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Coronavirus Pandemic

Clinical and imaging features of patients with COVID-19 in a double-center cohort study

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Abstract
Introduction: There is extensive published data on coronavirus disease 2019 (COVID-19). However, information on the effective factors that improve the pulmonary involvement of COVID-19 patients, and long-term clinical and imaging follow-up of these patients is limited.
Methodology: This is a prospective cohort study on patients with COVID-19 who were hospitalized in two major academic hospitals in Yazd, Iran. The correlation between the baseline demographic and clinical/para-clinical data with the imaging resolution status at day 60 was assessed.
Results: 122 patients, including 65 males, with an average age of 53.43 years participated in this study. Age, gender, baseline oxygen saturation (O_2Sat), and the percentage of lung involvement were the main prognostic factors. Our results suggest that with every year increase in age, the probability of complete imaging resolution decreases by 6.4%. In addition, women are 2.07 times more likely to recover completely. Moreover, each percent increase of baseline O_2Sat makes the patients 15.4% more likely to fully recover. As the patients' shortness of breath increases, the probability of recovery decreases by 9.8%.;56.7% of patients who did not recover after 60 days had persistent shortness of breath, while only 21% of those who recovered had symptoms of dyspnea after day 60.
Conclusions: Age, gender, baseline O_2Sat, percentage of lung involvement, and shortness of breath were identified as the main risk factors in the recovery of patients with COVID-19. Long-term follow-up of patients with COVID-19, especially patients with high-risk factors, is necessary.

Key words: COVID-19; follow-up; SARS-CoV-2; disease complications.

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Introduction
After three years, the coronavirus disease 2019 (COVID-19), seems to be shifting from pandemic to endemic. COVID-19 remains one of the biggest global problems. The World Health Organization (WHO) first declared the disease a pandemic on March 11, 2020. According to WHO, the total number of deaths (globally) attributed to the COVID-19 pandemic in 2020 was at least 3 million. Numerous research studies have been conducted to obtain more information on the disease. In 2002-2003, the severe acute respiratory syndrome coronavirus (SARS-CoV) resulted in death of 10% of the infected patients. Similarly, in 2012, the Middle East respiratory syndrome coronavirus (MERS-CoV) was a destructive pandemic that resulted in 37% of all deaths globally [1]. Complete genome sequencing and phylogenetic analysis showed that the novel coronavirus 2019 (nCoV-2019) is a beta-coronavirus and is associated with SARS and MERS [2]. COVID-19 has a high level of homology to SARS-CoV and may cause severe diseases like SARS [3].

Although all people are generally susceptible to the disease, the elderly and those with underlying diseases such as hypertension (HTN), diabetes mellitus (DM), and heart disease are at a much higher risk after infection [4,5]. Early progression of the disease can be very rapid and sometimes leads to severe respiratory distress syndrome, hospitalization in the intensive care unit (ICU, 26-32%), and death (4.3-15%). Symptoms of COVID-19 infection in the prodromal phase include nonspecific symptoms such as fever, dry cough, and weakness [2,4,6]. Symptoms that are less prevalent include sputum production, headache, bloody sputum, and diarrhea. Shortness of breath and pneumonia along with a series of abnormal findings on chest computerized tomography (CT) scans are common findings [7]. Imaging plays an important role in the diagnosis and evaluation of the disease [8,9]. Some patients may not have obvious symptoms; therefore, CT scans, and especially high-resolution computed tomography (HRCT) scans are valuable tools to identify such patients with nonspecific clinical symptoms of COVID-19 in the early stages [10,11]. Complications include RNAemia, acute respiratory distress syndrome, acute heart injury, and secondary infection [6]. Lymphopenia and elevated serum levels of aminotransferases are observed in most of the patients [12]. The final diagnosis is based on a positive real-time reverse transcriptase polymerase chain reaction (rRT-PCR) for the coronavirus [9,13,14].

Despite reduction in the incidence of COVID-19 due to mass population vaccination, severe cases of the disease are still seen, especially in unvaccinated individuals [15]. According to WHO, one billion people remain unvaccinated as of May 22, 2022. There are concerns about the recurrence of an outbreak; therefore, it is necessary to improve our understanding of COVID-19.

Although there is currently no specific treatment for COVID-19, many off-label medications are prescribed to control the disease and its complications [16]. The most commonly used drugs in moderate to severe COVID-19 during this pandemic are antiviral, anti-inflammatory, and anti-rheumatic agents, and immunoglobulins [17]. The results of some studies showed that the use of some drugs such as Remdesivir and anti-inflammatory drugs such as dexamethasone have improved the patients' outcomes [18]. Based on data from various trials, Remdesivir was approved for emergency use in the U.S. on March 1, 2020 [19-21].

