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KLİNİK ARAŞTIRMA

Mild/moderate and severe COVID-19 pneumonia: Can the clinical course be predicted?

Hafif/orta ve ağır COVID-19 pnömonisi: Klinik seyri öngörmek mümkün mü?

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SUMMARY

Aim: In this study, it was aimed to compare clinical and laboratory characteristics of cases with mild/moderate or severe COVID-19 pneumonia and to identify factors related to severe disease.

Material and Methods: We retrospectively reviewed the clinical and laboratory characteristics of adult patients who were hospitalized with a diagnosis of COVID-19 pneumonia. The study included patients in whom SARS-CoV-2 nucleic acid was found by real-time polymerase chain reaction (RT-PCR) and pneumonia was detected chest computed tomography scan.

Results: Of 94 patients (41 women, 53 men), 71 were classified as mild/moderate pneumonia while 23 were classified as severe pneumonia. Mean age was significantly higher in severe pneumonia group (p<0.001). Cough and dyspnea were most common complaints at presentation (53% and 44%, respectively). In multivariate logistic regression analysis, dyspnea (OR: 13.24; 95% CI: 1.14-153.12; p: 0.39), leukocytosis (OR: 1.29; %95 CI: 1.08-1.55; p: 0.006), CRP elevation (OR: 1.01; 95% CI: 1.00-1.02; p: 0.006) and D-dimer elevation (OR: 1.80; 95%:1.15-2.81; p: 0.01) were identified as independent factors related to severe pneumonia.

Conclusion: Our results emphasized that COVID-19 pneumonia may show a severe clinical course in patients presented with dyspnea without hypoxia and had elevated leukocyte count, CRP, and D-dimer values.

Keywords: COVID-19, pneumonia, SARS-CoV-2

ÖZET

Amaç: Bu çalışmada hafif/orta ve ağır pnömoni gelişen olgulardaki klinik ve laboratuvar özelliklerin karşılaştırılması ve ağır seyir ile ilişkili olan faktörlerin saptanması amaçlandı.

Materyal ve Metodlar: COVID-19 pnömoni tanısıyla hastaneye yatırılan erişkin hastaların klinik ve laboratuvar özellikleri geriye dönük olarak incelendi. Çalışmaya gerçek zamanlı polimeraz zincir reaksiyonu (RT-PCR) ile SARS-CoV-2 nükleik asidi bulunan ve akciğer bilgisayarlı tomografisinde pnömoni saptanan hastalar dahil edildi.

Bulgular: Çalışmaya alınan 94 (41'i kadın ve 53'ü erkek) olgudan 71'i hafif/orta pnömoni olarak tanımlanırken 23'ü ağır pnömoni olarak sınıflandırıldı. Ağır pnömoni grubunda yaş ortalaması belirgin olarak daha yüksek bulundu (p<0.001). Başvuru esnasında öksürük ve nefes darlığı en sık (sırasıyla %53, %44) saptanan yakınmalar idi. Yapılan çok değişkenli lojistik regresyon analizinde nefes darlığı (p:0.039, OR:13.24, %95CI: 1.14-153.12), lökositoz (p=0.006, OR: 1.29, %95CI: 1.08-1.55), CRP yüksekliği (p=0.006, OR: 1.01, %95CI: 1.00-1.02) ve D-dimer yüksekliği (p=0.01, OR:1.80 %95CI: 1.15-2.81) ağır pnömoni için bağımsız risk faktörü olarak saptandı.

Sonuç: Çalışma sonuçları, başvuru esnasında hipoksi olmadan nefes darlığı yakınması olan, lökosit, CRP ve D-dimer değerleri yüksek olan hastalarda, COVID-19 pnömonisinin ağır seyredebileceğine dikkat çekmiştir.

Anahtar kelimeler: COVID-19, pneumonia, SARS-CoV-2

INTRODUCTION

In December 2019, novel coronavirus-related pneumonia cases were identified in Wuhan Province, China, and the pathogen was denominated as severe acute respiratory syndrome (SARS-CoV-2) by the International Committee on Taxonomy of Viruses [1, 2]. The first COVID-19 case was detected in Turkey on March 9, 2020, and COVID-19-related death occurred on March 17, 2020 [3]. Although the disease is generally asymptomatic or mildly symptomatic, pneumonia, acute respiratory distress syndrome, multi-organ failure, and death can be seen in 15-20% of cases [4, 5]. The case fatality rate is estimated at 3.4% worldwide while it varies from 0.1% to 25% across countries [6-8]. The disease severity is an independent prognostic factor for mortality. In previous studies, it was found that age>50, comorbidity and, elevated inflammation markers were identified as risk factors for severe disease in cases with COVID-19 pneumonia [4, 9]. On the other hand, it was also shown that chest computed tomography (CT) findings are predictive of disease severity [10, 11]. The clinical and laboratory characteristics at presentation are important to predict the clinical course. In this study, it was aimed to address baseline clinical and laboratory findings in patients with mild/moderate and severe pneumonia and to determine the value of the findings in predicting disease severity.

