °C							
median (IQR)	36.7 (0.9)		36.6 (0.9)		37.1 (1.15)		**<0.001**
Respiratory rate/ minute							
median (IQR)	22 (4)		21 (2)		23 (11)		**<0.001**
Heart rate/minute							
median (IQR)	88 (16)		87 (17)		88.5 (20.5)		**0.016**
SpO2 (%)							

median (IQR)	94 (4)	95 (4)	90 (10)	**<0.001**

BP= Blood pressure; SpO2= peripheral capillary oxygen saturation; IQR= interquartile range

Table 3. Distribution of radiological findings

			ICU admission/Death				
	In total		Absence		Presence		
	n	%	n	%	n	%	p
Chest radiograph findings	202	72.1	161	68.8	41	89.1	
Unilateral	19	9.4	16	9.9	3	7.3	0.770
Bilateral	183	90.6	145	90.1	38	92.7	
Chest CT findings	336	100	283	100	53	100	
Unilateral	17	5.1	14	4.9	3	5.7	0.738
Bilateral	319	94.9	269	95.1	50	94.3	
Small patch	77	22.9	63	22.3	14	26.4	0.509
Ground glass	301	89.6	253	89.4	48	90.6	0.799
Consolidation	100	29.8	77	27.2	23	43.4	**0.018**
Air bronchogram	15	4.5	10	3.5	5	9.4	0.069
Interlobular septal thickening	31	9.2	26	9.2	5	9.4	1.000
Pulmonary nodules	18	5.4	16	5.7	2	3.8	0.749
Plevral fluid	12	3.6	9	3.2	3	5.7	0.412

CT= Computed tomography

Table 4. Laboratory parameters of patients with COVID-19 pneumonia [serum levels median (IQR)]

		ICU admission/Death		
	In total	**Absence**	**Presence**	
Neutrophil (/μL)	3590 (2050)	3470 (2075)	4450 (3570)	**<0.001**
Lymphocyte (/μL)	1290 (815)	1360 (827)	1090 (575)	**<0.001**
Neutrophil/ Lymphocyte ratio	2.78 (1.8)	2.60 (1.9)	4.64 (4.02)	**<0.001**
%Monocyte	8.8 (4.1)	9.0 (4.4)	8.0 (4.8)	**0.003**
Glucose (mg/dL)	117 (53)	116 (50)	133 (56)	**0.049**
Urea (mg/dL)	29 (14)	27 (12)	36.2 (29.5)	**<0.001**
Creatinine (mg/dL)	0.78 (0.38)	0.74 (0.31)	0.90 (0.44)	**<0.001**
Triglyceride (mg/dL)	110 (75)	101 (56)	159.5 (109)	**0.019**
ALT (IU/L)	22 (18.5)	23 (19)	21 (11)	**0.017**
LDH (U/L)	267 (126)	264 (264)	299 (162)	**<0.001**
Sodium (mmol/L)	137 (4)	137 (4)	136 (4)	**0.003**
CRP (mg/L)	41 (79)	30 (59)	108 (98)	**<0.001**
Troponin (mg/dl)	4.4 (5)	4 (4)	13.6 (46)	**<0.001**
Procalcitonin (μg/L)	0.05 (0.07)	0.05 (0.05)	0.23 (0.79)	**<0.001**

ALT= Alanine aminotransferase; LDH= Lactate dehydrogenase; CRP= C-reactive protein

Table 5. Univariate analysis for the composite endpoint including intensive care unit admission and in-hospital death

	OR	CI	p
Age	1.028	1.006-1.049	**0.011**
COPD	7.098	2.082-24.196	**0.002**
Chronic renal failure	5.231	1.810-15.119	**0.002**
Dyspnea	4.037	2.170-7.508	**<0.001**
Body temperature	1.611	1.174-2.212	**0.003**
Respiratory rate	1.114	1.036-1.197	**0.003**
Heart rate	1.035	1.009-1.061	**0.007**
SpO2	0.804	0.747-0.866	**<0.001**
Degree of consolidation in chest CT (>25%)	6.009	2.842-12.704	**<0.001**
Neutrophil	1.003	1.002-1.004	**<0.001**
Lymphocyte	0.999	0.998-1.000	**0.001**
Neutrophil/ Lymphocyte	1.003	1.002-1.004	**<0.001**
%Monocyte	0.999	0.998-1.000	**0.001**
Creatinine	1.571	1.123-2.197	**0.008**
Sodium	0.891	0.816-0.973	**0.010**
CRP	1.019	1.013-1.024	**<0.001**
Procalcitonin	36.568	5.145-259.915	**<0.001**

COPD= Chronic obstructive pulmonary disease; SpO2= peripheral capillary oxygen saturation; CT= Computed tomography; ALT= Alanine aminotransferase; CRP= C-reactive protein

Table 6. Multivariate analysis for the composite endpoint including intensive care unit admission and in-hospital death

	Univariate			Multivariate		
	OR	**CI**	**p**	**OR**	**CI**	**p**
Body temperature	1.611	1.174-2.212	**0.003**	1.489	1.023-2.167	**0.037**
SpO2	0.804	0.747-0.866	**<0.001**	0.835	0.773-0.901	**<0.001**
Creatinine	1.571	1.123-2.197	**0.008**	1.444	0.998-2.091	0.052
Consolidation in chest CT	2.051	1.122-3.749	**0.020**	3.170	1.218-8.252	**0.018**

SpO2= peripheral capillary oxygen saturation; CT= Computed tomography