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Long-Term Clinical Consequences of Patients Hospitalized for COVID-19 Infection

ABSTRACT

Background: Coronavirus disease 2019, putatively caused by infection with severe acute respiratory coronavirus 2, often involves injury to multiple organs and there are limited data regarding the mid- to long-term consequences of coronavirus disease 2019 after discharge from the hospital. The study aimed to describe the mid- to long-term consequences of coronavirus disease 2019 in hospitalized patients after discharge.

Methods: This single-center, prospective study enrolled coronavirus disease 2019 patients who were discharged uneventfully from our center. All participants underwent face-to-face interviews by trained physicians and were asked to complete a series of questionnaires on third and sixth months' follow-up visits.

Results: A total of 406 consecutive discharged coronavirus disease 2019 patients were enrolled in this study. Patients were divided into 3 groups according to World Health Organization classification as follows: World Health Organization-3 (n=83); World Health Organization-4 (n=291); and World Health Organization-5,6 (n=32). Length of hospital stay was highly, significantly increased in the higher World Health Organization groups (World Health Organization-3 vs. World Health Organization-4, $P < .0001$; World Health Organization-3 vs. World Health Organization-5,6, $P < .0001$; World Health Organization-4 vs. World Health Organization-5,6, $P < .0001$), whereas the length of intensive care unit stay was highly, significantly increased only in World Health Organization-5,6 group compared to other groups (World Health Organization-3 vs. World Health Organization-5,6, $P < .0001$; World Health Organization-4 vs. World Health Organization-5,6, $P < .0001$). The most frequent complaints were chest pain (39%), and the frequency of complaints decreased during the 3-6 months follow-up period. Multiple logistic regression analysis indicated that age, coronary artery disease, fibrinogen, C-reactive protein, troponin I, D-dimer, use of steroid and/or low molecular weight heparin, and World Health Organization class were found to be independent predictors of ongoing cardiovascular symptoms.

Conclusions: The current data demonstrated that persistent symptoms were common after coronavirus disease 2019 among hospitalized patients. This should raise awareness among healthcare professionals regarding coronavirus disease 2019 aftercare.

Keywords: Coronavirus disease 2019, long-term, cardiovascular symptoms, thromboembolic events

INTRODUCTION

Coronavirus disease 2019 (COVID-19), putatively caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), often involves injury to multiple organs (e.g., lung and heart).[1-4] The general signs and symptoms of COVID-19 include fever, cough, shortness of breath, headache, palpitation, chest discomfort, loss of smell, and gastrointestinal system impairment. Nearly one-fourth of individuals hospitalized with COVID-19 have been diagnosed with cardiovascular complications, which have been reported to contribute to approximately 40% of all COVID-19-related deaths.[2,3,5] Several clinical trials have focused on the epidemiological and clinical characteristics of patients with COVID-19. However, there are limited data regarding the long-term consequences of COVID-19 after discharge from the hospital. Only a few studies with a limited sample size have been published, with the longest follow-up being 3 months after discharge.[6-8] Although some persistent symptoms, such as fatigue, dyspnea, and impaired pulmonary function, have been described, the full spectrum of post-discharge characteristics

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remains unclear. Furthermore, no studies have yet described the cardiovascular pathological and clinical manifestations persisting after acute insult and/or developed at mid- to long-term follow-up. This study aimed to describe the mid- to long-term consequences of COVID-19 in hospitalized patients after discharge and to examine the cardiovascular system-related symptoms.

METHODS

Study Population

Consecutive patients, who were hospitalized at Bağcılar Training and Research Hospital (Istanbul, Turkey) with a diagnosis of COVID-19 confirmed by real-time polymerase chain reaction test of an oropharyngeal swab sample between March 11 and June 20, 2020, were included in this prospective study. Individuals who died before the follow-up visit, those for whom follow-up visits could not be easily performed (e.g., panic or psychotic disorders, dementia, patients requiring special assistance for orthopedic, pulmonary, and neurological conditions), those who declined to participate, individuals who failed to maintain contact during follow-up, and finally, those who are <18 years of age were excluded. World Health Organization (WHO) Covid-19 severity classification was designated in accordance with the literature.[4] The study included 406 eligible patients with WHO class 3 or higher who managed to survive and were discharged uneventfully.

All discharged patients fulfilled the uniform discharge criteria according to clinical guidance for COVID-19 pneumonia diagnosis and treatment issued by the National Health Commission (i.e., no fever for 48-72 h and improvement in respiratory symptoms). The present study was approved by the Institutional Research Ethics Committee (Ethics Committee Approval Number #2021.02.1.02.023), and written informed consent was obtained from all study participants.

Definitions

Hypertension (HT) was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg measured with the patient supine, or history of antihypertensive medication use.[9] Diabetes mellitus (DM) was defined as a fasting serum glucose level ≥ 126 mg/dL, glycated hemoglobin level ≥ 6.5%, or a history of hypoglycemic medication(s).[10] Chronic obstructive pulmonary disease (COPD) was defined according to the Global Initiative for Chronic Obstructive Lung Disease (i.e., "GOLD") criteria (based on medical records, not on biological data).[11] Cigarette smoking was defined as a history of smoking >10 cigarettes per day for at least 1 year without any attempt(s) to quit. World Health Organization COVID-19 severity classification was designated in accordance with the literature.[4] The definition of malignancy was made in accordance with the definition of the United States National Cancer Institute.[12] Coronary artery disease was defined as significant stenosis [>50%] in at least 1 epicardial artery.[13] COVID-19 related myocarditis was performed in accordance with the current literature.[14] The diagnosis of these patients was made by both echocardiography and cardiac magnetic resonance (cMR). Since cMR is the gold standard in the diagnosis of myocarditis, the diagnosis is confirmed with this imaging method. In addition, chronic kidney disease (CKD) was defined as the presence of kidney damage or glomerular filtration rate of <60 mL/min/1.73 m^2 for >3 months.[15] Coronavirus disease-related cardiovascular symptom was defined as the presence of at least one of the following: dyspnea, chest pain, palpitation, and early fatigue. Besides, these symptoms were defined in accordance with the literature.[16-18] The term "chest pain" was used by patients and applied by clinicians to describe the many unpleasant or uncomfortable sensations in the anterior chest that prompt concern for a cardiac problem. Chest pain definition included "typical" and "atypical" types. The atypical chest pain was used to report pressure, tightness, squeezing, heaviness, or burning, described as sharp, fleeting, related to inspiration (pleuritic) or position, or shifting locations—suggests a lower likelihood of ischemia. Moreover, the typical chest pain that is more likely associated with ischemia was described as substernal chest discomfort provoked by exertion or emotional stress and relieved by rest or nitroglycerin. Chest pain was evaluated according to the modified HEART score. Chest pain with typical or atypical symptoms and the modified HEART score of ≥1 was considered chest pain.[19] Palpitations were defined as increased or abnormal awareness of the heartbeat. All patients with palpitations were due to arrhythmias. These were supraventricular arrhythmias, including sinus tachycardia. Those with panic disorder were not evaluated as palpitations. The Fatigue Severity Scale (FSS) was used to measure fatigue and the FSS score ≥4 was defined as indicative of fatigue.[20] Other symptoms were also evaluated and defined in accordance with WHO guidelines.[4]