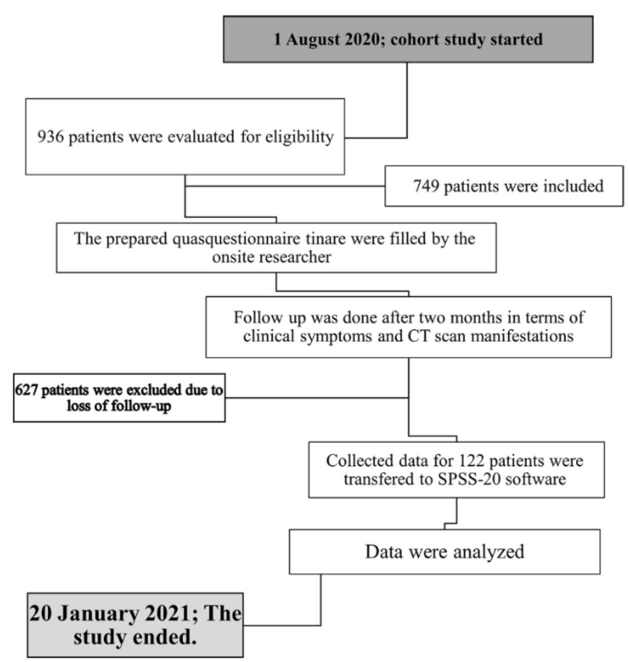
Although several studies have reported on clinical symptoms and early imaging manifestations in COVID-19 patients, there are limited studies on long-term clinical and imaging consequences and predictors of disease severity [22,23]. Previous studies in Iran have shown that Yazd province has the highest rate of diabetes in this country [24]. Diabetes is one of the main risk factors for the severity of COVID-19. Therefore, we decided to conduct this study on the long-term complications of COVID-19 on patients in Yazd province. This information is expected to help in planning for COVID-19 management. This study aimed to identify clinical and imaging consequences of COVID-19 patients admitted to the hospital and to identify factors involved in improving the clinical parameters and imaging manifestations.

Methodology

Patients

This double-center, prospective, cohort study was approved by the Research and Technology Department of Shahid Sadoughi University of Medical Sciences, Yazd, Iran (grant no. 7811). Ethical approval for this study was obtained from the ethics committee of Yazd University of Medical Sciences, and written informed consent was obtained from each patient (IR.SSU.REC.1399.156). Data were collected prospectively on patients with COVID-19 admitted to non-ICU wards in academic hospitals in Yazd, between August 1, 2020 and January 20, 2021. Eligible participants were adults aged 18 years or older, with COVID-19 infection confirmed by a positive result of the nasopharyngeal secretion reverse transcriptase polymerase chain reaction (RT-PCR) test (using the real-time PCR method with a Pishtazteb kit, Pishtazteb Company, Tehran, Iran) and clinical manifestations with typical imaging changes. Patients with a negative PCR test, as well as patients without written informed consent, were excluded from the study.

Figure 1. Flow chart of the study



CT: computerized tomography

Table 1. Demographics and baseline disease characteristics.

General data	**Overall (N = 122)**
Age, Mean (SD)	53.43 (15.270)
Gender, F (%)	
Male	65 (53.3)
Female	57 (46.7)
Location in Yazd city, F (%)	
District 1	36 (29.5)
District 2	10 (8.20)
District 3	20 (16.40)
District 4	18 (14.75)
District 5 (historical)	38 (31.15)
Comorbidities, F (%)	
DM	42 (34.4)
HTN	42 (34.4)
IHD	13 (10.7)
DLP	25 (20.5)
Asthma	2 (1.6)
COPD	11 (9.0)
Hypothyroidism	6 (4.9)
Rheumatoid arthritis	2 (1.6)
PMH, F (%)	
Yes	79 (64.8)
ARB	40 (32.8)
CCB	22 (18.0)
βB	15 (12.3)
Biguanides	19 (15.6)
Sulfonyl urea	19 (15.6)
Insulins	40 (32.8)
Thyroid hormone analog	8 (6.6)
Statins	23 (18.9)
Immunomodulators	5 (4.1)
Laboratory tests	
CRP at baseline, F (%)	
Negative	22 (18)
+	25 (20.5)
++	37 (30.3)
+++	38 (31.1)
ESR (Mean (SD))	43.70 (26.50)
CPK (Mean (SD))	225.38 (358.81)
LDH (Mean (SD))	532.67 (254.17)
WBC (Mean (SD))	7.83 (6.61)
NLR (Mean (SD))	4.94 (5.64)
RBC (Mean (SD))	4.82 (.78)
AST (Mean (SD))	40.93 (31.23)
ALT (Mean (SD))	43.88 (34.76)
ALP (Mean (SD))	197.24 (98.23)
Hgb (Mean (SD))	13.73 (1.92)
Signs and symptoms, F (%)	
Fever	83 (68.0)
Cough	84 (68.9)
Shortness of breath	94 (77.0)
Myalgia	68 (55.7)
Anorexia	23 (18.9)
Sputum	12 (9.8)
Weakness	55 (45.1)
Headache	25 (20.5)
Nausea and vomiting	31 (25.4)
O_2Sat, F (%)	
$O_2 < 88\%$	39 (32.0)
$93\% > O_2 \geq 88\%$	63 (51.6)
$O_2 \geq 93\%$	20 (16.4)
Body temperature, Mean (SD)	**37.39 (.74)**