MATERIAL AND METHODS

The study was approved by Turkish Health Ministry (approval number: 2020-05-04T23_15_13.xml). It was also approved by Ethics Committee on Non-interventional Trials of XXXX University (approval number: 77192459-050.99-E.21443). We retrospectively evaluated clinical and laboratory characteristics of adult patients (aged>18 years) who were admitted with diagnosis of COVID-19 disease to infectious disease department of Training and Research Hospital, XXX University between April 1, 2020, and May 31, 2020. The COVID-19 diagnosis was confirmed by detection of SARS-CoV-2 nucleic acid in oropharyngeal or nasopharyngeal swab using real-time polymerase chain reaction (RT-PCR). The patients with missed laboratory findings or those not confirmed by RT-PCR were excluded. The severe pneumonia was defined according to 2019 Clinical Practice Guideline for diagnosis of treatment of community-acquired pneumonia published by Infectious Diseases Society of America (IDSA) and American Thoracic Society (ATS) [12].

We retrospectively extracted data regarding complaints (fever, anorexia, fatigue, dyspnea, cough, sore throat, nausea, vomiting, diarrhea), physical examination findings (body temperature, respiratory rate, signs related to hypoxia, general health status), comorbid diseases, contact history and laboratory findings at presentation from hospital database. Clinical and laboratory characteristics were compared between patients with mild/moderate and severe pneumonia. In addition, data regarding treatment, need for intensive care and survival were also recorded.

Statistical Analysis

Data were analyzed using SPSS for Windows version 15.0 (SPSS Inc.; Chicago, IL, USA). Descriptive statistics are shown as mean and standard deviation. Categorical variables were assessed using the Chi-square test while data with normal distribution were assessed using Student's t-test. Data with skewed distribution were assessed using the Mann Whitney U test. Data found to be significant in univariate logistic regression analysis by forward LR were included to multivariate logistic regression model. A p value<0.05 was considered as statistically significant.

RESULTS

The study included 94 eligible patients (41 women, 53 men). Of patients included, 71 were classified as mild/moderate pneumonia while 23 were classified as severe pneumonia. Cough and dyspnea were most common complaints at presentation (53% and 44%, respectively). Mean age was significantly higher in severe pneumonia group (p<0.001). No significant difference was detected between groups regarding gender. The fatigue, anorexia and dyspnea were found to be markedly more common in severe pneumonia group. No significant difference was found between groups regarding body temperature. Among comorbid diseases, hypertension, coronary artery disease and heart failure were more common in severe pneumonia group (p<0.001). Table 1 presents demographic characteristics, presenting complaints and follow-up characteristics.

Table 1. Demographic and clinical features of mild/moderate and severe pneumonia

Characteristic	Total (n=94)	Severe (n=23)	Mild/moderate (n=71)	*P*
Median Age (years)	52.7±17.7	71.5 ±12.5	46.6±14.5	<0.001
Sex				
Female	41 (44)	8 (35)	33 (46.5)	0.435
Male	53 (56)	15 (65)	38 (53.5)	0.328
Complaint				
Fatigue	24 (26)	12 (52)	12 (17)	<0.001
Loss of apitite	13 (14)	8 (35)	5 (7)	<0.001
Fever	37 (39)	9 (39)	28 (39)	0.979
Muscle and joint pain	5 (5)	1 (4)	4 (6)	0.811
Sore throat	10 (11)	1 (4)	9 (13)	0.26
Cough	50 (53)	12 (52)	38 (53)	0.91
Dyspnea	41 (44)	21 (91)	20 (28)	<0.001
Nausea and vomiting	5 (5)	1 (4)	4 (6)	0.811
Diarrhea	7 (8)	1 (4)	6 (8)	0.515
Contact history	30 (32)	4 (17)	26 (37)	0.086
General health status				
Good	61 (65)	3	58	<0.001
Average	20 (21)	8	12	0.069
Bad	13 (14)	12	1	<0.001
Body Temperature (>38.3^{0}C)	12 (13)	4 (17)	8 (11)	0.444
Comorbidities				
Hypertension	23 (25)	12 (52)	11 (15)	<0.001
Diabetes mellitus	14 (15)	3 (13)	11 (15)	0.774
*COPD	14 (15)	5 (22)	9 (13)	0.289
Malignancy	3 (3)	2 (9)	1 (1)	0.084
Coronary artery disase	11 (12)	7 (30)	4 (6)	0.001
Heart failure	7 (8)	5 (22)	2 (3)	0.003
İmmunosuppression	4 (4)	2 (9)	2 (3)	0.225
Need for intensive care	21 (22)	19 (83)	2 (3)	<0.001
Theraphy				
**Combined therapy	35 (37)	19 (83)	16 (22)	<0.001
Azithromycin	61 (65)	8 (35)	53 (75)	<0.001
Quinolone	40 (43)	7 (30)	33 (46)	0.176
Carbapenem	9 (10)	6 (26)	3 (4)	0.002
Death	13 (14)	12 (52)	1 (1)	<0.001