Follow-up Evaluation and Questionnaires

The study consists of 2 periods: (1) between discharge and third month (first visit) and (2) between the third month and sixth month (second visit). The aim of this study is to follow up on the discharged patients and to investigate the mid- and long-term clinical outcomes. Baseline clinical data (pre-discharge) were obtained from electronic medical records or by taking a detailed medical history from the patient including demographics (age, sex, education, job, number of individuals residing in the household, number of individuals affected in the household, and smoking), clinical characteristics (self-reported comorbidities, time of symptom onset, and chest

HIGHLIGHTS

- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) often involves injury to multiple organs.
- There are very limited data in the literature on the long-term consequences of SARS-CoV-2 infection after discharge from the hospital.
- Cardiovascular symptoms are closely associated with disease severity during the acute phase.
- A close follow-up of patients after discharge is very important in terms of thromboembolic complications and ongoing cardiovascular symptoms in patients with SARS-CoV-2 infection.

images), laboratory test results, and treatment (corticosteroids, intravenous immunoglobulin, antibiotics, antiviral therapy, vitamin C, enoxaparin, N-acetylcysteine, and hydroxychloroquine).

Follow-up assessments were performed 3 and 6 months after discharge. The 3-month follow-up was performed by physicians in the cardiology outpatient clinic. Patients were evaluated in an outpatient clinic with anamnesis and a comprehensive physical examination. Using the modified HEART score[19] and FSS score,[20] cardiovascular symptoms were assessed by trained physicians by face-to-face interviews with all participants at 3 and 6 months. They were also asked to complete a questionnaire for the modified British Medical Research Council (mMRC) dyspnea scale.[21] In addition, medical histories, cardiovascular symptoms, and other possible COVID-19 symptoms of patients who applied to the emergency department were evaluated in detail. The mMRC dyspnea scale is a 5-category, self-rating tool that characterizes the level of dyspnea according to physical activity, with higher scores indicating increased dyspnea. More specifically, it measures the degree of disability that breathlessness poses in day-to-day activities on a scale from 0 to 4, as follows: 0, no breathlessness, except with strenuous exercise; 1, shortness of breath when hurrying on a level surface or walking up a slight inclination; 2, walks slower than individuals of the same age on level surface due to breathlessness or needs to stop to catch breath when walking at their own pace on a level surface; 3, stops for breath after walking approximately 100 m or after few minutes on a level surface; and 4, too breathless to leave the house, or breathless when dressing or undressing. A 12-lead electrocardiogram evaluation was evaluated in all patients who complained of palpitations. Besides, according to the patient's signs and symptoms, ambulatory electrocardiographic recording (palpitations), 24 hours blood pressure Holter monitoring (suspicion of HT/hypotension), ultrasonography of lower extremity vessels (DVT (deep venous thrombosis) findings or suspicion of), chest high-resolution computed tomography (COVID suspected or post-COVID control), and laboratory tests (routine COVID parameters and other routine tests) were performed according to patient symptoms and findings.

Sixth-month follow-up assessments, in addition to the 3-month follow-up evaluation parameters, were also evaluated by experienced physicians with at least one telephone interview over a 3-month period. Patients were asked to describe the presence or absence of symptoms after COVID-19 and whether each symptom persisted. Besides, emergency clinic admissions for COVID-related cardiovascular symptoms were recorded during the 3- and 6-month visits.

Clinical and Biological Parameters and Diagnostic Tools

The following variables were considered during patient admission: age, weight, height, body mass index, history of HT, history of DM (based on medical records and/or the presence of specific therapy at admission), active smoking status, coronary artery disease, and history of CKD (based on medical records, not on biological data). Biological data of interest were considered at the closest time of discharge (maximum 72 hours before discharge). All biological data were obtained from a single laboratory. The estimated glomerular filtration rate was calculated using the CKDepidemiology collaboration formula.[22] At each visit, all patients underwent transthoracic echocardiography in the left lateral decubitus position using a Vivid 5 echocardiography device (GE Vingmed Ultrasound AS, Horten, Norway) and a 3.2 mHz adult probe. Left ventricular ejection fractions (LVEF) of the patients were calculated using the biplane Simpson method. In all patients, left atrial diameter (LAD) was measured on the parasternal long-axis view with M-mode echocardiography. Systolic pulmonary artery pressure was calculated from the tricuspid valve regurgitation jet velocity in accordance with the modified Bernoulli equation, and the right atrial pressure was estimated as 10, 15, and 18 mm Hg for mild, moderate, and severe right atrial enlargement, respectively.[23] Holter electrocardiography analyses were performed using 12-channel recordings obtained from the ambulatory Holter monitors. Ambulatory electrocardiographic recordings (DMS 300-7 Holter Reader; DSM) were obtained for a period of at least 24 hours in all the patients. Before automatic analysis, the tapes were analyzed using the Holter program (CardioScan 12.0 DM Software, DSM). The recordings were evaluated for rhythm, premature atrial contraction, supraventricular tachycardia, ventricular extrasystole, paroxysmal atrial fibrillation, and atrioventricular block with or without pauses. A 24-hour blood pressure Holter monitoring (BPHM) was done by experienced medical staff. In all patients, 24-hour BPHM was performed using the Oscillographic Mobil-O-Graph New Generation 24-h BPHM classic (IEM GmbH, Stolberg, Germany). Extremity ultrasound was performed using a 9 MHz linear probe and a 5 MHz curved linear probe for deeper penetration in the setting of obesity or lower extremity edema (General Electric Medical Systems Logic S8 Portable machines and GE E10, with the 9 Linear C1-5 curved linear probes). All exams were performed either portably at the bedside or in the radiology ultrasound suite according to American Institute of Ultrasound in Medicine guidelines.[24] Evaluation of the lower extremities included graded compression grayscale and color Doppler evaluation of the common femoral vein, femoral vein, deep femoral vein, and popliteal vein in all cases, with spectral duplex Doppler evaluation of the common femoral and popliteal veins, and, where possible, graded compression and color flow evaluation of greater saphenous, external iliac, peroneal, posterior tibial, and anterior tibial veins as recorded from the venous duplex ultrasound reports. DVT diagnosis was only considered positive for thigh DVT, from popliteal vein to the common femoral or external iliac veins. Findings of acute calf DVT and chronic DVT without evidence for acute thrombosis were considered negative.

Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences version 19.0. (IBM Corporation, Armonk, NY, USA) for Windows (Microsoft Corporation, Redmond, Wash, USA). Descriptive statistics are expressed as mean ± standard deviation for continuous variables with normal distribution, or median [interquartile

range (IQR)] for continuous variables without normal distribution, and as frequencies with percentages for categorical variables. Fitness to the normal distribution was analyzed using the Kolmogorov–Smirnov test. Intergroup differences for normally distributed data of non-recurring variables were compared with a one-way analysis of variance (ANOVA). Pairwise post hoc tests were performed using either the Tukey honest significant difference test or the Tahmane's T2 test for further analysis of significant results between groups. The Kruskal–Wallis test was conducted to compare groups for mentioned parameters that were not distributed normally and for ordinal variables. Post hoc analyses were performed with the Mann–Whitney *U* test. Repeated measures ANOVA test was used to analyze normally recuring data and Friedman test was applied for continuous mentioned data that was not normally distributed. Post hoc analysis was also performed using the dependent samples *t* test for normally distributed data and Wilcoxon test for data not normally distributed. Logistic regression analysis was performed to identify any independent predictors of cardiovascular symptoms (shortness of breath, chest pain, palpitations, and fatigue). The results of multiple logistic regression analyses are expressed as odds ratio (OR) with corresponding 95% CI. Differences with a 2-sided $P < .05$ were considered to be statistically significant.

RESULTS

A total of 406 hospitalized COVID-19 patients were enrolled and divided into 3 groups according to WHO classification, as follows: WHO-3 (n=83); WHO-4 (n=291); WHO-5,6 (n=32). Patients in groups WHO-4 and WHO-5,6 were highly, significantly older than those in WHO-3 (WHO-3 vs. WHO-4, $P < .0001$; WHO-3 vs. WHO-5,6, $P < .0001$), percentage of male gender was very significantly lower in WHO-3 group in compared to WHO-4 and WHO-5,6 groups (WHO-3 vs. WHO-4, $P=.018$; WHO-3 vs. WHO-5, $P=.012$). Body mass index, number of family members, number of affected individuals, and echocardiographic parameters (LVEF, LAD, pulmonary arterial systolic pressure) were similar among the 3 groups ($P > 0.05$). Length of hospital stay was highly, significantly increased in the higher WHO groups (WHO-3 vs. WHO-4, $P < .0001$; WHO-3 vs. WHO-5,6, $P < .0001$; WHO-4 vs. WHO-5,6, $P < .0001$), whereas the length of intensive care unit (ICU) stay was highly significantly increased only in group WHO-5,6 in compared to other groups (WHO-3 vs. WHO-5,6, $P < .0001$; WHO-4 vs. WHO-5,6, $P < .0001$). Although the history of DM, CAD, COPD, and CKD was similar across all groups, there were highly significant inter-group differences interms of HT (WHO-3 vs. WHO-4, $P < .0001$; WHO-3 vs. WHO-5,6, $P < .0001$; WHO-4 vs. WHO-5,6, $P < .0001$), and malignancy (WHO-3 vs. WHO-5,6, $P < .0001$; WHO-4 vs. WHO-5,6. $P < .0001$).

On blood chemistry, there were highly significant inter-group differences in hemoglobin (WHO-3 vs. WHO-5,6, $P < .0001$; WHO-4 vs. WHO-5,6, $P < .0001$), leukocyte count (WHO-3 vs. WHO-5,6, $P < .0001$; WHO-4 vs. WHO-5,6, $P < .0001$), creatinine (WHO-3 vs. WHO-5,6, $P = .005$), brain natriuretic peptide (BNP) levels (WHO-3 vs. WHO-5,6, $P < .0001$; WHO-4 vs. WHO-5,6, $P < .0001$), C-reactive protein (CRP) (WHO-3 vs. WHO-4, $P < .0001$; WHO-3 vs. WHO-5,6, $P < .0001$; WHO-4 vs. WHO-5,6, $P < .0001$), high-sensitivity troponin I (hs-TnI) (WHO-3 vs. WHO-5,6, $P = .018$; WHO-4 vs. WHO-5,6, $P = .047$), D-dimer (WHO-3 vs. WHO-5,6, $P < .0001$; WHO-4 vs. WHO-5,6, $P < .001$), procalcitonin (WHO-3 vs. WHO-5,6, $P < .0001$; WHO-4 vs. WHO-5,6, $P < .0001$), lactate dehydrogenase (LDH) (WHO-3 vs. WHO-4, $P < .0001$; WHO-3 vs. WHO-5,6, $P < .0001$; WHO-4 vs. WHO-5,6, $P < .0001$), fibrinogen (WHO-3 vs. WHO-4, $P < .0001$; WHO-3 vs. WHO-5,6, $P < .0001$; WHO-4 vs. WHO-5,6, $P < .0001$), ferritin (WHO-3 vs. WHO-4, $P < .0001$; WHO-3 vs. WHO-5,6, $P < .0001$; WHO-4 vs. WHO-5,6, $P < .0001$), and albumin levels (WHO-3 vs. WHO-4, $P = .007$; WHO-3 vs. WHO-5,6, $P < .0001$; WHO-4 vs. WHO-5,6, $P < .009$). Demographic and clinical features of patients in these groups are given in Table 1.