N: number; SD: standard deviation; F: frequency; PMH: past medical history; DM: diabetes mellitus; HTN: hypertension; IHD: ischemic heart disease; DLP: dyslipidemia; COPD: chronic obstructive pulmonary disease; ARB: angiotensin receptor blocker; CCB: calcium channel blockers; βB: β blocker; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; CPK: creatine phosphokinase; LDH: lactate dehydrogenase; WBC: white blood cells; NLR: neutrophil-lymphocyte ratio; RBC: red blood cells; AST: aspartate transaminase; ALT: alanine transaminase; ALP: alkaline phosphatase; Hgb: hemoglobin; O_2Sat: oxygen saturation.

Study design

All patients meeting the inclusion criteria underwent anti-viral and anti-inflammatory therapies. Baseline demographic characteristics including age, gender, underlying comorbidities, initial clinical symptoms, laboratory data, and pulmonary involvement on chest HRCT scan were recorded in the questionnaire. Additionally, patients were evaluated in terms of shortness of breath according to the Modified Medical Research Council (MMRC) criteria. Cough, maximum body temperature during hospitalization (less or more than 38 °C), arterial oxygen saturation (SPO_2), ICU length of stay (LOS), and hospital LOS were recorded. The MMRC scale is a self-rating tool to measure the degree of dyspnea on day-to-day activities using a scale from 0 to 4 with 0 corresponding to no shortness of breath, except with strenuous exercise; 1, shortness of breath when hurrying on the level or walking up a slight hill; 2, walks slower than people of the same age on the level because of breathlessness or has to stop to catch a breath when walking at their own pace on the level; 3, stops for breath after walking ~100 m or after few minutes on the level; and 4, too breathless to leave the house, or breathless when dressing or undressing [25-27]. Treatments received, clinical responses, common drug side effects, and significant interactions observed during the treatment, were also recorded for all patients. Clinical symptoms and changes in HRCT (the degree of improvement or the subsequent sequela) were measured two months after hospital discharge.

Chest CT analysis

The evolution of chest CT images was analyzed at baseline and two months after hospital discharge. The score of lung involvement in CT scan imaging was explained using internationally standard nomenclature defined by the Fleischner Society glossary [1]. Pulmonary involvement scoring according to HRCT is based on two systems: 1) the percentage of general involvement from the radiologist's point of view; 2) total lobar scoring based on the percentage of involvement of each of the five lung lobes, which is calculated as follows: each of the 5 lung lobes are visually scored from 0 to 5; 0 for no involvement; 1, < 5% involvement; 2, 5-25% involvement; 3, 26-49% involvement; 4, 50-75% involvement; and 5 for > 75% involvement. The final score of each case was the sum of the individual lobar scores and represented as a range from 0 (no involvement) to 25 (maximum involvement) [28].

Sample size calculation

Given the importance of the degree of lung involvement in CT scans in this study and based on a similar study in Wuhan, China, in which bilateral involvement was at least 75%, a minimum sample size of 103 people was needed considering a 95% confidence level and 8% standard error, the sample size was calculated using the following equation:

$$n = \frac{z^2_{\left(1-\frac{\alpha}{2}\right)}\,(p)\,(1-p)}{E^2}$$

Eligible individuals were selected from the list of patients by simple random sampling.

Statistical analysis

Data analysis was done using the Statistical Package for the Social Sciences (SPSS) version 22 software. Descriptive statistics used included frequency, mean and standard deviation. Inferential statistics calculated included Pearson correlation coefficient, logistic regression analysis, and t-test with 95% confidence interval. Significant differences were defined at $p < 0.05$.

Results

Characteristics of patients

All 936 consecutively hospitalized patients with suspected COVID-19 between August 1, 2020 and January 20, 2021, were evaluated for eligibility. Among them, 84 patients had no desire to participate in the study and 103 patients did not meet the inclusion criteria; 19 were under 18 years old, 66 patients were admitted to ICU at the time of initial hospitalization and 18 patients had negative PCR tests.

A total of 749 patients participated in the study. The prepared questionnaires were filled out by the onsite researcher. The patients were followed up for clinical symptoms and CT scan manifestations after two

Figure 2. The total urban population distribution (A) and the COVID-19 incidence rate (B) in different districts of Yazd city.

