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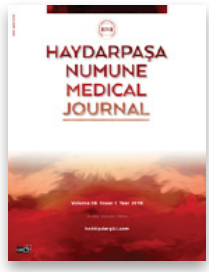

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ORIGINAL ARTICLE

Impact of Comorbidities on Prognosis in Asymptomatic, Mild, and Moderate COVID-19 Patients: A Retrospective Türkiye Study

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Abstract

Introduction: Predicting the mortality risk of 2019 coronavirus disease (COVID-19) patients in the early period is important in terms of using the limited health system's resources efficiently. The aim of this study was to determine the effects of comorbidities on the occurrence of pneumonia and prognosis in asymptomatic, mild, and moderate COVID-19 patients.

Methods: This retrospective, single-center, and cross-sectional study was conducted between April 1 and May 15, 2020, in the emergency department of a tertiary hospital in Istanbul, Türkiye. In our study, patients with laboratory-confirmed COVID-19 were examined for the occurrence of pneumonia and 28-day mortality.

Results: The study was included 3047 adult patients. In our study, pneumonia detection rate was 55.3%, hospitalization rate was 18.0%, and 28-day mortality rate was 0.7%. NCIP (85.3% vs. 47.7%; p<0.001) and mortality (2.8% vs. 0.1%; p<0.001) rates were higher in patients with at least one comorbidity disease than those without. Advanced age, smoking, hypertension, diabetes, asthma, chronic kidney disease (CKD), and malignancy were important risk factors for the occurrence of pneumonia. In addition, in our study, COVID-19 patients with hypertension, diabetes, CKD, chronic liver disease, or malignancy had a higher probability of 28-day mortality.

Discussion and Conclusion: In our study, the most important risk factors for both pneumonia and 28-day mortality were advanced age, diabetes, CKD, and malignancy. The effects of comorbidities should be considered when determining the risk stratification and need for hospitalization of asymptomatic, mild, and moderate COVID-19 patients.

Keywords: Comorbidities; COVID-19; diabetes; malignancy; pneumonia.

Since the World Health Organization (WHO) declared the 2019 coronavirus disease (COVID-19) a pandemic,[1] more than 273 million cases and more than 5.3 million deaths have been reported worldwide[2]. Despite the global impact, fundamental gaps in information remain. In the report published by the WHO, it is stated

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that patients with mild to moderate illness may not require urgent intervention or hospitalization[3]. However, it warns that patients with risk factors for severe disease should be closely monitored considering the possible risk of worsening[3]. Since COVID-19 emerged, many researchers have reported the epidemiology, clinical signs, laboratory, imaging finding, and prognosis of COVID-19, as well as associated risk factors[4,5]. Older age, smoking, and underlying diseases, such as diabetes, hypertension, cardiac disease, chronic lung disease, and cancer, have been reported as risk factors for severe disease and death[3]. Despite some consistent themes, reports from different geographic locations reported differences in risks[6-12].

The aim of this study is to determine the effect of demographic characteristics and comorbidities on mortality risk in COVID-19 patients.

Materials and Methods

This study was approved by the Ethics Committee of the research institution (Protocol no: 2020/234). It was conducted in accordance with the Declaration of Helsinki. The need for informed consent was waived due to the retrospective nature of the study.

Setting and Study Population

This retrospective, single-center, and cross-sectional study was conducted between April 1, 2020, and May 15, 2020, in the emergency department of a tertiary hospital. The studied population consisted of adult (≥18 years old) patients with asymptomatic mild or moderate disease who had chest computed tomography (CT) and confirmed as COVID-19 by reverse transcription polymerase chain reaction (rt-PCR).

Exclusion criteria included (1) patients with negative rt-PCR results; (2) patients without chest tomography imaging; (3) severe and critical COVID-19 patients; and (4) patients with missing data. The diagnosis and treatment of these patients were performed in line with the Novel Coronavirus Pneumonia Diagnosis and Treatment Guidelines published by the National Health Commission of Türkiye[13].