Recurrent emergency department admissions were also analyzed (Table 2) and were calculated as the total number of applications in each 3-month period in the calculation of recurrent emergency service admissions. The major causes of emergency department admission complaints were dyspnea, chest pain, arrhythmic event, suspected arterial or venous thromboembolic event, stroke, and acute abdomen. In the first 3 months after the index hospitalization, there were very significant inter-group differences in the number of emergency visits (WHO-3 vs. WHO-5,6, $P < .0001$; WHO-4 vs. WHO-5,6, $P = .003$), fatigue (WHO-3 vs. WHO-5,6, $P < .001$; WHO-4 vs. WHO-5,6, $P < .001$) and chest pain (WHO-3 vs. WHO-5,6, $P < .001$; WHO-4 vs. WHO-5,6, $P < .001$) (Table 2). Besides, at the sixth month clinical evaluation, there were very significant inter-group differences in the number of emergency visits (WHO-3 vs. WHO-5,6, $P < .001$; WHO-4 vs. WHO-5,6, $P < .001$), fatigue (WHO-3 vs. WHO-5,6, $P < .001$; WHO-4 vs. WHO-5,6, $P = .004$), and chest pain (WHO-3 vs. WHO-5,6, $P < .001$; WHO-4 vs. WHO-5,6, $P < .001$) (Table 2).

The distribution of symptoms within 3 months, and between 3 and 6 months, is depicted in Figure 1. Cardiovascular system-related symptoms were accounted as the most frequent among the study population. The symptoms resolved dramatically between 3 and 6 months compared with the initial 3-month period. In the later period, chest pain was the most frequent symptom among the study population. The severity of dyspnea was evaluated using the mMRC scale. The distribution of patients according to the mMRC scale at 3 and 6 months is presented in Figures 2 and 3. Symptoms and their severity improved over time in the majority of patients. According to the mMRC scale, only 2 (0.5%) patients experienced grade 0 symptoms, 252 (62%) grade 1 symptoms, 136 (33.5%) grade 2 symptoms, and 16 (3.9%) grade 3 symptoms during the first 3 months. At the 6-month follow-up visit, 166 (41.7%) patients reported grade 0 symptoms, 248 (62.3%) grade 1 symptoms, and 34 (8.5%) grade 2 symptoms.

A total of 213 patients underwent transthoracic echocardiographic examination during the 3-month follow-up period. Left ventricular ejection fraction was <40% in 5 patients and systolic pulmonary pressure was >30 mmHg in 26%. Mitral

Table 1. The Baseline Demographic, Laboratory, and Clinical Findings of COVID-19 Patients

Variable	WHO-3 (n = 83)	WHO-4 (n = 291)	WHO-5,6 (n = 32)	*P*
Clinical characteristics				
Age (years)	46.8 ± 13.3	52.8 ± 13.1	54.8 ± 11.8	**WHO-3 vs. WHO-4, *P* < .0001** **WHO-3 vs. WHO-5,6, *P* < .0001**
Male, n (%)	35 (42)	163 (56)	19 (60)	**WHO-3 vs. WHO-4, *P* = .018** **WHO-3 vs. WHO-5, *P* = .012**
Smoking, n (%)	4 (4.81)	15 (5.15)	1 (3.12)	.582
BMI (kg/m^2)	25.2 ± 2.1	24.7 ± 3.2	24.9 ± 3.4	.145
NFM, n	4.4 ± 2.0	4.9 ± 2.0	4.4 ± 1.3	.085
NAI, n	2(1-3)	2(1-4)	2(1-4)	.360
Hospital stay (days)	4 (3-5)	8 (5-11)	23 (17-36)	**WHO-3 vs. WHO-4, *P* < .0001** **WHO-3 vs. WHO-5,6, *P* < .0001** **WHO-4 vs. WHO-5,6, *P* < .0001**
ICU stay (days)	0	0	8 (5-14)	**WHO-3 vs. WHO-5,6, *P* < .0001** **WHO-4 vs. WHO-5,6, *P* < .0001**
LVEF (%)	59.5 ± 3.4	59.3 ± 2.9	60.0 ± 0.0	.788
LAD (mm)	34.4 ± 3.6	34.9 ± 3.4	35.5 ± 3.9	.541
PASP (mm Hg)	29 (28-32)	30 (26-32)	34 (28-37)	.543
Chronic medical illness				
HT, n (%)	13 (16)	52 (18)	12 (37)	**WHO-3 vs. WHO-4, *P* < .0001** **WHO-3 vs. WHO-5,6, *P* < .0001** **WHO-4 vs. WHO-5,6, *P* < .0001**
DM, n (%)	21 (25)	59 (20)	10 (31)	0.272
CAD, n (%)	4 (5)	18 (6)	2 (6)	0.591
Malignancy, n (%)	2 (2)	4 (1)	4 (12)	**WHO-3 vs. WHO-5,6, *P* < .0001** **WHO-4 vs. WHO-5,6, *P* < .0001**
COPD, n (%)	8 (10)	26 (9)	5 (15)	.381
CKD, n (%)	0 (0)	6 (2)	2 (6)	**WHO-3 vs. WHO-5,6, *P* = .009** **WHO-4 vs. WHO-5,6, *P* = .028**
Laboratory findings at admission				
Hemoglobin (g/dL)	13.0 ± 1.3	12.9 ± 1.8	11.4 ± 1.7	**WHO-3 vs. WHO-5,6, *P* < .0001** **WHO-4 vs. WHO-5,6, *P* < .0001**
WBC (10^3/μL)	5 (4-6)	5 (4-7)	8 (5-12)	**WHO-3 vs. WHO-5,6, *P* < .0001** **WHO-4 vs. WHO-5,6, *P* < .0001**
Creatinine (mg/dL)	0.68 (0.56-0.80)	0.72 (0.62-0.89)	0.87 (0.58-1.46)	**WHO-3 vs. WHO-5,6, *P* = .005**
Sodium (mmol/L)	139.2 ± 2.5	139.3 ± 2.7	138.4 ± 3.6	.382
Potassium (mmol/L)	4.1 ± 0.3	4.2 ± 0.3	4.2 ± 0.4	.735
Glucose (mg/dL)	117.3 ± 47.4	120.2 ± 58.9	124.0 ± 48.1	.601
CRP (mg/dL)	20 (8-47)	77 (32-142)	173 (132-282)	**WHO-3 vs. WHO-4, *P* < .0001** **WHO-3 vs. WHO-5,6, *P* < .0001** **WHO-4 vs. WHO-5,6, *P* < .0001**
Sedimentation	18 (8-32)	24 (12-43)	27 (12-71)	.078
hs-TnI (NR < 0.05 ng/mL)	3 (2-5)	5 (3-8)	15 (9-106)	**WHO-3 vs. WHO-5,6, *P* = .018** **WHO-4 vs. WHO-5,6, *P* = .047**
D-dimer (NR < 0.05 ng/mL)	0.19 (0.12-0.31)	0.27 (0.15-0.56)	1.18 (0.34-2.42)	**WHO-3 vs. WHO-5,6, *P* < .0001** **WHO-4 vs. WHO-5,6, *P* < .001**
Procalsitonin (ng/mL)	0.03 (0.02-0.04)	0.04 (0.03-0.08)	0.19 (0.09-5.15)	**WHO-3 vs. WHO-5,6, *P* < .0001** **WHO-4 vs. WHO-5,6, *P* < .0001**
LDH (U/L)	292.9 ± 121.8	389.6 ± 178.7	746.7 ± 241.2	**WHO-3 vs. WHO-4, *P* < .0001** **WHO-3 vs. WHO-5,6, *P* < .0001** **WHO-4 vs. WHO-5,6, *P* < .0001**