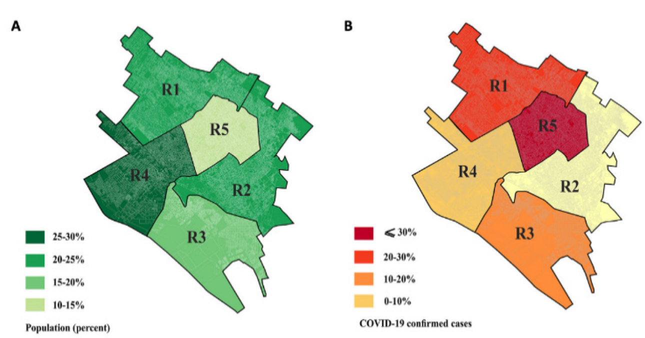


Table 2. Prescribed medicines for the treatment of COVID-19.

Parameters	Overall (N = 122)
Treatment, F (%)	
Hydroxychloroquine	77 (63.1)
Favipiravir	23 (18.9)
Remdesivir	28 (23.0)
Interferon β-1a	44 (36.1)
Tocilizumab	8 (6.6)
Colchicine	18 (14.8)
Lopinavir/Ritonavir	65 (53.3)
Corticosteroids	73 (59.9)
Convalescent plasma therapy	3 (2.5)
Observed side effects, F (%)	
Headache	5 (4.1)
Acute kidney injury	17 (13.9)
Elevated liver enzymes	16 (13.1)
Arrhythmia (AF/bradycardia)	16 (13.1)
Hematuria	3 (2.5)
Epigastric pain	1 (0.8)
Hypokalemia	1 (0.8)
Super infection	1 (0.8)
Edema	2 (1.6)
Hiccups	1 (0.8)
Significant drug interactions with increased risk of following adverse events, F (%)	
QTc interval prolongation	48 (39.3)
Coagulopathy	4 (3.3)
Serotonin syndrome	1 (.8)
Pharmacodynamic/pharmacokinetic interaction	14 (11.5)
Nothing	**55 (45.1)**

N: number; F: frequency; AF: atrial fibrillation.

months. Six hundred twenty-seven participants were excluded, out of which 34 were excluded due to death and 593 due to non-referral for clinical evaluation and imaging. Finally, 122 patients, including 65 males and 57 females, with an average age of 53.43 years participated in this study. A flow chart of the study is presented in Figure 1.

The baseline characteristics of the study population are shown in Table 1. The city of Yazd is the capital of Yazd Province. Yazd is located in the middle of Iran and has an area of about 108 km^2. This city has five municipality districts and a population of 529,673 people (based on the last national census in 2016). Although COVID-19 is a pandemic, the highest prevalence of patients with COVID-19 has been in the historical district of the city where the population density of Afghan immigrants and refugees is high (Figure 2). Overall, the most common underlying diseases were DM, HTN, and dyslipidemia (DLP) in 34.4%, 34.45%, and 20.55 of the patients, respectively. Seventy-nine (64.8%) patients had past drug history, most of which were insulins (32.8%), angiotensin receptor blockers (ARBs, 32.8%), and statins (18.9%). Elevated serum levels of C-reactive protein (CRP) were observed in 100 patients (81.9%). O_2Sat was reported to be between 88% to 93% in most patients (63, 51.6%). The mean body temperature (± standard deviation, SD) on the first day of administration was 37.39 (± 0.74) °C. The baseline characteristics of patients are shown in Table 1. The mean length (± SD) of hospital stay and ICU stay were 5.42 (± 2.76) and 2.34 (± 4.99) days, respectively.

Shortness of breath (94, 77.0%), cough (84, 68.0%), and fever (83, 68.0%) were the most reported clinical symptoms at baseline. After a mean of 60 days of follow-up, the most frequently reported persistent symptoms were fatigue and weakness (50.8%), dyspnea (38.5%), and hair loss (18.9%). Amnesia and insomnia were also reported as other persistent symptoms. Figure 3 presents the status of symptoms at baseline and day 60.

Table 2 lists the medicines used to treat COVID-19 patients. The most commonly prescribed drugs were hydroxychloroquine (63.1%), corticosteroids (59.9%), Lopinavir/Ritonavir (53.3%), and interferon β-1a (36.1%). Three patients required convalescent plasma therapy. As indicated, kidney and liver dysfunction and cardiovascular system diseases were the most common side effects of drugs, which were mostly related to antiviral drugs including Remdesivir, Favipiravir, Lopinavir/Ritonavir, interferon-β, and Tocilizumab. Considering the drug-drug interactions in the studied population and based on Lexicomp® and Medscape® drug interaction checker, 55.0 % of patients were exposed to at least one potential drug interaction. The increased risk of corrected QT for heart rate (QTc) interval prolongation was the most commonly observed drug interaction.

