Dicle Tıp Dergisi / Dicle Med J (2022) 49 (4) : 579-589

www.diclemedj.org

Original Article / Özgün Araştırma

Risk factors for hospital mortality of patients with COVID-19 and 6-month follow-up of discharged patients

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Received: 21.03.2022; Revised: 19.09.2022; Accepted: 27.09.2022

Abstract

Objective: COVID-19 continues to pose a public health threat globally. This study evaluated the risk factors of hospitalized patients associated with hospital mortality for COVID-19 and symptoms on days 14, 28, and 6th-month.

Methods: The study included 133 adults hospitalized due to COVID-19 between April 1, 2020 and June 30, 2020. Patient files were retrospectively reviewed. The demographic characteristics of the patients were evaluated by dividing them into two groups according to the clinical severity of COVID-19. (group 1: mild+moderate, group 2: severe+critical). Risk factors associated with mortality were revealed. Symptoms on day 14 and day 28 were questioned in person or by phone if patients were discharged and symptoms at 6 months were questioned by phone.

Results: Comparison of laboratory findings between the groups showed that patients in group 2 had lower serum lymphocyte count and higher levels of C-reactive protein, ferritin, D-dimer, procalcitonin, and troponin T at admission and during follow-up ($p<0.05$). Oxygen saturation at hospital admission and lymphocyte count on day 7 of hospitalization were found to be risk factors associated with mortality. The most common symptom at admission and on day 14 was a cough, while fatigue was most common on day 28 and month 6. At 6 months, 32 patients (28.8%) were symptom-free, 13 patients (11.7%) had sleep disorders, and 12 patients (10.8%) had an anxiety disorder. Five patients (4.5%) reported having dermatological complaints.

Conclusions: Periodic monitoring of laboratory parameters is important for predicting disease course, and oxygen saturation and serum ferritin levels at admission are important predictors of mortality. Patients should be followed for respiratory complications and sequelae as well as extrapulmonary involvement and complications. After a 6-month follow-up period, most patients have continued to have non-life-threatening symptoms.

Keywords: COVID-19, follow-up, hospital mortality, post-COVID

DOI: 10.5798/dicletip.1220745

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COVID-19 hastalarının hastane mortalitesi için risk faktörleri ve taburcu edilen hastaların 6 aylık takibi

Öz

Giriş: COVID-19, küresel olarak bir halk sağlığı tehdidi oluşturmaya devam etmektedir. Bu çalışmada COVİD-19 nedeniyle yatarak tedavi gören hastaların hastane mortalitesi ile ilişkili risk faktörleri ve 14. gün, 28. gün ve 6. ay semptomları değerlendirildi

Yöntemler: Çalışmaya 1 Nisan 2020 ile 30 Haziran 2020 tarihleri arasında COVİD-19 nedeniyle hastaneye yatırılan 133 yetişkin dahil edildi. Hasta dosyaları retrospektif olarak incelendi. Hastaların demografik özellikleri COVID-19 klinik şiddetine göre iki gruba ayrılarak değerlendirildi. (grup 1: hafif+orta, grup 2: şiddetli+kritik). Mortalite ile ilişkili risk faktörleri ortaya kondu. Hastaların 14. ve 28. gündeki semptomları taburcu olmayanlarda yüz yüze, taburcu olanlarda ise telefonla sorgulandı ve 6. ay semptom sorgulaması telefonla yapıldı.

Bulgular: Gruplar arasında laboratuvar bulgularının karşılaştırılmasında grup 2'deki hastaların başvuru ve takip sırasında serum lenfosit sayısının daha düşük, C-reaktif protein, ferritin, D-dimer, prokalsitonin ve troponin T düzeylerinin daha yüksek olduğu tespit edildi ($p<0.05$). Hastaneye yatışta oksijen satürasyonu ve yatışın 7. günündeki lenfosit sayısı mortalite ile ilişkili risk faktörleri olarak bulundu. Başvuruda ve 14. günde en sık görülen semptom öksürük iken, yorgunluk 28. gün ve 6. ayda en yaygın semptomdu. 6. ayda 32 hasta (%28.8) semptomsuz iken 13 hastada (%11.7) uyku bozukluğu ve 12 hastada (%10.8) anksiyete bozukluğu mevcuttu. Beş hasta (%4.5) dermatolojik şikayetlere sahipti.