(*Continued*)

Table 1. The Baseline Demographic, Laboratory, and Clinical Findings of COVID-19 Patients (*Continued*)

Variable	WHO-3 (n = 83)	WHO-4 (n = 291)	WHO-5,6 (n = 32)	*P*
Fibrinogen (mg/dL)	381.5 ± 112.5	457.1 ± 123.2	567.4 ± 162.8	**WHO-3 vs. WHO-4, *P* < .0001** **WHO-3 vs. WHO-5,6, *P* < .0001** **WHO-4 vs. WHO-5,6, *P* < .0001**
Ferritin (mL/ng)	95 (33-216)	222 (109-455)	578 (228-840)	**WHO-3 vs. WHO-4, *P* < .0001** **WHO-3 vs. WHO-5,6, *P* < .0001** **WHO-4 vs. WHO-5,6, *P* < .0001**
Albumine (g/dL)	3.8 ± 0.6	3.3 ± 0.4	2.5 ± 0.4	**WHO-3 vs. WHO-4, *P* = .007** **WHO-3 vs. WHO-5,6, *P* < .0001** **WHO-4 vs. WHO-5,6, *P* < .009**
BNP (pg/mL)	70 (70-70)	70 (70-77)	341 (164-641)	**WHO-3 vs. WHO-5,6, *P* < .0001** **WHO-4 vs. WHO-5,6, *P* < .0001**
Treatments				
Antiviral, n (%)	29 (35)	182 (62)	32 (100)	**WHO-3 vs. WHO-4, *P* < .0001** **WHO-3 vs. WHO-5,6, *P* < .0001** **WHO-4 vs. WHO-5,6, *P* < .0001**
Antibiotic, n (%)	63 (76)	281 (97)	32 (100)	**WHO-3 vs. WHO-4, *P* < .0001** **WHO-3 vs. WHO-5,6, *P* < .0001** **WHO-4 vs. WHO-5,6, *P* < .0001**
Hydroxychloroquine, n (%)	82 (99)	291 (100)	32 (100)	.157
LMWH, n (%)	51 (61)	223 (77)	31 (97)	**WHO-3 vs. WHO-4, *P* = .008** **WHO-3 vs. WHO-5,6, *P* < .0001** **WHO-4 vs. WHO-5,6, *P* < .0001**
Steroid, n (%)	0 (0)	14 (5)	21 (66)	**WHO-3 vs. WHO-4, *P* < .0001** **WHO-3 vs. WHO-5,6, *P* < .0001** **WHO-4 vs. WHO-5,6, *P* < .0001**
C vitamin, n (%)	21 (25)	147 (50)	18 (56)	**WHO-3 vs. WHO-4, *P* < .0001** **WHO-3 vs. WHO-5,6, *P* < .0001**
Others				
MV, n (%)	0 (0)	0 (0)	10 (31)	**WHO-3 vs. WHO-5,6, *P* < .0001** **WHO-4 vs. WHO-5,6, *P* < .0001**
NIMV, n (%)	0 (0)	0 (0)	30 (94)	**WHO-3 vs. WHO-5,6, *P* < .0001** **WHO-4 vs. WHO-5,6, *P* < .0001**

BMI, body mass index; NFM, number of family members; NAI, number of affected individuals; ICU, intensive care unit; LVEF, left ventricular ejection fraction; LAD, left atrium diameter; PASP, pulmonary artery systolic pressure; HT, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CKD, chronic kidney disease; WBC, white blood cell; CRP, C-reactive protein; hs-TnI, high sensitive-troponin I; NR, normal range; LDH, lactate dehydrogenase; BNP, brain natriuretic peptide; LMWH, low molecular weight heparin; MV, mechanical ventilation; NIMV, non-invasive mechanical ventilation; WHO, World Health Organization.

regurgitation was moderate to severe in 1 patient and moderate in 5, while a moderate degree of tricuspid regurgitation was detected in 5. Moreover, we found that 6.5% of patients exhibited cardiovascular sequelae on echo follow-up, the most important symptoms of which were increased resting heart rate and chest discomfort. In addition, 4 patients reported a recent diagnosis of HT after COVID-19 infection.

During follow-up, 23 (5.6%) patients experienced arterial or venous thromboembolic events; however, none of these complications resulted in death. Of the 8 patients who experienced acute cerebrovascular events, 6 exhibited acute coronary syndromes, 3 had deep venous thrombosis, 4 had acute pulmonary embolism, 1 had portal vein thrombosis, and 1 had mesenteric ischemia.

