



PREDICTION OF MORTALITY, HOSPITALIZATION AND MECHANICAL VENTILATION NEEDS OF PATIENTS WITH PNEUMONIA IN COVID-19 OUTBREAK

COVID-19 SALGININDA PNÖMONİSİ OLAN HASTALARDA MORTALİTE, HASTANEYE YATIŞ VE MEKANİK VENTİLASYON GEREKSİNİMLERİNİN DEĞERLENDİRİLMESİ

✉ Nurettin Özgür Doğan^{1*}, Sevtap Doğan², Murat Pekdemir¹, Serkan Yılmaz¹, Duygu Ferek Emir³,
 Kutlu Barış Teke¹

Kocaeli University, Faculty of Medicine, ¹Department of Emergency Medicine; ²Department of Radiology; Kocaeli, Turkey; ³Başakşehir City Hospital, Department of Emergency Medicine, Istanbul, Turkey

ORCID iD: Nurettin Özgür Doğan: 0000-0002-5209-8076; Sevtap Doğan: 0000-0002-5862-6730; Murat Pekdemir: 0000-0002-3917-0192; Serkan Yılmaz: 0000-0003-1496-6976; Duygu Ferek Emir: 0000-0002-4024-7468; Kutlu Barış Teke: 0000-0003-4161-7712

***Sorumlu Yazar / Corresponding Author:** Nurettin Özgür Doğan, e-posta / e-mail: nurettinozgurdogan@gmail.com

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Abstract

Objective: The COVID-19 pandemic has brought considerable loss to the world by means of pneumonia related mortality. In the current study, we aimed to discover the predictors of mortality and other worse outcomes in atypical pneumonia cases during the COVID-19 outbreak.

Methods: A prospective cohort study was carried out in our emergency department (ED) between March and May, 2020. All adult patients presented to the ED with atypical pneumonia patterns related to COVID-19 based on a chest CT scan were included in the study, and patients with bacterial pneumonia patterns were excluded. The primary outcome measure was determined as the composite outcome, including mortality and intensive care unit admission or mechanical ventilation needs within a one-month period. A binary logistic regression model was constructed to predict the worse outcomes in those patients.

Results: Of the 271 suspected pneumonia cases, 146 patients were included in the final analysis. The composite outcome occurred in 31 patients (21.2%), 17 of whom died within one month. The patients' age, history of heart failure, history of stroke, body temperature, dyspnea, cough, altered mental status, serious bronchospasm, bilateral lung involvement, hemoglobin level, LDH, lactate level, and bicarbonate and creatinine levels were added to the final model. Finally, patients' altered mental status (OR:15.7, 95%CI:1.7-141.6), serious bronchospasm (OR:12.4, 95%CI:1.6-97.9), and lactate levels (OR:1.1, 95%CI:1.0-1.2) were found to be independent predictors for worse outcomes.

Conclusion: Among various clinical and laboratory variables, altered mental status, serious bronchospasm, and lactate levels can be used to predict worse outcomes.

Keywords: COVID-19, pandemics, mortality, emergency department, pneumonia (MeSH Database)

Öz

Amaç: COVID-19 salgını, pnömoniye bağlı mortalite nedeniyle önemli kayıpları beraberinde getirmiştir. Bu çalışmada, COVID-19 salgını sırasında başvuran atipik pnömoni vakalarında mortalite ve diğer kötü sonuçları prediktörlerini bulmayı amaçladık.

Yöntem: Bu araştırma Mart ve Mayıs 2020 tarihleri arasında acil servisimizde yürütülen ileriye dönük kohort bir çalışmadır. Acil servise başvuran, toraks bilgisayarlı tomografisinde COVID-19 ilişkili atipik pnömoni paterni tespit edilen tüm erişkin hastalar çalışmaya dahil edildiler, bakteriyel pnömoni paterni olan hastalar ise dışlandılar. Araştırmanın primer sonuçları noktası; bir aylık süre içinde mortalite, yoğun bakım yatışı ve mekanik ventilasyon gereksinimi şeklinde birleşik sonuçları olarak planlandı. Bu hastalarda belirtilen kötü sonuçları prediktörlerinin araştırılması için bir lojistik regresyon modeli oluşturuldu.