***COPD:** chronic obstructive pulmonary disease. ****Combined therapy:** hydroxychloroquine + favipravir

In addition to supportive treatment, all patients received hydroxychloroquine over 5 days. Of patients included, 27% received hydroxychloroquine plus favipravir combination. Hydroxychloroquine therapy was extended to 10 days in a patient from severe pneumonia group. Azithromycin use was more common in mild-to-moderate pneumonia group while carbapenem antibiotic use was more common in severe pneumonia group. IL-6 receptor antagonist, tocilizumab, was given to 3 patients with consideration of secondary hemophagocytic lymphohistiocytosis; of these, one patient died. Two patients required intensive care in mild/moderate pneumonia group; of these, one patient died. There were 12 deaths (52%) in severe pneumonia group and one death (1%) in mild/moderate pneumonia group.

Leukocyte count, C-reactive protein (CRP), D-dimer, ferritin and procalcitonin levels were found to be significantly higher in severe pneumonia group. No significant difference was found in transaminase level, hemoglobin and platelet counts between groups. In addition LDH was found to be significantly higher in the severe pneumonia group (P<0.001). Table 2 present laboratory findings.

Table 2. Laboratory features of mild / moderate and severe pneumonia

Laboratory Findings	Total	Severe Pneumonia (n=23)	Mild/Moderate Pneumonia (n=71)	*P*
Leukocyte(10^3/mm^3)	7,552±3,992	10,833±5,123	6,489±2,870	<0,001
Hemoglobin (g/dL)	13,81±3,03	13,56±5,53	13,89±1,59	0,65
Trombocyte(10^3/mm^3)	234,09±77,90	240,35±112,77	232,06±63,62	0,66
Aspartate aminoteransferase (U/L)	40,0±35,4	53,13±62,88	35,69±18,69	0,25
Alanin aminoteransferase (U/L)	33,1±30,6	38,61±55,10	31,25±16,62	0,07
Lactate dehydrogenase (U/L)	309,5±145,0	416,13±189,28	274,99±108,26	<0,001
C-reactive protein (mg/dL)	46,4±77,1	123,21±113,95	21,56±35,46	<0,001
D.dimer(ng/mL)	1,797±4,464	5,145±8,088	0,713±1,022	<0,001
Ferritin (ng/L)	337,48±462,35	660,73±619,93	232,77±343,18	<0,001
Procalcitonin (ng/mL)	0,200±0,700	0,745±1,328	0,053±0,082	<0,001

In multivariate logistic regression analysis, dyspnea (OR: 13.24; 95% CI: 1.14-153.12; p: 0.39), leukocytosis (OR: 1.29; %95 CI: 1.08-1.55; p: 0.006), CRP elevation (OR: 1.01; 95% CI: 1.00-1.02; p: 0.006) and D-dimer elevation (OR: 1.80; 95%:1.15-2.81; p: 0.01) were identified as independent factors related to severe pneumonia (Table 3). However, no procalcitonin nor LDH was an independent risk factor in multivariate analysis.