Sonuçlar: Laboratuvar parametrelerinin periyodik olarak izlenmesi, hastalığın seyrini tahmin etmek için önemlidir ve başvurudaki oksijen satürasyonu ve serum ferritin seviyeleri, mortalitenin önemli belirleyicileridir. SARS-CoV-2'nin diğer organ ve sistemleri etkileyebileceği düşünüldüğünde, hastalar solunum komplikasyonları ve sekellerinin yanı sıra ekstrapulmoner tutulum ve komplikasyonlar açısından da takip edilmelidir. 6 aylık bir takip döneminin sonunda çoğu hastada yaşamı tehdit etmeyen semptomlar görülmeye devam etmiştir.

Anahtar kelimeler: COVID-19, izlem, hastane mortalitesi, post-COVID.

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a pandemic resulting in significant morbidity and mortality. As of March 14, 2022, the number of confirmed cases worldwide was reported as 456,797,217 and the number of deaths as 6,043,094[1]. Since the first case in Turkey was documented on March 11, 2020, the disease spread rapidly and continues to pose a public health threat in our country.

Although the large majority of infected patients are asymptomatic or have mild clinical presentations, the remaining patients experience a severe and potentially fatal disease course with serious systemic complications. Numerous clinical studies have demonstrated the acute signs and symptoms of COVID-19[2-6]. The main clinical symptoms include fever, cough, dyspnea, myalgia, fatigue, diarrhea, headache, loss of taste/smell, nausea, and vomiting. Laboratory findings include lymphopenia, leukopenia, and elevated C-reactive protein (CRP), D-dimer, ferritin, and muscle and liver enzyme levels. Typical findings on chest computed tomography (CT) include ground-glass opacities, patchy infiltrations, air bronchogram, halo or reverse-halo sign, cobblestone appearance, and consolidations[7-9].

While many patients recover with no long-term effects, some patients develop various sequelae associated with COVID-19. Close follow-up is necessary to reveal the potential long-term effects of COVID-19. In one study, patients were found to have persistent symptoms of chest tightness and palpitations upon exertion, cough, fatigue, sputum, diarrhea, and fever at 3 months after hospital discharge[10].

The present study aimed to evaluate risk factors associated with hospital mortality, and symptoms at day 14 and day 28 of follow-up among patients hospitalized for COVID-19. In addition, 6-month symptoms and follow-up results were evaluated in order to reveal the long-term effects of the disease in hospitalized patients.

METHODS

Study design and patient selection

This retrospective, observational study included 133 adult patients (age ≥ 18 years) with laboratory-confirmed COVID-19 who were hospitalized in a 570-bed tertiary-care hospital between April 1 and June 30, 2020.

The patients were admitted according to the COVID-19 hospitalization criteria from the Turkish Ministry of Health. Patients meeting any of the following criteria were hospitalized for inpatient treatment:

- Respiratory distress, tachypnea (respiratory rate ≥ 30/min) or oxygen saturation (SpO2) < 90% on room air,

- Age ≥ 50 years,

- Comorbidity (cardiovascular disease, diabetes mellitus, hypertension, cancer, chronic lung disease, immunosuppressive conditions),

- Poor prognostic markers in blood tests performed at admission (blood lymphocyte count < 800/μL, CRP > 40 mg/L, ferritin > 500 ng/ml, or D-dimer > 1000 ng/ml),

- Chest x-ray or CT findings of bilateral diffuse pneumonia.

Diagnosis of COVID-19 was made in the presence of:

- Positive SARS-CoV-2 real-time polymerase chain reaction test of respiratory tract samples or

- Typical findings of COVID-19 on chest CT and presence of SARS-CoV-2 IgM or IgM+IgG positivity in serum samples.

Patients were classified into four COVID-19 clinical severity groups according to the classification recommended by the World Health Organization11:

- Mild: Presenting with mild upper and lower respiratory tract symptoms but no signs of hypoxia or viral pneumonia

- Moderate: Presenting with signs of pneumonia but SpO2 ≥ 90 mmHg on room air

- Severe: Presenting with clinical signs of pneumonia and severe respiratory distress or SpO2 < 90 mmHg on room air

- Critical: Presenting with acute respiratory distress syndrome (ARDS)

When evaluating demographic, laboratory, and clinical findings by disease severity, the patients were divided into two groups, mild+moderate (group 1) and severe+critical (group 2).

Data collection

Data regarding the patients' demographical, clinical, and radiological characteristics, comorbid status, laboratory findings such as serum leukocyte, neutrophil, lymphocyte, and platelet counts, biochemical and coagulation parameters, acute phase reactants, procalcitonin, troponin levels and at first admission and during follow-up (day 3, 7, and 14), symptoms at first admission, treatments, complications, and outcomes were obtained by retrospective review of electronic patient records. Symptoms at day 14 and day 28 were questioned in person or by phone if patients were discharged and symptoms at 6 months were questioned by phone.