Eight patients died within 35 days (IQR, 18-110 days). One patient died from intracranial bleeding, and 3 died of sudden cardiac arrest. One of these patients exhibited reduced LVEF on echocardiography and cMR and was diagnosed with COVID-19-related myocarditis. Four patients were re-hospitalized for respiratory distress and died in the ICU after intubation due to respiratory failure. One of these patients was diagnosed with re-infection with SARS-CoV-2.

Ongoing cardiovascular symptoms, including dyspnea, chest pain, palpitation, and early fatigue, were evaluated at 3 months. Multiple logistic regression analysis was performed to predict patients with one of these symptoms at 3 months (Table 3). The regression model was designed using parameters that were believed to affect symptoms. Age, sex, HT, DM, CAD, malignancy, COPD, creatinine, fibrinogen, ferritin, CRP, procalcitonin, albumin, hs-TnI, D-dimer, BNP, LVEF, WHO class, and medications were included in the model. Age, CAD, COPD, fibrinogen, CRP, hs-TnI, D-dimer, BNP, use of steroid and/or low molecular weight heparin, and WHO

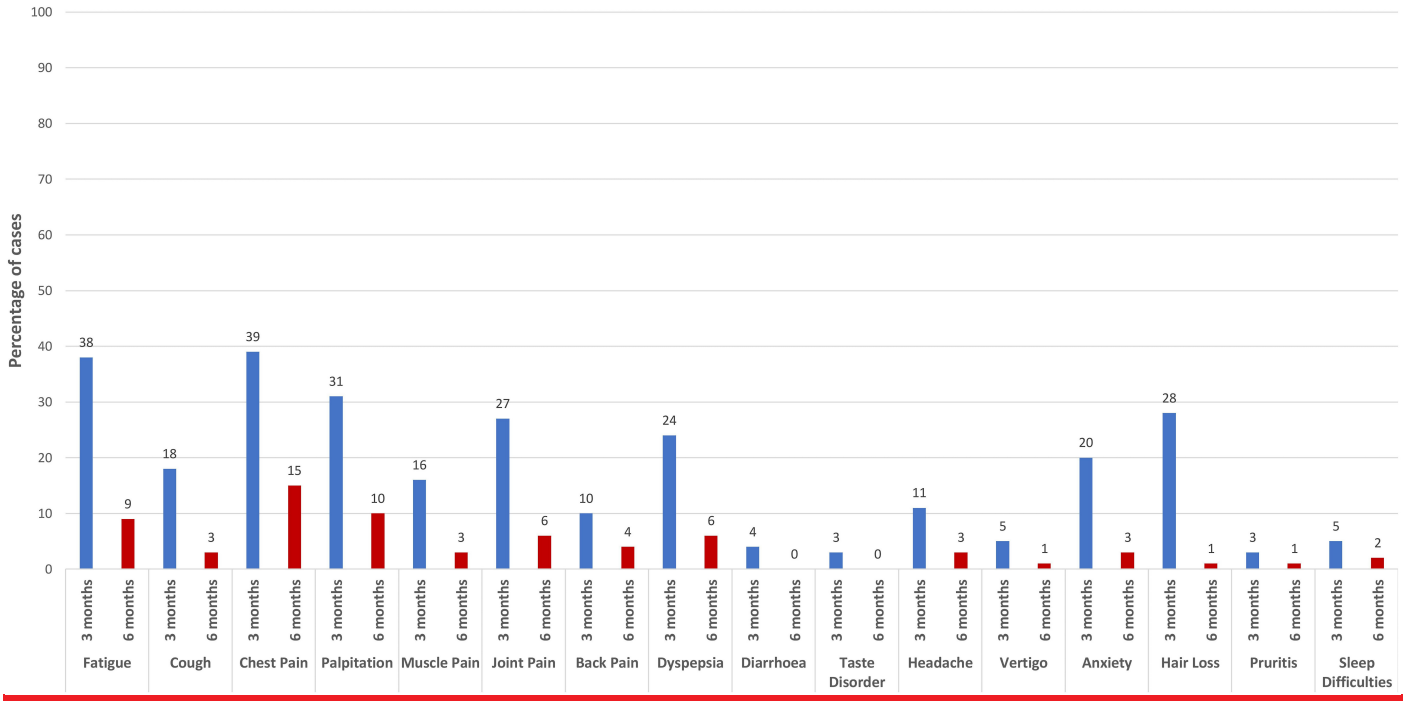

Figure 1. Distribution of symptoms of COVID-19 patients at 3 and 6 months. COVID-19, coronavirus disease 2019.

class were found to be independent predictors of ongoing cardiovascular symptoms.

DISCUSSION

This prospective study aimed to evaluate ongoing symptoms of hospitalized COVID-19 patients after discharge. The major findings of the current study are as follows: (1) symptom duration and severity after discharge were associated with disease severity; (2) recurrent emergency department visits were not rare after hospital discharge; (3) deaths were also not infrequent after discharge; (4) ongoing cardiovascular symptoms were common after discharge; (5) venous and arterial thromboembolic events occurred after discharge, older age, CAD, COPD, fibrinogen, CRP, hs-TnI, D-dimer, BNP, use of steroid and/or low molecular weight heparin during the index hospitalization, and WHO class were independent predictors of ongoing cardiovascular symptoms.

Coronavirus disease 2019 survivors are significantly more likely to develop clinical sequelae 3-6 months after discharge from the hospital than those without COVID-19. This is true not only for general and respiratory symptoms but also for cardiovascular and psychosocial symptoms. This suggests that these symptoms may, in fact, be sequelae of recovery for COVID-19 survivors. In this study, we report the 3- and 6-month post-COVID-19 outcomes of a comprehensive health assessment. Our results suggest that, 6 months after disease onset, most patients

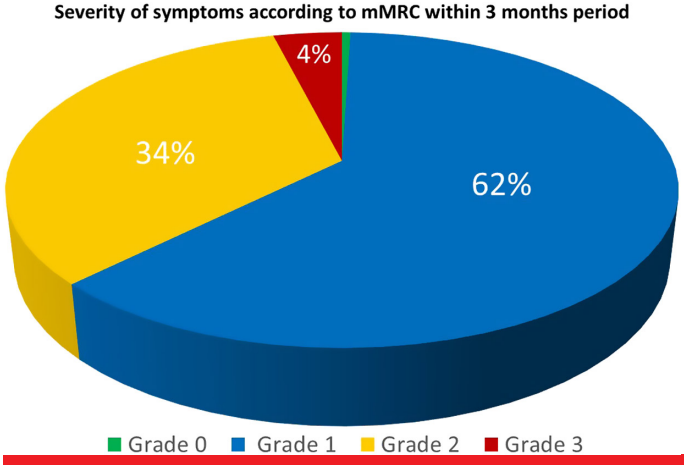

Figure 2. Severity of symptoms according to the modified British Medical Research Council dyspnea scale within 3 months.