Bulgular: Toplam 271 pnömoni olgusundan 146'sı son analize dahil edildi. Dahil edilen hastaların 31'inde (%21,2) birleşik sonuçları gerçekleşti, 17 hasta bir aylık dönem içinde öldü. Son regresyon modeline hastaların yaşları, kalp yetmezliği öyküsü bulunması, inme öyküsü bulunması, vücut sıcaklığı, dispne, öksürük, bilinç değişikliği, ciddi bronkospazm, tomografide bilateral akciğer bulgusu olması, hemoglobin, LDH, laktat, bikarbonat ve kreatinin düzeyleri dahil edildi. Buna göre; hastalarda bilinç değişikliği olmasının (odds oranı [OO]:15,7, %95'lik güven aralığı [GA]: 1,7-141,6), ciddi bronkospazmın (OO:12,4, %95 GA:1,6-97,9) ve laktat düzeyindeki artışın (OO:1,1, %95 GA: 1,0-1,2) kötü sonuçlarının bağımsız prediktörleri olduğu bulundu.

Sonuç: Birçok klinik ve laboratuvar değişkeni arasında; bilinç değişikliği, ciddi bronkospazm ve laktat düzeylerinin kötü sonuçları öngördüğü belirlenmiştir.

Anahtar Kelimeler: COVID-19, pandemi, mortalite, acil servis, pnömoni (MeSH veritabanına göre)

Introduction

The coronavirus disease 2019 (COVID-19) rapidly became an important health concern that has a huge impact on emergency departments (EDs), intensive care units (ICUs), and other healthcare centers. According to the World Health Organization (WHO), the current situation has resulted in over 1,000,000 deaths worldwide.¹ Early data from China suggests that a majority of COVID-19 deaths occurred among older adults and among persons with serious underlying health conditions.²⁻³ However, after the disease spread all over the world, it has been suggested that many other variables can predict mortality and poor clinical outcome.⁴⁻⁸

Currently, it is known that the novel coronavirus can lead to a wide spectrum of conditions, from asymptomatic carriage to severe pulmonary disease.^{9,10} In addition, it is also known that the diagnosis of COVID-19 should be based on real-time polymerase chain reaction (PCR) tests whose sensitivity is not perfect.^{11,12} The WHO is currently only suggesting PCR testing for definitive diagnoses; however, the accuracy of PCR testing is likely to vary depending on the stage of the disease and the degree of viral dissemination or clearance.¹³ As repeat PCR testing may have additional benefits on diagnosis, the sensitivity of the PCR test was still 63% for nasal swabs and 32% for throat swabs.¹⁴

While this diagnostic challenge still persists, clinicians encountered cases of atypical pneumonia whose clinical signs and symptoms were indistinct. Accordingly, all patients having respiratory symptoms suggestive of atypical pneumonia were treated like COVID-19 pneumonia during this period. Thus, some authors argue that patient symptoms and computed tomography (CT) findings may help with early recognition and isolation of COVID-19 patients.^{15,16} Radiologist had high specificity (between 93% and 100%) and moderate sensitivity (between 67% and 97%) in distinguishing COVID-19 from viral pneumonia on chest CT.¹⁷ Whether patients are diagnosed with COVID-19 or not, severe and rapidly progressing atypical pneumonia cases were observed and presented to all EDs and other healthcare facilities during this period. In this study, we aimed to find the poor outcome predictors of atypical pneumonia cases by following the patients for one month.

Methods

Study Design and Setting

A single-center prospective cohort study was carried out in our academic ED between March and May, 2020. The study center is one of the pandemic hospitals approved by the government, which has an annual patient capacity of 60,000. Before the study began, an institutional review board approval was obtained and the patients were asked to read and sign an informed consent form.

Selection of Participants

All patients over 18 years with COVID-19 like atypical pneumonia who presented to the ED and agreed to participate were included in the study during the outbreak. All patients had symptoms suggesting pneumonia, and diagnoses were confirmed by CT scan. Patients were excluded if they had typical bacterial pneumonia patterns present in chest CT scans with lobar consolidation, dependent peribronchial infiltration with bronchial obstruction, or if the CT scan was consistent with aspiration pneumonia. In addition, patients were excluded if they

refused to participate in the study or if we lost the patient during the follow-up period.