Ethics approval

Ethics committee approval was received from Niğde Ömer Halisdemir University Ethics Committee (No: 2020/05-03). This study was

conducted in accordance with the principles of the Declaration of Helsinki.

Statistical analyses

The data were analyzed using SPSS Statistics version 22.0 software (IBM Corp, Armonk, NY, USA). Continuous variables were evaluated for normal distribution using the Shapiro-Wilk test. Categorical variables were expressed as frequency (n) and percentage (%), continuous variables that met the assumptions for parametric tests were presented as mean and standard deviation (SD), and those that did not were presented as median, minimum, and maximum values. Chi-square and Fisher's exact significance tests were used in the analysis of categorical variables. Pairwise comparisons of group means were done using Student's t-test if parametric test assumptions were met and Mann-Whitney U test if parametric test assumptions were not met. Logistic regression analysis was performed to identify independent risk factors associated with mortality.

RESULTS

Demographics, characteristics, and medications

The study included a total of 133 patients admitted to our hospital due to COVID-19 between April 1, 2020 and June 30, 2020. SARS-CoV-2 RT-PCR was positive in 82 (61.6%) patients, SARS-CoV-2 IgM was positive in 42 (31.6%) patients, and SARS-CoV-2 total antibody was positive in 9 (6.8%) patients. One hundred thirteen (85%) of the patients were treated in COVID-19 inpatient wards and 20 (15%) were admitted to the intensive care unit (ICU). The patients' mean age was 56.3±17.37 years; 69 (51.9%) were men. The most common comorbidities were hypertension (n=42, 42%) and diabetes mellitus (n=32, 24.1%) (Table I).

All patients received hydroxychloroquine, 85 (63.9%) received oseltamivir, 82 (61.7%) received low-molecular-weight heparin, and 20 (15%) received favipiravir. Seventeen patients (12.8%) received short-term glucocorticoid therapy. Two patients were treated with mesenchymal stem cell therapy, and 1 of those patients died.

Fifty-nine patients (44.4%) did not require oxygen support during treatment, while 10 patients (7.5%) in the ICU received mechanical ventilation. Fourteen patients (10.5%) developed healthcare-associated infections and 14 (10.5%) developed ARDS. One hundred twenty-two patients (91.7%) survived to discharge.

Evaluation of patients based on COVID-19 severity

When the patients were evaluated according to the clinical classification of COVID-19, there were 74 patients (55.6%) in group 1 (mild+moderate) and 59 patients (44.4%) in group 2 (severe+critical). Mean age and rates of hypertension, chronic pulmonary disease, and cardiovascular disease were significantly higher in group 2 than in group 1 ($p<0.05$).

Comparison of laboratory parameters showed that group 2 had significantly higher serum troponin-T, CRP, ferritin, D-dimer, procalcitonin, aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and erythrocyte sedimentation rate (ESR) and significantly lower serum lymphocyte and platelet counts compared to group 1 ($p<0.05$). When the results of follow-up examinations were compared, Group 2 had significantly lower lymphocyte count and significantly higher troponin-T, CRP, ferritin, D-dimer, and procalcitonin levels on days 3 and 7. The demographic, clinical, and laboratory characteristics of the patients are shown in Table I.