Table 3. Trends of changes in primary and secondary outcomes (N=122).

Variable	Baseline	Day 60	*p value*
O_2Sat, Mean (SD)	87.29 (7.09)	91.09 (9.15)	< 0.001
Percentage of lung involvement based on CT score, Mean (SD)	10.66 (6.45)	3.17 (4.60)	< 0.001
Percentage of general pulmonary involvement, Mean (SD)	27.95 (25.18)	7.24 (13.49)	< 0.001
Score of lung involvement ranges, F (%)			
0-8	54 (44.3)	107 (87.7)	
9-16	45 (36.9)	10 (8.2)	< 0.001
17-25	23 (18.9)	5 (4.1)	
Shortness of breath, F (%)			
Yes	94 (77)	47 (38.5)	0.88
No	47 (23)	75 (61.5)	
Shortness of breath based on MMRC criteria, F (%)			
Breathless with strenuous exercise	40 (32.8)	79 (64.8)	
Short of breath when hurrying or walking up a slight hill	30 (24.6)	24 (19.7)	
Has to stop for breath when walking at own pace	22 (18)	14 (11.5)	< 0.001
Stops for breath after walking 100 m or after a few minutes on the level	15 (12.3)	5 (4.1)	
Too breathless to leave the house	15 (12.3)	0 (0)	

N: number; F: frequency; O_2Sat: oxygen saturation; SD: standard deviation; CT: computed tomography; MMRC: Modified Medical Research Council.

Clinical outcomes

As mentioned in Table 3, assessment of resolution status according to lung involvement recovery indicated that 62 patients had complete resolution and 60 patients had incomplete resolution, including 18 patients with relative recovery lower than 50%, 34 patients with relative recovery more than 50%, and 8 patients with increased lung involvement. The mean baseline O_2Sat in the patients was 87.29% and changed to 91.09% at discharge time, which was significantly higher compared to the baseline ($p < 0.001$). Lung involvement was measured based on two systems of total lobar scoring and the percentage of general involvement, was significantly reduced on day 60 compared to the baseline ($p < 0.001$).

Shortness of breath was evaluated according to MMRC criteria in patients with dyspnea at baseline and day 60. MMRC grades in 40, 30, 22, 15, and 15 patients were 0, 1, 2, 3, and 4, respectively at baseline, whereas these changed to 79, 24, 14, 5 and 0 on day 60. This difference between baseline and day 60 was statistically significant ($p < 0.001$).

To conduct a more detailed analysis we assessed the correlation between different variables with resolution status (Table 4). Complete resolution in lung CT scan images was seen significantly in women compared with men ($p < 0.001$). The older the age and longer the duration of hospitalization in the ICU, the lower was the probability of a full recovery.