Classification of Patients

Clinical classification of the patients was performed according to the WHO's COVID-19 clinical management living guidance[3].

Mild disease: Symptomatic patients meeting the case definition for COVID-19 without evidence of viral pneumonia or hypoxia. Moderate disease: Adolescent or adult with clinical signs of pneumonia (fever, cough, dyspnea, and fast breathing) but no signs of severe pneumonia, including SpO_2 ≥90% on room air. Severe disease: Adolescent or adult with clinical signs of pneumonia (fever, cough, dyspnea, and fast breathing) plus one of the following: respiratory rate >30 breaths/min; severe respiratory distress; or SpO_2 <90% on room air.

Outcomes

The primary outcome was the occurrence of pneumonia on chest CT of the patients. The secondary outcome was 28-day mortality status of the patients.

Data Collection

Patients meeting the inclusion and exclusion criteria were consecutively included in the study. Demographic data (age, gender, and comorbidity diseases), radiological imaging, rt-PCR results, treatment in the hospital or intensive care unit (ICU), and prognosis were recorded for the study by recording electronic medicine and/or interviewing patients. SARS-CoV-2 infection was confirmed by rt-PCR analysis using the combined throat and nose swab SARS-CoV-2 nucleic acid detection kit. Chest CT was used for imaging analysis. All chest CT images were examined by radiologists who were blinded to rt-PCR results. It was decided whether the radiology findings were negative or positive for the typical findings of COVID-19 pneumonia (bilateral, multilobar, and posterior peripheral ground-glass opacities) according to the Radiological Society of North America Consensus statement[14].

Imaging

Unenhanced chest CT scans were obtained with the patient in the supine position. All patients underwent scanning with one scanner: SOMATOM Perspective (Siemens Healthcare). The acquisition parameters were set at 130 kVp; 100–200 mAs; pitch, 0.75–1.5; and collimation, 0.625–5 mm. All imaging data were reconstructed by the use of a medium sharp reconstruction algorithm with a slice thickness of 0.625–5 mm.

Statistical Methods

The statistical analyses were run in SPSS 21 for Windows (Chicago, IL). Normality analyses of the data were con-

ducted using histograms and the Kolmogorov–Smirnov test. Continuous variables were presented as mean±SD or median (25% to 75% interquartile range [IQR]) as appropriate, and the categorical variables were presented as counts and percentages. Normal distribution data were analyzed using the Student's t-test. Abnormal distribution data were analyzed using Mann–Whitney U-tests. Intragroup comparisons of the categorical variables were made using the Chi-square test and Fisher's exact test. To explore the risk factors associated with pneumonia, univariable and multivariable logistic regression models were used. $p<0.05$ was considered as statistically significant.

Results

A total of 27,166 patients were screened, and 3,047 patients were included in this study (Fig. 1).

The median age was 40 (IQR: 31–50) years and 58.7% of the patients were male. 3.1% of the patients were asymptomatic when they visited the ED. The most common symptoms were myalgia (83.3%), fatigue (64.1%), cough (58.7%), sore throat (41.6%), anosmia/dysgeusia (36.1%), fever (35.9%), and headache (35.9%).

A total of 20.2% of the patients were afflicted with at least one comorbidity disease, and the most common comorbidities were hypertension (10.1%) and diabetes (7.7%) (Table 1).