Table I: Demographic and laboratory features and medical history of the patients

		COVID-19 severity		
Variables	**Allpatients**	**Group 1** (Mild+Moderate) (n=74)	**Group 2** (Severe+Critical) (n=59)	**pvalue**
Age	56.25±17.4	50.5±16.34	63.46±15.9	**<0.001**
Sex, n(%)				
Male	69 (51.9)	34 (49.3)	35 (50.7)	0.125
Female	64 (48.1)	40 (62.5)	24 (37.5)	
Body mass index, n(%)				
<25	41 (30.8)	19 (46.3)	22 (53.7)	0.149
≥25	92 (69.2)	55 (59.8)	37 (40.2)	
Underlying diseases, n (%)				
Hypertension	42 (31.6)	15 (35.7)	27 (64.3)	**0.002**
Diabetes mellitus	32 (24.1)	14 (43.8)	18 (56.3)	0.120
Chronicpulmonary disease	27 (20.3)	5 (18.5)	22 (81.5)	**<0.001**
Cardiovascular disease	27 (20.3)	10 (37)	17 (63)	**0.029**
Chronic renal disease	4 (3.0)	1 (25)	3 (75)	0.322
Malignancy	4 (3.0)	1 (25)	3 (75)	0.322
Immunosuppression	3 (2.3)	1 (33.3)	2 (66.7)	0.584
White blood cell count (×10^9/L)				
On admission	6400 (400-19600)	6200 (2200-19600)	6700 (400-16200)	0.098
Day-3	6000 (800-29000)	6000 (2500-29000)	6550 (800-18800)	0.104
Day-7	6400 (1630-21400)	6100 (1630-11900)	6525 (1800-21400)	0.257
Day-14	6800 (2690-26100)	7000 (2690-11700)	6770 (3300-26100)	0.965
Lymphocyte count (×10^9/L)				
On admission	1580 (70-5730)	1810 (470-5730)	1220 (70-3740)	**0.003**
Day-3	1515 (100-4290)	1845 (690-3060)	1120 (100-4290)	**<0.001**
Day-7	1390 (120-3280)	1730 (510-3280)	1125 (120-3140)	**<0.001**
Day-14	1380 (190-4480)	1560 (700-3200)	1350 (190-4480)	0.096
Platelet count (×10^9/L)				
On admission	212000 (11000-550000)	219000 (86000-550000)	191000 (11000-542000)	**0.041**
Day-3	217500 (22000-686000)	217500 (120000-686000)	214500 (22000-467000)	0.399
Day-7	245000 (13000-710000)	245000 (100000-617000)	245500 (13000-710000)	0.659
Day-14	308700±143740	300900±117042	312900±157800	0.773
Troponin (µg/L)				
On admission	6.33 (3-6903)	4 (3-3863)	13 (3-6903)	**<0.001**
Day-3	7 (2-1694)	4 (3-561)	11 (2-1694)	**<0.001**
Day-7	8 (3-1772)	5 (3-412)	15 (3-1772)	**<0.001**
Day-14	10 (3-414)	6 (3-41)	15 (3-414)	**0.007**
C-reactive protein (mg/L)				
On admission	20.2 (0.2-399.3)	7.45 (0.2-294)	51.4(0.2-399.3)	**<0.001**
Day-3	16.5 (0.2-317.5)	3.7 (0.2-112.2)	65.75 (0.2-317.5)	**<0.001**
Day-7	15.7 (0.3-278.2)	6.6 (0.3-94.1)	38.35 (1.1-278.2)	**<0.001**
Day-14	13.8 (0.2-275)	3.5 (0.2-87.8)	19.7 (1-275)	**0.009**
Ferritin (µg/L)				
On admission	188 (11.2-2000)	117.5 (11.2-1378)	264 (24-2000)	**0.008**
Day-3	193 (10-2000)	126 (10-1047)	271 (17.9-2000)	**<0.001**
Day-7	276 (10.5-2000)	170 (10.5-926)	506 (38.4-2000)	**0.001**
Day-14	241 (20.5-2000)	229 (39-909)	253 (20-2000)	0.566
D-dimer (µg/L)				
On admission	203 (49-15673)	124 (49-10924)	341 (63-15673)	**<0.001**
Day-3	227 (12-7745)	158.5 (12-1602)	349 (39-7745)	**<0.001**
Day-7	287 (36-13513)	151 (36-988)	457 (74-13513)	**<0.001**
Day-14	348 (16-12539)	126 (16-1714)	413 (71-12539)	**0.001**
Procalcitonin (µg/L)				
On admission	0.06 (0.02-100)	0.03 (0.02-2.03)	0.08 (0.02-100)	**<0.001**
Day-3	0.04 (0.01-100)	0.02 (0.02-0.62)	0.085 (0.01-100)	**<0.001**
Day-7	0.05 (0.02-31.4)	0.03 (0.02-2)	0.065 (0.02-31.4)	**0.003**
Day-14	0.05 (0.02-40)	0.035 (0.02-0.34)	0.06 (0.02-40)	**0.007**
AST (U/L) (On admission)	24 (6-636)	21.5 (12-58)	30 (6-636)	**0.008**
ALT (U/L) (On admission)	20 (3-266)	19 (8-100)	20 (3-266)	0.946
CreatineKinase (µ/L) (On admission)	75 (9-3092)	70 (19-1523)	89 (9-3092)	0.214
LDH (U/L) (On admission)	265.5 (107-969)	241 (107-731)	331 (139-969)	**<0.001**
Erythrocyte sedimentation rate (mm/hr) (On admission)	22 (2-120)	15 (2-71)	33 (2-120)	**<0.001**
Smoking, n (%)	32 (24.1)	21 (65.6)	11 (34.4)	0.192

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase

Risk factors associated with hospital mortality for COVID-19

Eleven patients (8.3%), 9 of whom were in the ICU, died. SpO2 and serum lymphocyte count at admission were significantly lower among non-surviving patients (p<0.001, p=0.016), whereas qSOFA score, CURB-65 score, ESR, and serum ferritin, CRP, procalcitonin, and troponin-T levels were significantly higher compared to surviving patients (p<0.005) (Table II). SpO2 level (on room air) at admission (odds ratio: 1.141, 95% CI: 1.017-1.281; p=0.025) and lymphocyte count on day 7 of hospitalization (odds ratio: 1.003, 95% CI: 1.001-1.006; p=0.024) were independent mortality risk factors (Table III).