Figure 3. Trends of symptoms at baseline and day 60

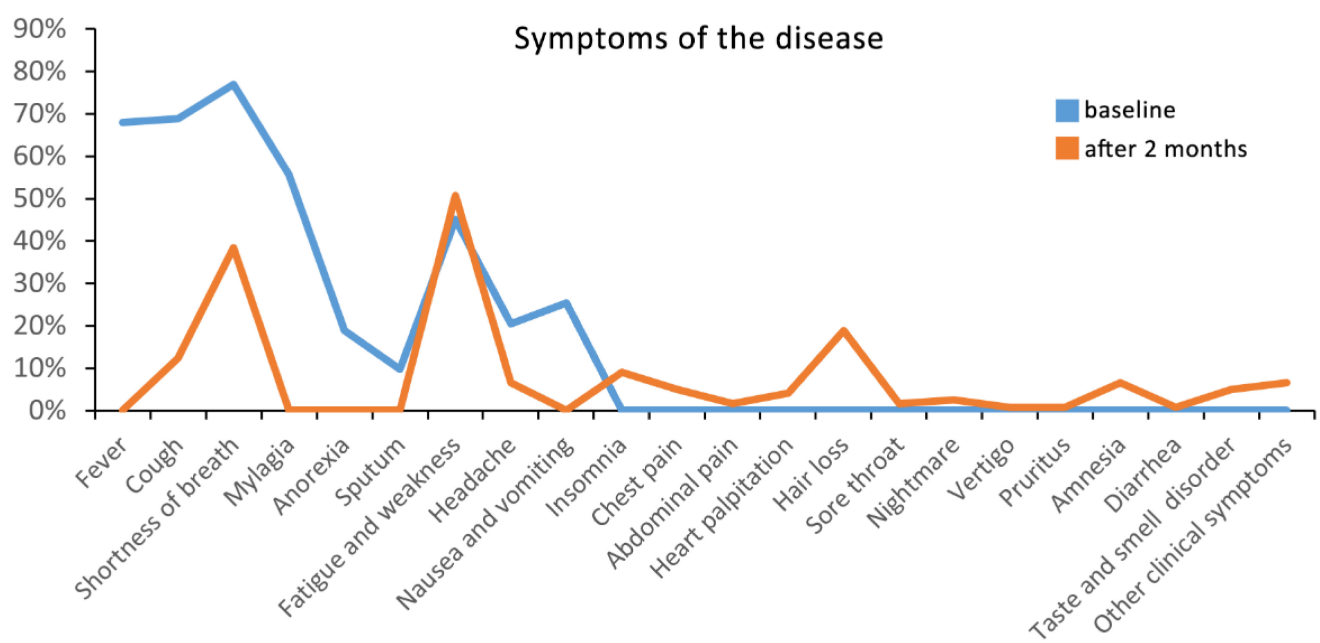


Table 4. Correlation between demographic and primary clinical data with imaging resolution status.

		Resolution status		Total	*p* value
		Complete resolution	**Incomplete resolution**		
Gender	Male	20	45	65	< 0.001
	Female	42	15	57	
Comorbidities					
Diabetes	Yes	21	21	42	0.896
	No	41	39	80	
Hypertension	Yes	20	22	42	0.608
	No	42	38	80	
Ischemic heart disease	Yes	6	7	13	0.722
	No	56	53	109	
Dyslipidemia	Yes	10	15	25	0.225
	No	52	45	97	
Asthma	Yes	2	0	2	0.161
	No	60	60	120	
COPD	Yes	3	8	11	0.101
	No	59	52	111	
Hypothyroidism	Yes	6	0	6	0.013
	No	56	60	116	
Rheumatoid arthritis	Yes	1	1	2	0.981
	No	61	59	120	
O_2 saturation ranges at baseline	$O_2 < 88\%$	10	29	39	0.001
	$93\% > O_2 \geq 88\%$	39	24	63	
	$O_2 \geq 93\%$	13	7	20	
Shortness of breath at baseline	Yes	43	51	94	0.040
	No	19	9	28	
Shortness of breath by MMRC criteria at baseline	Grade 0	27	13	40	0.016
	Grade 1	15	15	30	
	Grade 2	12	10	22	
	Grade 3	5	10	15	
	Grade 4	3	12	15	
Score of lung involvement at baseline	0-8	35	19	54	0.012
	9-16	20	25	45	
	17-25	7	16	23	
Type of intervention					
Hydroxychloroquine	Yes	40	37	77	0.744
Favipiravir		11	12	23	0.750
Remdesivir		12	16	28	0.337
Interferon beta 1a		17	27	44	0.043
Tocilizumab		1	7	8	0.025
Colchicine		11	7	18	0.344
Lopinavir/ritonavir		30	35	65	0.271
Convalescent plasma therapy		0	3	3	0.075
Significant drug interaction	↑QTc interval	22	26	48	0.112
	Coagulopathy	0	4	4	
	Serotonin-syndrome	0	1	1	
	Pharmacokinetic	7	7	14	
	Nothing	33	22	55	
CRP at baseline	Negative	15	7	22	0.008
	+	18	7	25	
	++	13	24	37	
	+++	16	22	38	
Percentage of general pulmonary involvement at baseline	0	0	0	0	.009
	< 25%	39	21	60	
	25-50%	16	27	43	
	> 50%	7	12	19	
Percentage of lung involvement based on CT score at day 60	0	61	1	62	< 0.001
	< 25%	1	45	46	
	25-50%	0	10	10	
	> 50%	0	4	4	

Table 4 (continued). Correlation between demographic and primary clinical data with imaging resolution status.

		Resolution status		Total	*p* value
		Complete resolution	Incomplete resolution		
Age	Mean (SD)	48.85 (14.33)	58.17 (14.86)	122	0.001
ESR at baseline		40.84 (28.16)	46.67 (24.56)	122	0.226
CPK at baseline		196.69 (347.38)	255.02 (370.84)	122	0.372
LDH at baseline		535.27 (292.15)	529.98 (210.32)	122	0.909
WBC at baseline		7.57 (7.52)	8.11 (5.57)	122	0.658
NLR at baseline		3.87 (3.91)	6.04 (6.85)	122	0.033
Hgb at baseline		13.33 (1.65)	14.14 (2.10)	122	0.019
RBC at baseline		4.79 (0.62)	4.84 (0.627)	122	0.738
AST at baseline		44.32 (39.86)	37.42 (18.25)	122	0.224
ALT at baseline		48.68 (44.97)	38.92 (18.40)	122	0.122
ALP at baseline		206.98 (117.18)	187.17 (73.41)	122	0.267
O2Sat at baseline		89.35 (4.93)	85.15 (8.30)	122	0.001
O_2Sat at discharge time		93.16 (3.06)	88.85 (12.31)	122	0.009
ICU length of stay		1.03 (4.45)	3.70 (5.18)	122	0.003
Hospital length of stay		5.18 (2.10)	5.67 (3.32)	122	0.331

COPD: chronic obstructive pulmonary disease; MMRC: Modified Medical Research Council; CR: complete recovery; RR: relative recovery; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; CPK: creatine phosphokinase; LDH: lactate dehydrogenase; NLR: neutrophil-lymphocyte ratio; WBC: white blood cells; Hgb: hemoglobin; O_2Sat: oxygen saturation; ICU: intensive care units.