Study Protocol

All cases with suspected pneumonia who presented to the ED were evaluated by a senior emergency medicine resident regarding their pneumonia symptoms. If patients' symptoms were suggestive of pneumonia, a nasopharyngeal specimen for COVID-19 PCR testing was obtained in a specialized area near the ED, and patients underwent non-contrasted CT scanning. The demographic and disease characteristics included comorbidities, symptoms, physical examination findings, and vital signs of which were queried using standardized charts. Laboratory characteristics of the patients acquired by hospital database system. Chest CT images were evaluated and reported by a radiologist with ten years of experience in the field of chest CT imaging. The radiologist performed an interpretation of the CT images by considering the COVID-19 classification of the Radiological Society of North America (RSNA).¹⁸ COVID-19 pneumonia pattern was mainly established using the radiological criteria of RSNA when ground-glass opacities were combined with consolidations. All patients received hydroxychloroquine with or without azithromycin according to Turkish governmental guidelines on COVID-19 pneumonia. Care and treatments in the ICUs were not standardized and were left to the initiative of the caring physician. Patients were followed one month after the initial presentation to the ED. One month later, questions were directed to the patients about outcome measures via phone calls.

Outcome Measures

The primary outcome measures were determined as the composite outcome, including mortality, ICU admission, or mechanical ventilation needs within a one-month period. Accordingly, patients were classified into poor outcome (first group) or good outcome (second group) groups.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows (Version 20.0. Armonk, NY: IBM Corp.). The Kolmogorov-Smirnov test was used to test for a normal distribution of the continuous variables. The continuous variables were tested using the Student t or Mann-Whitney U tests and were expressed as means (with standard deviation) and medians (with interquartile ranges [IQRs]). Categorical variables were tested using the Chi-square or Fisher's exact tests. A binary logistic regression model was created to evaluate the independent predictors of the primary composite outcome. Only variables that were statistically significant were included in the multivariate model. Prior to the establishment of the final model, a multicollinearity analysis was performed. The Hosmer-Lemeshow test was used to assess the fitness of the model, and the effect sizes were expressed with odds ratios (ORs) and 95% confidence intervals (CIs). All the statistical analyses were two-sided. A p value of <0.05 was considered to be the nominal level of significance.

Results

A total of 271 patients with suspected pneumonia were assessed for eligibility. Patients with bacterial pneumonia patterns (n=27) and patients with other pathologies shown on the chest CT scan (n=45) were excluded. No chest CT scan was obtained in 15 patients, and 38 patients had normal

CT scan results. Ultimately, 146 patients were included in the final analysis (Figure 1).

Composite outcomes occurred in 31 patients (first group, 21.2%), and 17 patients died within one month. No patients died or had mechanical ventilation needs in the second group, which consisted of 115 patients (78.8%). The first group was older than the second group. In addition, congestive heart failure, stroke history, and tachypnea were more prominent in the first group. The body temperatures of the patients in the second group were higher than in the first group; however, they were in normal ranges for both groups (Table 1).

Regarding disease characteristics, the first group was more dyspneic compared to the second group. In addition, complaints including altered mental status, and bronchospasm were mostly seen in the first group. According to the chest CT scan results, bilateral lung involvement was more prominent in the first group (80.6%) compared with the second group (50.4%) ($p=0.003$) (Table 2). Only one patient reported contact with a confirmed COVID-19 case (3.2%) in the first group; however, 27 cases (23.5%) had contact with patients participating in the second group ($p=0.011$). Lactate, lactate dehydrogenase, BUN, and

creatinine were higher in the first group, whereas hemoglobin, pH, and bicarbonate levels were lower in this group. Laboratory values seemed to be within normal ranges, although statistically significant differences were observed between the groups for some variables (Table 3).