Table II: Demographic, laboratory, and clinical evaluation of patients in terms of survival

	Survivors (n=122)	**Nonsurvivors** (n=11)	**pvalue**
Age, median (min-max)	55 (18-93)	77 (32-85)	**0.02**
Sex, n (%)			
Female	58 (47.5)	6 (54.5)	0.656
Male	64 (52.5)	5 (45.5)	
sO2 (%, roomflow) on admission	91 (65-98)	60 (55-84)	**<0.001**
qSOFAscore, on admission	0 (0-2)	3 (1-3)	**<0.001**
White bloodcellcount, ($x10^9$/L)			
On admission	6250 (2200-19600)	7800 (400-15200)	**0.03**
Day-3	6000 (2500-29000)	7400 (800-18800)	0.068
Day-7	6400 (1630-14700)	11100 (1800-21400)	**0.025**
Day-14	6757 ±2211.6	17366.7 ±8376.6	**0.027**
Lymphocytecount, ($x10^9$/L)			
On admission	1650 (180-5730)	1090 (70-2000)	**0.016**
Day-3	1575 (380-4290)	935 (100-1930)	**0.006**
Day-7	1565 (480-3280)	680 (120-1210)	**<0.001**
Day-14	1410 (520-3200)	900 (190-4480)	0.121
D-dimer (µg/L)			
On admission	200 (49-15673)	408 (63-7960)	0.089
Day-3	213.5 (12-7745)	403 (39-1974)	0.151
Day-7	280 (36-6916)	834 (132-13513)	**0.024**
Day-14	305 (16-3276)	2669 (1185-12539)	**<0.001**
Serum ferritin (µg/L)			
On admission	168.5 (11.2-1378)	554.5 (52.8-2000)	**0.004**
Day-3	182 (10-1210)	721 (44.2-2000)	**0.003**
Day-7	238 (10.5-1356)	1291 (506-2000)	**>0.001**
Day-14	222 (20.5-1775)	1253 (85-1775)	**0.03**
C-reaktive protein (mg/L)			
On admission	17.8 (0.2-399.3)	68.2 (2.7-266)	**0.002**
Day-3	13 (0.2-317.5)	120.4 (3.4-226.8)	**<0.001**
Day-7	12.6 (0.3-194.2)	183 (1.6-278.2)	**<0.001**
Day-14	12 (0.2-105.5)	157.5 (13.8-275)	**0.001**
Procalcitonin (µg/L)			
On admission	0.05 (0.02-8.66)	0.5 (0.06-100)	**0.001**
Day-3	0.04 (0.01-8)	0.53 (0.04-100)	**<0.001**
Day-7	0.04 (0.02-2)	1.21 (0.02-31.4)	**<0.001**
Day-14	0.04 (0.02-0.34)	1.68 (0.24-40)	**<0.001**
Eritrocytesedimentation rate (mm/hr)			
On admission	21 (2-79)	37 (12-20)	**0.018**
Troponin T (µg/L)			
On admission	6 (3-2863)	31 (5-6903)	**<0.001**
Day-3	6 (2-561)	42 (5-1694)	**<0.001**
Day-7	8 (3-1772)	40.5 (18-1310)	**0.004**
Day-14	9 (3-97)	36 (10-414)	**<0.001**
CURB65 score, on admission	1 (0-4)	3 (3-5)	**<0.001**
UnderlyingDiseases, n (%)			
Hypertension	36 (29.5)	6 (54.5)	0.101
Diabetes mellitus	29 (23.8)	3 (27.3)	0.725
Chronic pulmonary disease	20 (16.4)	7 (63.6)	**0.001**
Coronary artery disease	23 (18.9)	4 (36.4)	0.233
Chronic renal disease	4 (3.3)	0 (0.0)	1.0
Malignancy	2 (1.6)	2 (18.2)	**0.034**
Immunosupression	1 (0.8)	2 (18.2)	**0.018**
Body mass index, n(%)			
<25	38 (31.1)	3 (27.3)	0.789
≥25	84 (68.9)	8 (72.7)	
Smoking, n (%)	31 (25.4)	1 (9.1)	0.296