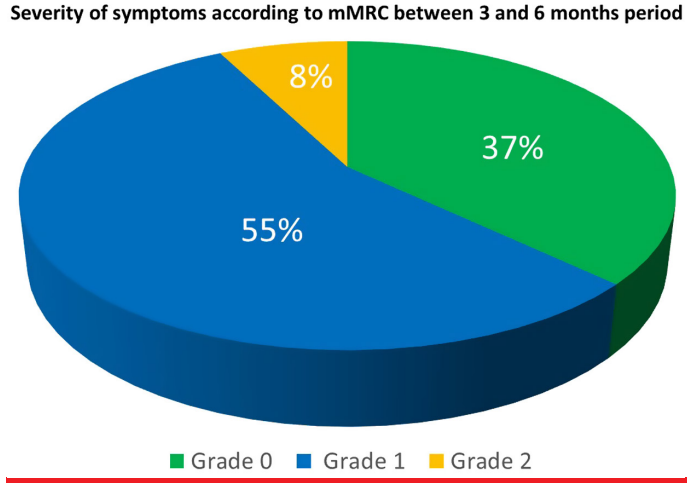

Figure 3. Severity of symptoms according to the modified British Medical Research Council dyspnea scale between 3 and 6 months.

Table 2. Clinical and Laboratory Parameters of Third and Sixth Months Follow-Up of COVID-19 Patients

Parameter	WHO-3 (n=83)	WHO-4 (n=291)	WHO-5,6 (n=32)	*P*
Third month follow-up data				
Hemoglobin (g/dL)	13.5 ± 1.7	13.3 ± 1.5	12.9 ± 1.9	.078
WBC (10^3/μL)	7 (2-11)	6 (3-10)	7 (3-10)	.367
Creatinine (mg/dL)	0.88 (0.56-1.06)	0.86 (0.60-1.10)	0.85 (0.52-1.05)	.734
Sodium (mmol/L)	136.1 ± 3.1	136.3 ± 2.5	137.4 ± 2.9	.816
Potassium (mmol/L)	4.6 ± 0.2	4.5 ± 0.5	4.4 ± 0.6	.881
Glucose (mg/dL)	119.3 ± 41.8	120.1 ± 36.7	118.2 ± 43.5	.692
CRP (mg/dL)	4 (0-11)	5 (0-13)	5 (0-15)	.917
D-dimer (NR < 0.05 ng/mL)	0.02 (0-0.06)	0.02 (0-0.10)	0.03 (0.02-0.12)	.874
AST, (U/L)	24 ± 9.9	26 ± 5.4	27 ± 8.1	.461
ALT, (U/L)	26 ± 8.6	27 ± 7.1	25 ± 7.3	.671
NEV, n	1.95 ± 0.98	2.40 ± 1.12	3.59 ± 1.85	**WHO-3 vs. WHO-5,6, *P* < .0001** **WHO-4 vs. WHO-5,6, *P* = .003**
Fatigue, n (%)*	33 (39.75)	109 (37.45)	17 (53.12)	**WHO-3 vs. WHO-5,6, *P* < .001** **WHO-4 vs. WHO-5,6, *P* < .001**
Chest pain, n (%)⁺	31 (37.34)	108 (37.11)	16 (50)	**WHO-3 vs. WHO-5,6, *P* < .001** **WHO-4 vs. WHO-5,6, *P* < .001**
Sixth month follow-up data				
Hemoglobin (g/dL)	13.4 ± 1.4	13.6 ± 1.2	13.0 ± 1.6	.783
WBC (10^3/μL)	4 (2-8)	5 (3-9)	5 (3-9)	.801
Creatinine (mg/dL)	0.75 (0.41-1.14)	0.77 (0.50-1.03)	0.83 (0.42-1.15)	.595
Sodium (mmol/L)	137.3 ± 2.1	137.3 ± 2.4	139.4 ± 2.9	.875
Potassium (mmol/L)	4.3 ± 0.2	4.3 ± 0.5	4.4 ± 0.4	.981
Glucose (mg/dL)	122.3 ± 51.8	124.1 ± 46.7	121.2 ± 47.6	.792
CRP (mg/dL)	2 (0-5)	3 (0-4)	3 (0-5)	.715
D-dimer (NR < 0.05 ng/mL)	0.01 (0-0.04)	0.01 (0-0.05)	0.02 (0-0.05)	.693
AST, (U/L)	34 ± 8.6	35 ± 7.6	33 ± 6.9	.251
ALT, (U/L)	36 ± 8.6	35 ± 6.1	35 ± 5.4	.671
NEV, n	1.52 ± 0.57	1.80 ± 0.82	2.54 ± 1.10	**WHO-3 vs. WHO-5,6, *P* < .001** **WHO-4 vs. WHO-5,6, *P* < .001**
Fatigue, n (%)*	15 (18.07)	55 (18.90)	7 (21.8)	**WHO-3 vs. WHO-5,6, *P* < .001** **WHO-4 vs. WHO-5,6, *P* = .004**
Chest pain, n (%)⁺	25 (30.12)	88 (30.24)	13 (40.62)	**WHO-3 vs. WHO-5,6, *P* < .001** **WHO-4 vs. WHO-5,6, *P* < .001**

*FSS ≥ 4 defined as fatigue; ⁺HEART score ≥ 1 with typical or atypical symptoms defined as chest pain
WBC, white blood cell; CRP, C-reactive protein; AST, asparatate aminotransferase; ALT, alanine amino transferase; NEV, number of emergency visits; WHO, World Health Organization.

experienced at least one symptom(s), particularly chest pain, palpitations, fatigue, muscle weakness, arthralgia, and anxiety. More severely ill patients had an increased risk for dyspnea, fatigue/muscle weakness, and anxiety. Moreover, our results suggest that it may take months for symptoms to resolve completely among hospitalized patients. Ongoing symptoms are associated with recurrent emergency ward admissions.[25] Fortunately, most survivors reported that these symptoms improved over time.[26] The patients in our study did not undergo objective respiratory function examination(s); as such, the specific degree of functional decline was unclear. Instead, they only compared their perceptions with their previous respiratory function from a subjective perspective. Further studies are needed to assess the association between the duration of COVID-19 and damage to respiratory organs and functions.