Before the multivariate logistic regression analysis was carried out, a multicollinearity analysis was conducted for correlated variables at the $r>0.5$ level. Regarding this analysis, BUN and creatinine values had a strong correlation ($r=0.709$); thus, creatinine was added to the final model. In addition, bicarbonate was added to the model instead of pH level. Ultimately, age, history of heart failure, history of stroke, body temperature, dyspnea, cough, altered mental status, serious bronchospasm, bilateral lung involvement, hemoglobin levels, LDH, lactate levels, bicarbonate, and creatinine levels were added to the final model.

Regarding the final analysis, patients' altered mental status (OR:15.7, 95% CI: 1.7 to 141.6), serious bronchospasm (OR: 12.4, 95% CI: 1.6 to 97.9), and lactate levels (OR: 1.1, 95% CI: 1.0 to 1.2) were found to be independent predictors for worse outcomes in those patients. The result of the Hosmer–Lemeshow test was 0.300, and the model was accepted as a fit.

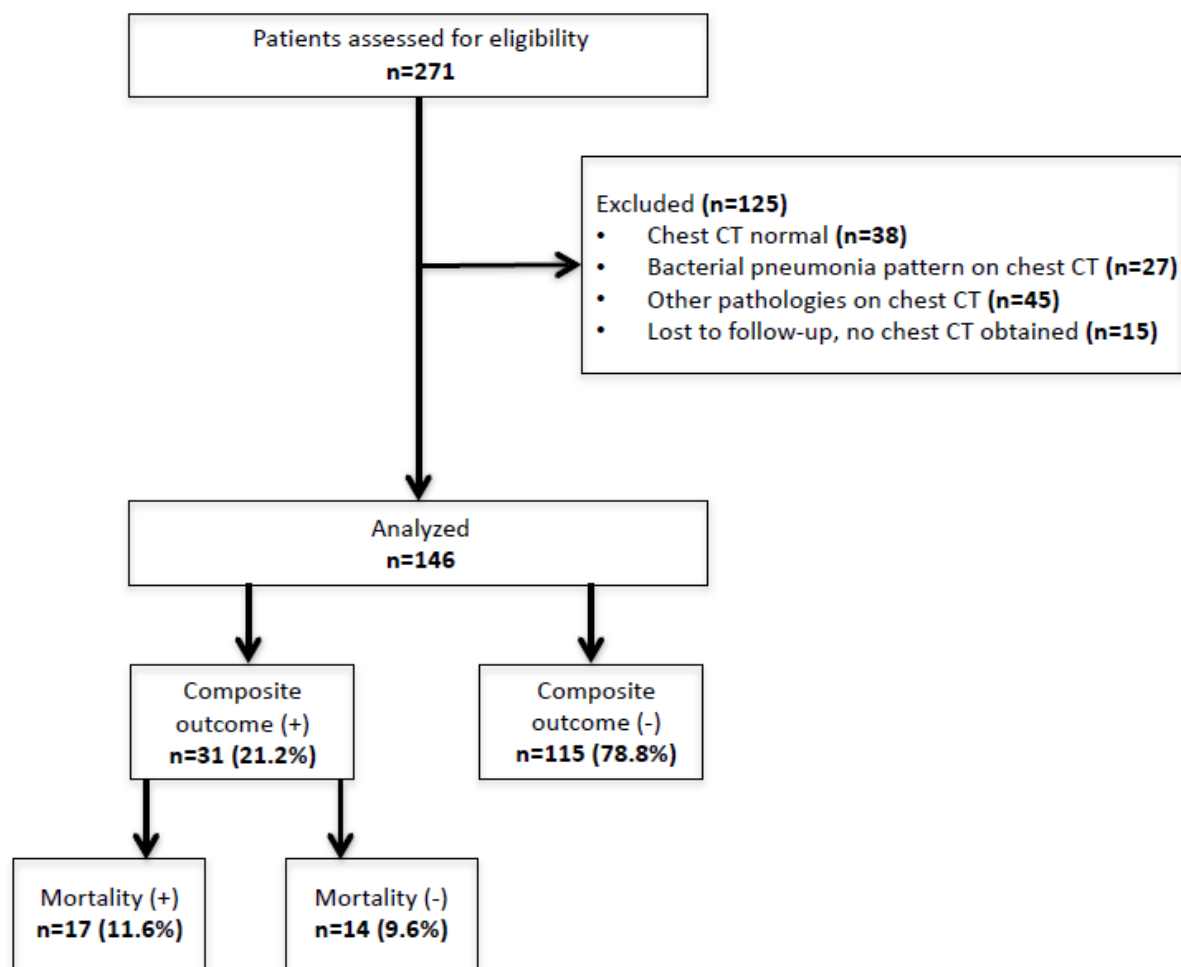


Figure 1. Patient flow chart

Table 1. Baseline characteristics, comorbidities and vital signs of the study population