Table III: Analysis of independent risk factors associated with mortality

Variables	Univariate OddsRatio (95% CI)	pvalue	Multivariate OddsRatio (95% CI)	pvalue
Age	0.936 (0.893-0.981)	0.006		
spO2 (on roomflow)	1.201 (1.107-1.304)	**<0.001**	1.141 (1.017-1.281)	**0.025**
qSOFA	0.078 (0.024-0.254)	<0.001		
CURB65 score	0.241 (0.117-0.497)	<0.001		
White blood cell count (On admission)	1.0 (1.0-1.0)	0.043		
White blood cell count (Day-7)	1.0 (0.999-1.0)	0.005		
White blood cell count (Day-14)	1.0 (0.999-1.0)	0.011		
Lymphocyte count (On admission)	1.001 (1.0-1.002)	0.02		
Lymphocyte count (Day-3)	1.002 (1.0-1.003)	0.008		
Lymphocyte count (Day-7)	1.004 (1.001-1.007**)**	**0.002**	1.003 (1.001-1.006)	**0.024**
D-dimer (Day-14)	0.998 (0.997-1.0)	0.006		
Ferritin (On admission)	0.998 (0.997-0.999)	0.001		
Ferritin (Day-3)	0.997 (0.995-0.999)	<0.001		
Ferritin (Day-7)	0.995 (0.993-0.998)	0.001		
Ferritin (Day-14)	0.997 (0.995-0.999)	0.007		
C-Reactive Protein (On admission)	0.991 (0.985-0.998)	0.007		
CRP (Day-3)	0.980 (0.970-0.991)	<0.001		
CRP (Day-7)	0.975 (0.963-0.987)	<0.001		
CRP (Day-14)	0.962 (0.932-0.992)	0.015		
Procalcitonin (On admission)	0.744 (0.480-1.151)	0.184		
Procalcitonin (Day-3)	0.895 (0.581-1.376)	0.612		
Procalcitonin (Day-7)	0.074 (0.016-0.332)	0.001		
Procalcitonin (Day-14)	0.001 (0.001-0.014)	0.016		
Eritrosit sedimentasyon rate (On admission)	0.963 (0.937-0.989)	0.006		
Troponin T (On admission)	0.999 (0.999-1.000)	0.077		
Troponin T (Day-3)	0.996 (0.991-1.001)	0.095		
Troponin T (Day-7)	0.998 (0.997-1.000)	0.106		
Troponin T (Day-14)	0.970 (0.943-0.999)	0.04		
Chronic Pulmonary Disease	8.925 (2.387-33.365)	**0.001**	3.089 (0.449-21.242)	0.252
Malignancy	0.75 (0.009-0.597)	0.014		
Immunosuppression	0.037 (0.003-0.450)	0.01		

CRP: C-Reactive Protein

Symptom-based evaluation of COVID-19 patients at admission and after discharge

The five most common symptoms at hospital admission were cough (n=119, 89.5%), dyspnea (n=72, 54.1%), fever (n=62, 46.6%), myalgia (n=54, 40.6%), and attenuated sense of taste (n=43, 32.3%) (Table 2). On day 14 of hospitalization, the most common symptoms were cough (n=66, 52.4%), fatigue (n=37, 29.4%), dyspnea (n=34, 27%), myalgia (n=11, 8.7%) and nausea (n=9, 7.1%).

Symptoms on day 28 were evaluated in 122 patients and the most common were fatigue (n=80, 65.6%), dyspnea (n=15, 12.3%), insomnia (n=12, 9.8%), cough (n=8, 6.6%), and myalgia (n=3.5%); 37 (30.3%) patients had no symptoms on day 28. The patients' symptoms on days 0, 14, and 28 are presented in Table IV.

Table IV: Clinical symptoms on admission, follow up 14 and 28 days

Symptoms	On admission (n, %) n=133	Followup – 14 day (n, %) n=126*	Followup – 28 day (n, %) n=122**
Cough	119 (89.5)	66 (52.4)	8 (6.6)
Dispnea	72 (54.1)	34 (27)	15 (12.3)
Fever	62 (46.6)	1 (0.8)	-
Myalgia	54 (40.6)	11 (8.7)	3 (2.5)
Arthralgia	54 (40.6)	1 (0.8)	-
Decreased taste	43 (32.3)	24 (19)	2 (1.6)
Headache	24 (18.0)	3 (2.4)	1 (0.8)
Sore throat	24 (18.0)	1 (0.8)	-
Diarrhea	16 (12.0)	-	-
Chest pain	10 (7.5)	-	-
Anorexia	10 (7.5)	4 (3.2)	1 (0.8)
Nausea	5 (3.8)	9 (7.1)	-
Runny nose	1 (0.8)	-	-
Fatigue	-	37 (29.4)	80 (65.6)
Insomnia	-	9 (7.1)	12 (9.8)
Anxiety	-	5 (4)	9 (7.4)
No symptom	-	3 (2.4)	37 (30.3)

*It was evaluated out of 126 patients, since 2 patients were followed up with invasive mechanical ventilation in the Intensive Care Unit, and 5 patients died.