We found that fatigue or muscle weakness, arthralgia, palpitation, chest pain, dyspepsia, hair loss, and anxiety were common at 3 and 6 months after symptom onset. This is consistent with data reported in previous long-term SARS follow-up studies.[6-8,26] Canadian researchers found that most SARS survivors experienced good physical recovery from their illness; however, 33% reported a significant decrease in mental health 1 year later.[27] A follow-up study of SARS survivors reported that 40% of patients continued to experience chronic fatigue for a mean of 41 months after SARS. Female

Table 3. Univariate and Multiple Logistics Regression Analysis on the Risk Factors Associated with Cardiovascular Symptoms in Patients with COVID-19.

Variable	Univariate			Multiple		
	OR	95% CI	*P*	OR	95% CI	*P*
Age	1.030	1.014-1.047	**<.001**	1.032	1.015-1.058	**.002**
Gender (male)	0.938	0.635-1.387	.749			
HT	1.229	0.748-2.019	.417			
DM	1.308	1.099-2.873	**.007**	1.261	0.628-2.224	.231
CAD	1.212	1.085-1.388	**<.001**	1.264	1.065-1.540	**.008**
Malignancy	1.198	0.792-1.941	.412			
COPD	2.212	1.393-4.531	**.001**	2.998	1.346-5.961	**.003**
Creatinine	1.291	1.114-1.481	**<.001**	1.316	0.841-2.181	.652
Fibrinogen	3.157	1.945-5.469	**<.001**	2.006	1.042-4.912	**.002**
Ferritin	1.009	1.003-1.0020	**<.001**	1.003	0.998-1.008	.428
CRP	1.141	1.050-1.401	**<.001**	1.085	1.011-1.198	**.010**
Procalsitonin	1.149	1.060-1.234	**<.001**	1.097	0.902-1.217	.762
Albumine	0.465	0.266-0.789	**<.001**	0.689	0.322-1.951	.132
hsTnI ≥ 0.05	7.671	4.931-11.956	**<.001**	9.581	3.723-18.075	**<.001**
D-dimer ≥ 0.05	3.757	2.127-7.181	**<.001**	2.580	1.281-4.731	**.005**
BNP	4.534	2.109-8.861	**<.001**	2.412	1.098-5.023	**.014**
LVEF	1.131	0.903-3.215	.301			
Steroid	0.398	0.251-0.532	**<.001**	0.421	0.268-0.731	**<.001**
LMWH	0.563	0.361-0.802	**<.001**	0.612	0.374-0.841	**<.001**
Antiviral therapy	0.997	0.902-1.147	.730			
WHO class	2.998	1.346-5.966	**.003**	2.576	1.271-5.802	**.007**

HT, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; hs-TnI, high sensitive-Troponin I; BNP, brain natriuretic peptide; LVEF, left ventricular systolic function; LMWH, low molecular weight heparin; WHO, World Health Organization; COVID-19, coronavrius disease 2019; OR, odds ratio.

SARS survivors exhibited higher stress levels and higher levels of depression and anxiety. In a 3-month follow-up survey of 538 COVID-19 patients, Xiong et al[28] found that physical decline or fatigue, post-activity polypnea, and alopecia were more common in women than in men.[28] The underlying mechanism of the psychiatric consequences of COVID-19 is likely to be multifactorial and may include the direct effects of viral infection, immunological response, corticosteroid therapy, ICU stay, social isolation, and stigma.

Previously, several studies have shown that cardiac injury is a common condition among hospitalized patients and is associated with a higher risk for in-hospital mortality.[7] This may be related to angiotensin-converting enzyme 2, which acts as the receptor for SARS-CoV-2.[29] Various factors such as loss of angiotensin-converting enzyme 2 increased the activity of Ang II (Angiotensin II), oxidative stress, cytokine storm, direct myocardial damage, hypoxia, shear stress, increased metabolic demand, decreased coronary blood flow with hypercoagulable environment, neuronal damage leading to dysfunction of cardiovascular centers, increased sympathetic activity, electrolyte imbalance, and drugs that increase the QT interval are responsible for cardiovascular dysfunction and consequent co-morbidity.[30] Post-discharge venous thromboembolic and arterial thromboembolic events can occur during and after COVID-19 hospitalization.[31,32] In our study, 5.6% of patients experienced venous or arterial thromboembolism after discharge from the hospital. Therefore, post-discharge anticoagulation is reasonable in high-risk patients.

Although some COVID-19 patients have underlying cardiovascular diseases that affect disease progression and outcome, those with advanced disease progression may develop new cardiovascular signs and symptoms or develop cardiovascular complications.[33,34] In our study, dyspnea and cardiovascular symptoms were more prevalent in patients with more severe disease and more comorbidities. These results suggest that patients with severe disease require post-discharge care. Studies with longer follow-up and larger populations are necessary to understand the full spectrum of the health consequences of COVID-19. These findings may provide evidence supporting long-term damage to the cardiovascular system from COVID-19. Further research investigating the long-term cardiac effects of COVID-19, therefore, is warranted.

Limitations of Study

Our study was limited by its single-center design and the relatively small number of patients. Moreover, patients in our study did not undergo respiratory function examination(s); as such, the specific degree of functional decline was not clear.

CONCLUSION

The current data demonstrated that persistent symptoms were common after COVID-19 among hospitalized patients.

The number and severity of ongoing symptoms were closely associated with disease severity during the acute phase. Although patient symptoms at 3 months decreased at 6 months, they continued. This should raise awareness among healthcare professionals regarding COVID-19 aftercare.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Health Sciences University, Bağcılar Training and Research Hospital, (Ethics Committee Approval Number #2021.02.1.02.023).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

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