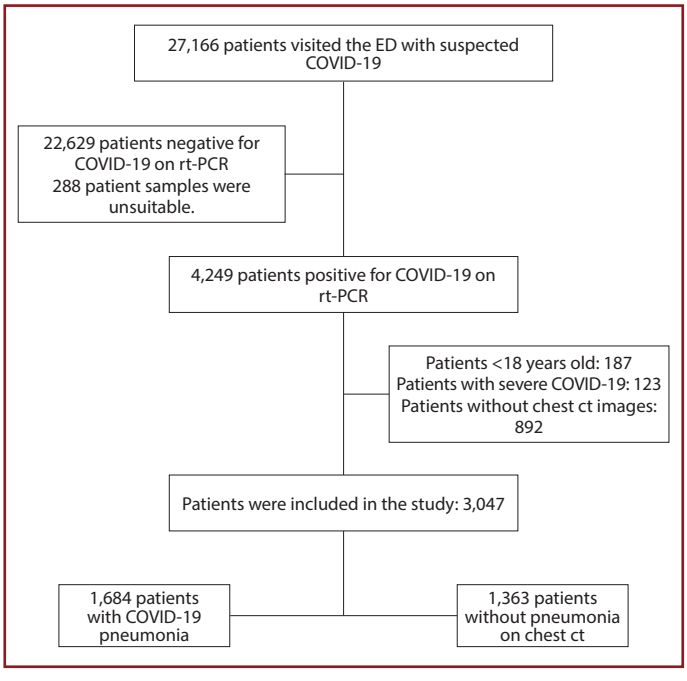

Figure 1. Flow diagram of the study.

COVID-19: Coronavirus disease 19; Rt-PCR: Real-time reverse transcription polymerase chain reaction; CT: Computer tomography, ED: Emergency department.

Hospitalization rate was 18% (n=547), ICU admission rate was 1% (n=29), and 28-day mortality rate was 0.7% (n=20). The median length of stay in the hospital of the hospitalized patients was 7 (IQR=5–10) days. Among patients with comorbidities, the highest mortality rate was in patients with malignancy (8.8%). The mortality rate was not increased in patients with chronic obstructive pulmonary disease (COPD), asthma, coronary heart disease (CHD), and hypo/hyperthyroidism (Table 1).

COVID-19 pneumonia was imaged in the thorax CT of 55.3% of the patients. The types of involvement in chest CT were as follows: bilateral in 75.2% (n=1.267), posterior in 53.9% (n=908), multilobed in 80.5% (n=1.356), and peripheral in 70.7% (n=1.191). In the thorax CT of asymptomatic patients, 23.7% (n=22) had mild and 2.2% (n=2) had moderate-severe findings consistent with COVID-19. The two patients with moderate-to-severe pneumonia were male patients aged 35–40 years with no comorbidities.

The majority of our patients were between the ages of 18 and 65, but it was observed that a greater proportion of pneumonia developed in the age group 65 and over (35.7% between 18 and 40 years; 71.5% between 40 and 65 years; and 90.2% in 65 years and older). The rate of developing pneumonia was statistically higher in patients with at least one comorbidity disease compared to those without (85.3% [n=524], 47.7% [n=1.160], $p<0.001$). The demographic and comorbidity data of the study population are summarized in Table 1.

In our study, the parameters that were found to be statistically significant in terms of pneumonia occurrence were examined using the multivariate logistic regression backward method. Advanced age, smoking, hypertension, diabetes, asthma, chronic kidney disease (CKD), and malignancy were found to be associated with higher rates of pneumonia occurrence (Table 2).

Treatment was initiated in 98.3% (n=2996) of the patients. Administered treatments are as follows: oseltamivir in 87.4% (n=2662), favipiravir in 2.9% (n=87), chloroquine in 95.9% (n=2921), azithromycin in 23.7% (n=722), moxifloxacin in 3.1% (n=93), cephalosporin in 0.9%, and amoxicillin in 0.1%.

Table 1. Distribution of asymptomatic, mild, or moderate COVID-19 patients according to demographic characteristics and comorbidities