**It was evaluated out of 122 patients since 1 patient was followed up with invasive mechanical ventilation in the Intensive Care Unit and 10 patients died.

Long-term evaluation of symptoms at 6 months included 111 patients, 32 (28.8%) of whom reported having no symptoms. Thirty-six patients (32.4%) reported having fatigue, 13 patients (11.7%) had sleep disorder, and 12 patients (10.8%) had anxiety disorder. In addition, 8 patients (7.2%) had dyspnea, 6 (5.4%) had sore throat, and 5 (4.5%) reported persistent cough (Figure I). Two patients who had been treated in the ICU reported having dyspnea and using oxygen therapy at home. Four patients (3.6%) reported having pruritus and 1 patient was diagnosed with lichen sclerosus 2 months after COVID-19 infection. This patient had no history of previous chronic disease, autoimmunity, dermatological disease, or medication use and tested negative for hepatitis, HIV, and syphilis.

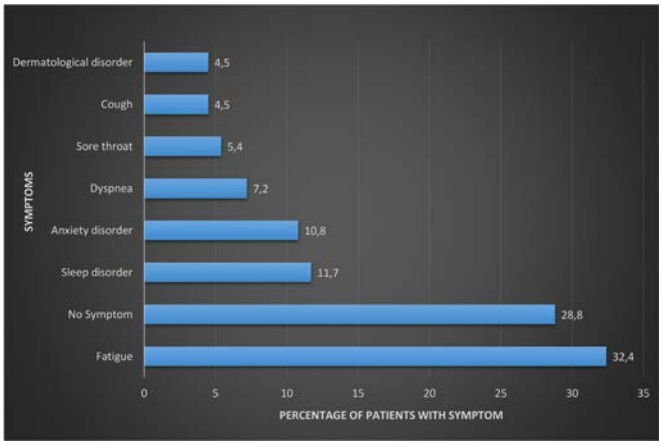

Figure I. Six–month symptoms of discharged patients of COVID-19 (n=111)

DISCUSSION

This study identified the presenting symptoms, clinical and laboratory findings, and risk factors for mortality in hospitalized COVID-19 patients, as well as evaluated the patients' symptoms at follow-up on day 14, day 28, and month 6. Our study provides a wider spectrum of the disease, as it includes the symptoms and signs of hospital admission and follow-up of patients with a diagnosis of COVID-19. It is also planned to contribute to the literature about which clinical pictures the patients will encounter in the long term.

There are many studies on the presenting symptoms, findings, and prognosis of COVID-19[4,5,12-15]. The results of these studies are similar to those in our study. Hypertension and diabetes mellitus were found to be the most common comorbid diseases in our study, consistent with the previous reports[12,14,15]. The results of a meta-analysis indicated that BMI is an independent risk factor for hospitalization, ICU admission, invasive mechanical ventilation, and mortality[16]. Many comorbid diseases are associated with advanced age and obesity. Although severe/critical COVID-19 patients in our study showed higher mean age and comorbid disease rates, there was no significant difference in BMI when compared with mild/moderate patients.

Laboratory parameters are another factor affecting the prognosis of COVID-19. Most studies evaluating laboratory data only examine hospital admission values, but in this study we also evaluated the relationship between the laboratory parameters and COVID-19 course and mortality by evaluating the results of serial data from days 3,7, and[14]. Low serum lymphocyte count and high CRP, procalcitonin, D-dimer, ferritin, troponin, and IL-6 levels should be considered in terms of severe or fatal course[17]. Zhou et al. determined that advanced age, high SOFA score, and D-dimer level higher than 1 µg/mL at admission were associated with higher mortality[13]. Our findings were similar to those in these two studies and suggested that the follow-up of serum lymphocyte, D-dimer, ferritin, CRP, procalcitonin, and troponin levels is important in predicting disease severity and mortality. Patients with low SpO2 and high qSOFA scores

at hospital admission should be considered at risk of mortality. In the presence of nonmodifiable risk factors affecting course and prognosis, such as comorbid diseases, age, sex, obesity, and epigenetic factors, initiating evidence-based treatment in a timely manner and closely monitoring patients are critical.