	Group 1	Group 2	
	<i>Composite outcome</i>	<i>Composite outcome did</i>	<i>p value</i>
	<i>occurred (n=31)</i>	<i>not occurred (n=115)</i>	
Age, year (median, IQR)	68 (56-80)	57 (39-71)	0.015
Male (n,%)	18 (58.1%)	61 (53.0%)	0.619
Diabetes mellitus (n,%)	10 (32.3%)	28 (24.3%)	0.373
Hypertension (n,%)	17 (54.8%)	43 (37.4%)	0.080
Congestive heart failure (n, %)	9 (29.0%)	13 (11.3%)	0.022
Chronic kidney disease (n, %)	4 (12.9%)	11 (9.6%)	0.524
Previous stroke (n, %)	8 (25.8%)	6 (5.2%)	0.002
Asthma (n,%)	3 (9.7%)	14 (12.2%)	1.000
COPD (n, %)	3 (9.7%)	11 (9.6%)	1.000
Interstitial lung disease (n,%)	0 (0.0%)	1 (0.9%)	1.000
Cancer (n, %)	4 (12.9%)	14 (12.2%)	1.000
Vital signs			
Temperature, °C	36.4 (36.0-36.8)	36.6 (36.2-37.2)	0.029
Pulse, beat/min	95 (85-114)	97 (82-108)	0.769
Systolic blood pressure, mmHg	125 (104-141)	133 (113-148)	0.118
Diastolic blood pressure, mmHg	73 (60-88)	79 (69-90)	0.207
Respiratory rate, breath/min	25 (22-31)	22 (20-26)	0.025
Saturation, %	94 (87-98)	96 (94-98)	0.059

IQR: Interquartile range, N/A: Non applicable

Table 2. Disease characteristics of atypical pneumonia cases

	Group 1	Group 2	p value
	(n=31)	(n=115)	
Duration of symptoms (days, median, IQR)	3 (2-8)	3 (2-6)	0.356
Positive COVID-19 PCR result (n, %)	8 (25.8%)	37 (32.2%)	0.496
Travel to abroad (n, %)	1 (3.2%)	0 (0.0%)	N/A
Active pregnancy (n, %)	0 (0.0%)	1 (0.9%)	N/A
History of fever (n, %)	11 (35.5%)	51 (44.3%)	0.376
Dyspnea (n, %)	19 (61.3%)	42 (36.5%)	0.013
Cough (n, %)	11 (35.5%)	70 (60.9%)	0.012
Sputum (n, %)	5 (16.1%)	12 (10.4%)	0.360
Myalgia (n, %)	5 (16.1%)	29 (25.2%)	0.288
Nausea (n, %)	6 (19.4%)	19 (16.5%)	0.710
Chest pain (n, %)	1 (3.2%)	11 (9.6%)	0.462
Altered mental status (n,%)	10 (32.3%)	3 (2.6%)	<0.001
Diarrhea (n,%)	1 (3.2%)	6 (5.2%)	1.000
Sore throat (n, %)	0 (0.0%)	8 (7.0%)	0.203
Headache (n, %)	0 (0.0%)	3 (2.6%)	1.000
Nasal discharge (n, %)	0 (0.0%)	1 (0.9%)	1.000
Physical Examination			
Throat congestion (n, %)	2 (6.5%)	9 (7.9%)	1.000
Rales (n, %)	10 (32.3%)	27 (23.7%)	0.332
Ronchus (n, %)	2 (6.5%)	16 (14.0%)	0.363
Serious bronchospasm (n, %)	9 (29.0%)	2 (1.7%)	<0.001
Peripheral edema (n, %)	4 (12.9%)	10 (8.8%)	0.499
Radiological features			
Peripheral GGO (n,%)	18 (58.1%)	54 (47.0%)	0.272
Multifocal GGO (n,%)	10 (32.3%)	20 (17.4%)	0.069
Bilateral lung involvement (n, %)	25 (80.6%)	58 (50.4%)	0.003