	COVID-19 pneumonia, n (%)			28-year mortality, n (%)		
	Yes	No	p	Live	Ex	p
Age, median (IQR)	46 (37–56)	33 (26–42)	<0.001[a]	40 (30–50)	59 (53–75)	<0.001[a]
18–40 years	525 (31.2)	944 (69.3)	<0.001[b]	1467 (48.5)	2 (10.0)	0.001[c]
40–65 years	1011 (60)	403 (29.6)	<0.001[b]	1404 (46.4)	10 (50.0)	0.746[b]
> 65 years	148 (8.8)	16 (1.2)	<0.001[b]	156 (5.2)	8 (40.0)	<0.001[b]
Male	1008 (59.9)	782 (57.4)	0.166[b]	1775 (58.6)	15 (75.0)	0.138[b]
Current smoker	610 (36.2)	260 (19.1)	<0.001[b]	867 (28.6)	3 (15.0)	0.178[c]
Hypertension	263 (15.6)	46 (3.4)	<0.001[b]	300 (9.9)	9 (45.0)	<0.001[b]
Diabetes	203 (12.1)	31 (2.3)	<0.001[b]	228 (7.5)	6 (30.0)	0.003[b]
COPD	33 (2.0)	7 (0.5)	<0.001[b]	39 (1.3)	1 (5.0)	0.233[c]
Asthma	60 (3.6)	3 (0.2)	<0.001[c]	63 (2.1)	0	
CHD	111 (6.6)	18 (1.3)	<0.001[b]	126 (4.2)	3 (15.0)	0.050[c]
CKD	53 (3.1)	7 (0.5)	<0.001[b]	56 (1.9)	4 (20.0)	0.001[c]
CLD	36 (2.1)	10 (0.7)	0.002[b]	44 (1.5)	2 (10.0)	0.036[c]
CVD	11 (0.7)	1 (0.1)	0.011[c]	12 (0.4)	0	
Hyperthyroidism	15 (0.9)	4 (0.3)	0.037[c]	19 (0.6)	0	
Hypothyroidism	15 (0.9)	3 (0.2)	0.016[c]	18 (0.6)	0	
Malignancy	33 (2.0)	1 (0.1)	<0.001[c]	31 (1.0)	3 (15.0)	0.001[c]
Comorbidity diseases						
At least one	524 (31.1)	90 (6.6)	<0.001b	597 (19.7)	17 (85.0)	<0.001[b]
At least two	218 (12.9)	28 (2.1)	<0.001b	238 (7.9)	8 (40.0)	<0.001[b]
At least three	68 (4.0)	7 (0.5)	<0.001b	72 (2.4)	3 (15.0)	0.012[c]

[a]Mann–Whitney U-test; [b]Chi-square test; [c]Fisher's exact test; COVID-19: Coronavirus disease 19; COPD: Chronic obstructive pulmonary disease; CHD: Coronary heart disease; CLD: Chronic liver disease; CKD: Chronic kidney disease; CVD: Cerebrovascular disease; IQR: interquartile range.

Table 2. Risk factors associated with COVID-19 pneumonia

	Univariable OR (95% CI)	p	Multivariable OR (95% CI)	p
Age (years)	1.08 (1.07–1.08)	<0.001	1.07 (1.06–1.08)	<0.001
18–40 years	1 (ref)			
40–65 years	4.49 (3.84–5.26)	<0.001		
>65 years	16.63 (9.82–28.65)	<0.001		
Current smoker (versus nonsmoker)	2.41 (2.03–2.85)	<0.001	2.83 (2.35–3.40)	<0.001
Comorbidity present (versus not present)				
Hypertension	5.29 (3.84–7.31)	<0.001		
Diabetes	5.89 (4.00–8.65)	<0.001	1.81 (1.18–2.78)	0.006
COPD	3.87 (1.70–8.78)	0.001		
Asthma	16.74 (5.24–53.52)	<0.001	10.37 (3.12–34.5)	<0.001
CHD	5.27 (3.18–8.72)	<0.001		
CKD	6.29 (2.85–13.89)	<0.001	3.36 (1.41–8.03)	0.006
CLD	2.95 (1.46–5.97)	0.002		
CVD	8.95 (1.15–64.99)	0.035		
Hyperthyroidism	3.05 (1.01–9.22)	0.047		
Hypothyroidism	4.07 (1.17–14.10)	0.026		
Malignancy	27.22 (3.71–199.3)	0.001	8.78 (1.14–67.40)	0.036

COPD: Chronic obstructive pulmonary disease; CHD: Coronary heart disease; CLD: Chronic liver disease; CKD: Chronic kidney disease; CVD: Cerebrovascular disease; IQR: Interquartile range; OR: Odds ratio; CI: Confidence interval.