At first admission, the most common symptoms among patients in this study were cough and dyspnea. Fever was detected in 46.6% of the patients; this is similar to the results of some studies, whereas higher rates of fever were reported in other studies[5,12,18]. Myalgia, arthralgia, and loss of taste and smell were among the other common clinical symptoms reported by patients at the time of admission.

Symptoms experienced by COVID-19 patients after discharge vary considerably. In the present study, the major symptoms on day 14 were cough, dyspnea, and fatigue, whereas the predominant symptom on day 28 was fatigue. Another interesting finding was that insomnia and anxiety were not seen during inpatient treatment but appeared after discharge. In a study examining persistent symptoms in the post-acute period, most patients reported at least one complaint, the most common of which were fatigue, dyspnea, joint pain, chest pain, cough, and anosmia[19]. Wang et al. evaluated symptoms in the short term after discharge and found that most patients (86.3%) were asymptomatic at 3 and 4 weeks[20]. In contrast, only 30.3% of the patients in our patient population were asymptomatic on day 28. Sami et al. followed 490 patients for 1 year after discharge and determined that cough, dyspnea, and fatigue were the most common symptoms in the severe and non severe patient group at 4 weeks[21]. In another study evaluating the data of 33 patients hospitalized for severe COVID-19, dyspnea was reported by 11 patients (33%), cough by 11 (33%), and fatigue by 15 (45%) at 6 weeks after discharge, and the authors concluded that this group of patients who did not require mechanical ventilation were at low risk of developing cardiac, pulmonary, and thromboembolic complications[22]. In our evaluation of respiratory symptoms at 6 months after hospitalization, 8 patients continued to have dyspnea, 2 of whom were receiving oxygen therapy at home, and all had a history of ICU admission. There is a direct correlation between COVID-19 severity and rates of complications and sequelae, and patients with severe disease should be followed more closely after discharge. Huang et al. investigated symptoms and sequelae at 6 months after initial symptom onset and emphasized that because of impaired pulmonary diffusion capacity in patients classified as having severe disease, this patient population should be prioritized in terms of follow-up[23].

The incidence of post-COVID mental health problems such as anxiety and sleep disorders is also considerable. Mazza et al. detected at least one psychopathological finding in 56% of patients at 1-month follow-up after inpatient treatment, with anxiety disorder in 42%, insomnia in 40%, and depression in 31% of patients[24]. SARS-CoV-2 has central nervous system tropism and the resulting neuroinflammatory response may lead to major depressive disorder, bipolar disorder, various psychoses, obsessive-compulsive disorder, and post-traumatic stress disorder[25]. Milder mental health problems such as sleep and anxiety disorders were also detected during follow-up in the patients in our study. The prevalence of these psychological disorders was lower in the acute period and increased starting after 2 weeks. Close follow-up and support are needed to protect patients' mental health.

Dermatological findings can also be seen in the course of COVID-19, including manifestations such as maculopapular rash, urticaria, petechiae, purpura, and distal extremity ischemia26. The most common cutaneous complaint in our patients was an itch, while one

patient developed lichen sclerosus at 2 months post-COVID. Our search of the literature yielded no data on the association of COVID-19 and lichen sclerosis, but we believe it may have occurred as a result of the inflammatory response caused by the disease, as in other viral infections.

Limitations of our study include its retrospective nature, the inability to analyze IL-6, and those evaluations on day 28 and month 6 were based on self-reported symptoms. Tests providing objective assessment of pulmonary, cardiac, and other sequelae could not be performed. Therefore, our findings must be supported by larger studies. As it is known, post-COVID complications such as MIS-A can be seen in patients in the asymptomatic or mild classification. Another limitation is that only the long-term results of the patients followed up in the hospital were evaluated.

CONCLUSIONS

In conclusion, this study showed that periodic follow-up of laboratory parameters may provide an early warning in terms of disease severity, and SpO2 at presentation and particularly serum ferritin level may be important indicators of mortality. Most patients hospitalized for COVID-19 in this study did not have serious symptoms at 28 days and 6 months after admission, but those who were treated in the ICU had more respiratory symptoms. In addition to pulmonary rehabilitation, patients with other organ and system involvement should be provided the necessary follow-up, support, and treatment.

Ethics Committee Approval: Ethics committee approval was received from Niğde Ömer Halisdemir University Ethics Committee (No: 2020/05-03). This study was conducted in accordance with the principles of the Declaration of Helsinki.

Conflict of Interest: The authors declared no conflicts of interest.

Financial Disclosure: The authors declared that this study has received no financial support.

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