Table 3. Factors associated with severe pneumonia according to multivariate logistic regression result

Variables	Multivariate logistic regression analysis		
	P	Odss Ratio	95% Confidence Interval
Dyspnea	0.039	13.24	1.14-153.12
D-dimer	0.01	1.80	1.15-2.81
C-reactive protein (mg/dL)	0.006	1.01	1.00-1.02
Leukocyte (10^3/mm^3)	0.006	1.29	1.08-1.55

DISCUSSION

Based on our study, presence of dyspnea and elevated leukocyte, CPR and D-dimer levels at presentation were associated with severe pneumonia. In previous studies, it was shown that advanced age is a risk factor for severe pneumonia [9, 13, 14]. In our study, although the mean age was significantly higher in the severe pneumonia group, no correlation with the severe clinical course was found in logistic regression analysis. In preliminary studies, it was shown that the mortality of COVID-19 is higher in the male gender when compared to the female gender [15, 16]. However, effect of gender on clinical course of COVID-19 hasn't been clearly established, emphasizing need for evaluating absolute number of patients from different countries [17]. In our study, no difference was detected in gender distribution between groups. In previous studies, it was reported that fever and cough are most common symptoms [1, 9, 13, 18]. In a study comparing severe and non-severe COVID-19 pneumonia, fever and cough were detected in 95.2% and 75.5% of patients, respectively; however, no significant difference was detected between severe and non-severe pneumonia groups [13]. In our study, cough and fever were detected in 53% and 39% of patients, respectively. These rates were lower than those reported in previous studies. Similarly, no significant difference was detected between mild/moderate and severe pneumonia groups. On the other hand, in a recent study from Turkey, fever was detected in only 30.4% of cases in agreement with our study [19]. In a study on 250 patients with COVID-19 disease, Aslan et al. [20] reported myalgia and fatigue as most common symptom (76%). In our study, fatigue was found in 26% of cases with markedly higher rate in severe pneumonia group; however, no significant association was detected in multivariate logistic regression analysis. In a study by Li et al. [13] fatigue was detected in 47.1% of cases but there was no significant difference between groups. In a multicenter study, it was found that history of hypertension and diabetes mellitus was more common in patients with severe disease [18]. In our study, hypertension was detected in 25% of cases with markedly higher rate in the severe pneumonia group; however, no significant difference was detected between groups regarding diabetes mellitus. Again in this study, elevated CRP, D-dimer, and fibrinogen levels as well as leucopenia, thrombocytopenia, and decreased albumin level were more common in patients with severe disease [18]. Similarly, CRP and D-dimer elevation was more common in severe pneumonia group in our study; in addition, leukocytosis was found to be higher in severe pneumonia group. In multivariate analysis, elevated CRP, D-dimer and leukocyte count were found to be associated with severe pneumonia in logistic regression analysis. In a study, it was shown that D-dimer level>2 µg/mL was predictive for in-hospital mortality [21]. In our study, mortality rate was 52% while mean D-dimer level (5.15 µg/mL) was higher in severe pneumonia group. In a study by Yu et al., [22] it was found that procalcitonin was a significant predictor for mortality. In another study, the proportion of patients with procalcitonin>0.5 ng/mL was found to be significantly higher in severe pneumonia group when compared to non-severe pneumonia group [13]. Similarly, the mean procalcitonin value (0.754 ng/mL)

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was found to be higher in the severe pneumonia group in our study. In previous studies, it was shown that LDH is a significant, independent risk factor for disease severity and mortality [23-25]. In our study, LDH was found to be significantly higher in the severe pneumonia group; however, no procalcitonin nor LDH was an independent risk factor in multivariate analysis. In previous studies, CRP elevation is a marker for the severe clinical course [26, 27]. Similarly, in our study, CRP was found to be markedly higher. In cases with COVID-19, it was found that elevated ferritin level is a marker for hemophagocytic lymphohistiocytosis and associated with severe clinical course [28]. Although mean ferritin value was markedly higher in severe pneumonia group, multivariate logistic regression analysis showed no significant association. In a meta-analysis evaluating effects of patient characteristics on mortality in COVID-19, presence of elevated ALT, CRP and D-dimer levels at presentation were found to be associated with mortality [29]. In our study, ALT was found to be higher in severe pneumonia group but the difference did not reach statistical significance (p=0.07).

This study has some limitation. Due to retrospective design, all parameters could not be recorded. Thus, results might have been affected by missed data such as smoking status or obesity. In addition, limited sample size might prevent to draw a general conclusion.

CONCLUSIONS

We think that clinicians may predict clinical course of patients with COVID-19 pneumonia by assessing clinical and laboratory findings at presentation. According to the results of this study, we draw attention to the importance of leukocytosis, high CRP, elevated D. dimer, and dyspnea.

Highlight key points

- According to this study, Cough and dyspnea were the most common complaints at the presentation in COVID-19 pneumonia
- As clinical finding dyspnea was identified as independent factors related to severe COVID-19 pneumonia
- As laboratory findings leukocytosis, elevated CRP, and D-dimer were factors related to severe COVID-19 pneumonia
- There were 12 deaths (52%) in the severe pneumonia group and one death (1%) in the mild/moderate pneumonia group

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