CRP levels were positively correlated with the incomplete resolution, as were creatine phosphokinase (CPK), neutrophil-to-lymphocyte ratio (NLR), and hemoglobin levels ($p < 0.05$). Among the medications used in the treatment of COVID-19, ReciGen®, a biosimilar of IFN-β-1a, and Tocilizumab resulted in a reduction of radiologic signs of lung resolution.

Logistic regression was used to investigate the effect of contextual and clinical variables on the recovery process of patients with COVID-19. The forward likelihood ratio method was used to enter the variables into the model.

Hosmer and Lemeshow test (p value = 0.007) showed the model fit accuracy. By fitting the logistic regression model, the predictor variables were entered into the model in blocks in four stages, and the model was fitted. The results of the fourth stage of the model showed that the variables of age, gender, percentage of primary oxygen saturation, and lung involvement affected the recovery of patients with COVID-19. The results demonstrated that for each year increase in age, the probability of complete recovery of patients with COVID-19 decreased by 6.4%. Women were 2.079 times more likely to recover completely than men. In addition, with each percentage increase in the primary blood oxygen of patients, they were 15.4% more likely to fully recover. As patients' shortness of breath increased, the probability of recovery decreased by 9.8% (Table 5).

The relationship between shortness of breath and pulmonary involvement on day 60 was investigated. The results showed that there was a significant relationship between the existence of shortness of breath and MMRC grading in patients with pulmonary involvement ($p < 0.05$). The 56.7% of patients who did not recover had shortness of breath, while only 21% of those who recovered had symptoms of shortness of breath. Also, the grade of shortness of breath in 23.3% of unrecovered patients was more than 2, while only 8.1% of patients who fully recovered had shortness of breath with a grade of more than 2 (Table 6).

Discussion

Despite the publication of several studies on COVID-19, information on the factors that are effective in improving the pulmonary involvement of COVID-19 patients is limited. Based on previous studies, imaging changes were seen in the follow-up of patients with the older species of coronavirus such as SARS-CoV1 [29,30]. Studies on long-term clinical and imaging follow-up of COVID-19 patients are limited, and a few studies have reported on imaging changes in COVID-19 patients retrospectively [31,32]. In this study, in addition to examining the clinical features and CT scan scoring, we evaluated the correlation between demographic and primary clinical and paraclinical data with imaging resolution status, prospectively.

The major clinical symptoms observed at baseline included shortness of breath (77%), cough (68%), and fever (68%), which was consistent with previous reports [6,33,34]. This study showed that a high proportion of patients who were hospitalized due to COVID-19, had post-discharge persistent symptoms, especially fatigue and dyspnea. It is worth noting that studies have shown that patients with symptomatic COVID-19 had a lower maximal aerobic capacity at about 45-day follow-up than non-COVID-19 patients [35-36]. Although its pathophysiology is not yet fully understood, reduced maximal aerobic capacity is a sign of interstitial lung disease. Taken together, these studies

Table 5. Correlation between primary variables and imaging resolution based on logistic regression.

Variables	B (SE)	Odds ratio (OR)	*P-value*	95% CI for OR	
				Lower	Upper
Age	-0.066 (.019)	0.936	< 0.001	0.902	0.971
Gender[a]	3.079 (.615)	21.738	< 0.001	6.515	72.531
O_2Sat at baseline	0.143 (.047)	1.154	0.002	1.053	1.265
Total lobar scoring	-0.103 (.044)	0.902	0.019	0.827	0.983
Constant	-9.176 (4.101)	0.000	0.025	-	-

All the variables shown in table are -2loglikelihood = 104.765; χ^2 (4) = 64.330, *p value* < 0.001; Hosmer-Lemeshow statistics = 20.971 with df = 8, *p* value = 0.007. [a] = male.

suggest that pulmonary scarring may be responsible for shortness of breath, fatigue, and persistent cough in long COVID-19 [7,35,36]. It seems that incomplete resolution or even worsening of pulmonary involvement in HRCT scan led to gas exchange abnormalities and a sense of dyspnea in these patients.