GGO: Ground-glass opacity

Table 3. Baseline laboratory values of patients on presentation in emergency department

	Group 1 (n=31)	Group 2 (n=115)	p value
Hemoglobin, g/dL	11.3 ± 2.8	12.5 ± 2.3	0.014
Leukocyte, 10³/μL	8600 (6000-13100)	7550 (5300-10300)	0.129
Neutrophil, 10³/μL	5900 (3800-7400)	5450 (3375-8400)	0.535
Lymphocyte, 10³/μL	1300 (700-2200)	1100 (800-1625)	0.236
Neutrophil / Lymphocyte ratio	4.1 (2.2-9.6)	4.2 (2.5-9.1)	0.725
C-reactive protein, mg/L	29 (13-126)	23 (7-90)	0.179
Increased procalcitonin*	7 (29.2%)	23 (22.1%)	0.462
LDH, U/L	296 (225-587)	259 (202-356)	0.034
D-dimer, mg/L	1.8 (0.5-5.1)	0.7 (0.3-2.1)	0.054
Lactate, mg/dL	18.0 (12.5-27.0)	14.0 (10.0-18.0)	0.027
pH	7.37 (7.33-7.41)	7.40 (7.35-7.42)	0.020
HCO₃, mEq/L	22.7 (18.7-24.5)	24.0 (22.1-26.4)	0.006
Na, mEq/L	135 (131-140)	137 (135-140)	0.114
K, mEq/L	4.4 (3.8-5.1)	4.2 (3.9-4.6)	0.174
AST, U/L	32 (20-57)	26 (20-46)	0.375
BUN, mg/dL	22 (14-41)	17 (12-25)	0.009
Creatinine, mg/dL	1.1 (0.6-1.5)	0.8 (0.6-1.0)	0.013

*: Procalcitonin level above 0.25 ng/mL, LDH: Lactate dehydrogenase

Table 4. Multivariate logistic regression analysis to determine worse composite outcome in atypical pneumonia case

	Wald	OR (95% CI)	p value
Age	0.03	1.00 (0.96 to 1.04)	0.872
Heart failure	2.62	3.82 (0.75 to 19.36)	0.106
History of stroke	1.53	3.29 (0.50 to 21.69)	0.217
Body temperature	1.94	0.55 (0.23 to 1.28)	0.164
Respiratory rate	3.52	0.87 (0.75 to 1.01)	0.061
Dyspnea	0.09	1.24 (0.31 to 4.93)	0.764
Cough	0.01	0.93 (0.24 to 3.62)	0.913
Altered mental status	6.03	15.72 (1.74 to 141.61)	0.014
Serious bronchospasm	5.71	12.41 (1.57 to 97.93)	0.017
Bilateral lung involvement	1.84	2.88 (0.62 to 13.25)	0.175
Hemoglobin	1.29	0.84 (0.62 to 1.14)	0.256
LDH	0.07	1.00 (1.00 to 1.00)	0.799
Lactate	5.74	1.10 (1.02 to 1.19)	0.017
Bicarbonate	1.35	0.89 (0.73 to 1.08)	0.246
Creatinine	0.79	0.80 (0.48 to 1.32)	0.375

Discussion

COVID-19 has a significant impact on the healthcare system both in direct and indirect ways. One of the possible mechanisms of this indirect impact is the large size of undiagnosed severe COVID-19 cases and the reduced access to healthcare due to the disruption of the normal working processes.¹⁹ Diagnostic challenges also complicate the selection of patients with poor health outcomes. Under these circumstances, mortality cohorts can be a method used to recognize patients who will use the healthcare system more, as well as to identify which patients' health conditions may worsen. In our study, we intended to establish a composite outcome that included mortality, ICU care, and the need for mechanical ventilation. Although there was a statistically significant difference between the two groups in terms of clinical and laboratory variables, this difference did not correspond to the clinical significance for many aspects.