Discussion

The clinical spectrum of SARS-CoV-2 infection ranges from asymptomatic infection to critical illness and even death[1,15]. Patients with mild-to-moderate illness may not require urgent intervention or hospitalization[3]. However, identifying the subpopulation that is more susceptible to the development of the adverse consequences of COVID-19 is critical to prevent degradation from mild or moderate conditions to severe conditions and to reduce the mortality rate. Since COVID-19 emerged, many researchers have reported risk factors associated with the poor outcome of COVID-19. Despite some consistent themes, reports from different geographic locations reported differences in risks. For this purpose, our study has focused on patients with asymptomatic, mild, or moderate clinical settings. In our study, advanced age, smoking, hypertension, diabetes, asthma, CKD, and malignancy were the most important risk factors for the development of NCIP in asymptomatic, mild, or moderate COVID-19 patients. However, our findings suggested a higher likelihood of mortality in asymptomatic, mild, or moderate COVID-19 patients with hypertension, diabetes, CKD, CHD, or malignancy.

Several publications have reported that older age predicts higher mortality in patients with NCIP[16,17]. In the study of Güven et al.[18] in young adult COVID-19 patients, 69.5% of non-survivors were in the age group of 40–49 years. In our study consisting of asymptomatic, mild, and moderate COVID-19 patients, a significant proportion of the patients was under 65 years of age. In our study, older age was an important risk factor for the development of NCIP and was found to be associated with increased hospitalization and mortality rates, and this is consistent with the literature.

In the meta-analysis conducted in the Chinese population, in COVID-19 patients, the pooled prevalence of cardiovascular (6.9% vs. 1.8%), cerebrovascular (2% vs. 0.9%), and cancer (1% vs. 0.6%) was much higher than the general population, conversely, COPD (3% vs. 8.6%), CKD (2% vs. 9.5%), and CHD (3% vs. 24.8%) were significantly lower in prevalence[6]. In addition, the predicted prevalence of hypertension (19% vs. 23.2%) and diabetes (9% vs. 10.9%) in COVID-19 patients was not clearly different from the general population[6]. However, the same meta-analysis also stated that diabetes is a risk factor for critically ill patients (OR=2.49, 95% CI=2.10–2.96)[6].

In many meta-analyzes, they stated that diabetes was associated with increased severe illness and mortality in COVID-19 patients[19,20]. In the meta-analysis by Miller et al.,[21] the only variable that statistically significantly affected the mortality rate was the prevalence of diabetes where each 1% increase in diabetes prevalence was associated with an absolute increase in mortality of 1.5%. Yang et al.[7] noted that diabetes was one of the most common comorbidities in COVID-19 patients, however, there was no significant difference in diabetes between the severe and non-severe group. In our study, diabetes was an important risk factor for the development of NCIP and was found to be associated with increased hospitalization and mortality rates.

It is one of the most common comorbidity diseases in hypertension, such as diabetes, in severe COVID-19 patients[21,22]. A meta-analysis by Naeni et al.[8] reported that the probability of having severe COVID-19 was 2.5 times in patients with HT compared to those without HT (OR=2.68) and 3 times in patients with CHD compared to those without CHD (OR=3.44).

Pranata et al.[23] showed that CHD (RR=2.23 [1.71–2.91], p<0.001) and cerebrovascular (RR=2.04 [1.43–2.91], p<0.001) diseases (CVDs) are connected with worse results on COVID-19. Furthermore, in COVID-19 patients, relation between CVD and worse outcomes has not been affected by CHD and vice versa. Singh et al.[11] showed that CVD is not significantly correlated with severe COVİD-19 cases. Conversely, Yin et al.[6] showed that CVD (OR=3.70, 95% CI=2.51–5.45) was found to be the strongest risk factor in severe cases, followed by CKD (OR=3.60, 95% CI=2.18–5.94) and COPD (OR=3.14, 95% CI=2.35–4.19).