Recently, a prospective cohort study determining predictors of mortality for patients with COVID-19 was published.⁶ In this study, age, preexisting concurrent cardiovascular or cerebrovascular diseases, CD3+ CD8+ T cells ≤ 75 cell/ μ L, and cardiac troponin I ≥ 0.05 ng/mL were determined as factors that increase the risk of mortality for patients with COVID-19. According to Ruan et al., the predictors for fatal COVID-19 outcomes include age, the presence of underlying diseases, the presence of secondary infection, and elevated inflammatory indicators in the blood.⁸ Zhou et al. also retrospectively evaluated the predictors of in-hospital deaths in a Chinese COVID-19 population. According to this study, older age, higher Sequential Organ Failure Assessment (SOFA) scores, and a D-dimer greater than 1 μ g/mL on admission could help clinicians identify patients with poor prognosis at an early stage.²⁰

Most of the aforementioned studies only dealt with PCR-positive patients without taking into account pneumonic involvement. Among them, Du et al. described a COVID-19 pneumonia cohort consisting of 179 patients having positive or negative PCR results similar to our study.⁶ They collected data prospectively; however, the time interval for mortality was not specified. Similar to their study, we found that increased age and the existence of cardiovascular comorbidities, including heart failure and stroke history, renal involvement, dyspnea, and tachypnea were more prevalent in the poor outcome group. They did not report lactate levels or physical examination findings, such as bronchospasm, which were found to be predictors of poor health outcomes in our study. It should be noted that increased respiratory rates and oxygen requirements at initial admission were the most important determinants of the severity of the disease, and those variables were significant predictors of clinical deterioration.^{4,5}

Previous studies have highlighted the effects of increased age and many comorbid diseases in COVID-19 related mortality and morbidity.^{8,21,22} Furthermore, cardiovascular comorbidities, including hypertension and renal involvement, also play an important role in assessing the severity of the disease.^{4,21,23} A large retrospective cohort from New York City claimed that patients admitted to ICUs were older, predominantly male (78.0%), had developed acute kidney injury, and 35.2% needed dialysis.²⁴ Hypertension was the leading comorbidity in the ICU group in this study with a frequency of 66.9%; this ratio was also higher in our poor outcome group (54.8%). This finding was followed by congestive heart failure in this study (10.2%),

which was more prevalent in the poor outcome group (29.0%).

In this study, we found that two variables that remind us of the criteria related to sepsis can be valuable for COVID-19 related pneumonia. Moreover, patients' altered mental status was accepted as one of the determinants of quick SOFA criteria, and lactate was an essential part of septic shock evaluation.²⁵ Considering that these criteria are independent predictors of clinical deterioration in our study, it can be interpreted that COVID-19 related atypical pneumonia may correspond to sepsis related processes in the advanced stages of the disease.

Limitations

Our study has several limitations. First, this study was a single-center experience of COVID-19 pneumonia cases with a relatively small sample size. Thus, the generalizability of our results is limited. Second, some patients had secondary PCR testing, whereas others did not. As previously discussed, the results of PCR testing are time-sensitive and mostly related to a swab technique. Therefore, the number of patients with positive PCR tests may actually be higher. Third, patients received different treatments after their initial visit to the ED, and we cannot follow patients' compliance with treatments. However, treatment regimens were mostly already set by the government's scientific guidelines for COVID-19, of which many and all physicians try to adhere to.

Conclusion

During the COVID-19 outbreak, many patients were subjected to PCR testing to establish an exact diagnosis. However, the recognition of atypical pneumonia patients with poor clinical outcomes may provide clinicians with greater benefits in daily practice. Furthermore, patients' altered mental status, serious bronchospasm, and increases in lactate levels were found to be independent predictors for worse healthcare outcomes for those patients. Future studies may involve the prognostic value of other sepsis criteria for severe COVID-19 related pneumonia.

Conflict of Interest

None declared

Author Contributions

NÖD, SD, MP: Design; NÖD, SD, MP: Project development; DFE, KBT, NÖD: Data collection; KG, BA, NÖD, MP: Analysis; NÖD, MP, SY: Literature search; KG, NÖD, SD, MP: Manuscript writing; MP, SY, SD, NÖD: Critical review

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