According to a large multinational meta-analyses, chronic liver disease (CLD) and CKD were predictors for severe COVID-19 with similar power[24]. However, Wang et al.[12] did not provide sufficient evidence that there was a correlation between CKD, CLD or cancer, and COVID-19 patients' aggravation. Two multinational meta-analyses with 38,000 and 27,670 cases showed that patients with CLD were more inclined to develop severe outcomes of COVID-19 than those without[24,25]. On the other hand, a meta-analysis consisting Chinese population showed no correlation between CLD and increased disease severity[9].

The general pooled prevalence of cancer in COVID-19 infections was higher than the Chinese population[6]. Furthermore, Singh et al.[11] reported that cancer (RR=2.48, 95% CI=1.46–4.19) was significantly associated with a higher risk of severe COVID-19, compared to patients without comorbidities. The study of Liang et al.[26] reported that patients with cancer had a higher risk of severity than non-cancer patients, possibly due to suppressed immune response as a result of chemo- and radiotherapies.

Four meta-analyzes have agreed that COPD is associated with poor outcome of COVID-19[6,11,24,27]. Conversely, the meta-analysis by Ssentongo et al.[10] stated that COPD and asthma comorbidities were not significantly associated with a greater risk of mortality. Our study observed that patients with COPD had more developed pneumonia than those without, but sufficient evidence was not provided that it caused an increase in mortality rate.

As noted above, several studies show that different comorbidities have disparate risks of poor outcome in COVID-19 patients[10-12]. This may be due to differences in size and sources of the sample included, different statistical methods used, outcome criteria, and ethnic background. The present study revealed that 11 underlying diseases exhibited a statistically significant correlation with pneumonia, of which asthma was the strongest risk factor, followed by CKD, diabetes, and malignancy.

In addition, advanced age and smoking were important factors in the occurrence of pneumonia in our study. Gender had no meaningful statistical effect on the occurrence of pneumonia or mortality. Our findings suggested that patients with comorbidities had more severe disease than those without. Furthermore, a greater number of comorbidities correlated with greater disease severity of COVID-19. The proper triage of patients should be implemented by carefully inquiring about the medical history because this will help identify patients who would be more likely to develop serious adverse outcomes of COVID-19.

Limitations

This study has several limitations. First, this is a retrospective study. Results and clinical follow-ups were accessed from the hospital registry system without seeing the patients; therefore, additional laboratory examinations could not be made. In addition, under-expression of comorbidities may lead to under or over-estimation of the strength of the true association with clinical prognosis. However, significantly underreporting was unlikely as the medical backgrounds of the patients were retrospectively screened from the hospital system.

Conclusion

In our study, advanced age, smoking, hypertension, diabetes, asthma, CKD, and malignancy were the most important risk factors for the development of NCIP in asymptomatic, mild, or moderate COVID-19 patients. The effects of comorbidities should be considered when determining the risk stratification and need for hospitalization of asymptomatic, mild, and moderate COVID-19 patients.

Ethics Committee Approval: This study was approved by the Ethics Committee of the research institution (Protocol no: 2020/234). It was conducted in accordance with the Declaration of Helsinki.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: H.A., H.D., D.T.; Design: H.A., H.D., F.Y.; Supervision: H.A., H.D., D.T.; Fundings: H.A.; Materials: H.A., F.Y., Ö.F.C., D.T.; Data Collection or Processing: H.A., H.D., D.T., F.Y.; Analysis or Interpretation: H.A., H,.D., F.Y., M.K.E.; Literature Search: H.A., Ö.F.C., F.Y., M.K.E.; Writing: H.A., Ö.F.C., H.D., M.K.E.; Critical Review: H.A., H.D., F.Y.

Conflict of Interest: None declared.

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