The present study showed a high level of reported fatigue in post-discharge COVID-19 patients. This is in agreement with many studies including that of El Sayed *et al*. who pointed out that post-COVID-19 fatigue and anhedonia were prevalent in the post-COVID-19 period [37-39]. It has been stated that the increase in activity of inflammatory cytokines as well as the disturbance in gamma–aminobutyric acid may cause neuro psychomotor disorders and fatigue in patients [40-42]. Another common symptom reported after 60 days was hair loss, which can be attributed to secondary hair loss in response to a viral infection or the stress of hospitalization and illness [22]. In the two-month follow-up of the patients in our study, 8 patients complained of amnesia. Ritghie *et al.* [43] reported that coronavirus has the ability to cross the blood-brain barrier and can cause memory impairment in patients by damaging the hippocampus. These findings highlight the need for long-term follow-up of patients after discharge, so that necessary intervention can be performed to eliminate the remaining sequel in a timely manner.

In this study DM and HTN were the most common comorbidities, followed by DLP and ischemic heart disease, which is inconsistent with other studies [44,45]. Considering complete and incomplete imaging resolution, the relation between DM, HTN, and resolution was not significant. Another subgroup analysis of incomplete resolution (relative recovery > 50%, relative recovery < 50%, and increased lung involvement) showed significant differences in the relation between DM and HTN and resolution status, which is inconsistent with the findings of In-Kyung *et al.* [46]. HTN and diabetes in the context of metabolic syndrome create a hyperinflammatory state that leads to a cytokine storm associated with the severity of COVID-19 [47]. In fact, it is shown that patients with DM and HTN had worse prognoses.

Understanding drug interactions and side effects is of particular importance because patients with COVID-19 admitted to the hospital received a wide range of antibiotics, anti-viral and anti-inflammatory drugs. The risk of drug interactions or side effects should not preclude the use of experimental therapy for patients with COVID-19, as they can often be controlled and are not always problematic. In fact, it is possible to stop prescribing all unnecessary drugs to minimize serious drug interactions and side effects when prescribers are aware of the potential risks of these interactions and side effects. Our study showed that renal and hepatic dysfunction, and cardiovascular disease were the most common side effects of medications received by patients, even in patients who had no underlying disease. Therefore, it is recommended that COVID-19 patients with/without underlying cardiovascular, liver, and kidney diseases should be monitored for drug side effects. It should be noted that monitoring of these common adverse effects in COVID-19 patients who suffered from underlying renal, hepatic, or cardiovascular disease is even more important [48]. This is in parallel with Aygun *et al.* who reported that the hematopoietic system and the cardiovascular system are exposed to more side effects than other organs [49].

The most significant drug-drug interaction identified in our study was QTc interval prolongation. That is why it is necessary to further investigate cardiovascular patients in terms of drug interactions. Of course, considering the benefits of new therapies over existing drug interactions and side effects is something that must be balanced. One of the recommendations for better monitoring of these cases is the effective presence of a clinical pharmacist in the wards and examination of patients, especially polypharmacy and comorbid patients, in terms of side effects and drug interactions.

In the current study, during follow-up of patients, it was found that almost half of the patients (49.1%) still had some degree of involvement in the CT scan after

Table 6. Correlation between dyspnea score on day 60 with imaging resolution.

	Resolution status		*p* value
	Complete n (%)	**Incomplete n (%)**	
Shortness of breath			
yes	13 (21)	34 (56.7)	**< 0.001[a]**
no	49 (79)	26 (43.3)	
MMRC grading			
Grade < 2	57 (91.9)	46 (76.7)	**0.020[a]**
Grade ≥ 2	5 (8.1)	14 (23.3)	

[a]: Chi-squared test.

two months. This finding is consistent with previous studies, which showed significant imaging involvement remained in a large number of the study population [31,32].

This study aimed to determine whether we could use the initial clinical, imaging, and laboratory data to predict whether patients would improve after 60 days follow-up with CT scans or not. The analysis showed that older age, male gender, having initial shortness of breath, higher grade of shortness of breath by MMRC criteria, higher CT scan score or percentage of lung involvement, lower initial O_2Sat percentage, higher ranges of CRP and NLR and more days of hospitalization in ICU have a significant relationship with incomplete resolution at 60 days follow-up of patients. To the best of our knowledge, "cytokine storm", which is one of the causes of mortality and complications associated with COVID-19 disease, is due to inflammation caused by a viral infection and an increase in inflammatory biomarkers like CRP. Along with the cytokine storm, lymphopenia is an important factor in the greater severity of COVID-19 [50-52]. In the study by Tu Haitao *et al.,* it was shown that most of the biomarkers tested for the risk of infection and the severity of COVID-19 differed based on gender. Men were significantly more likely to have severe consequences of coronavirus disease, including higher mortality than women. This was possibly due to genetic factors, hormonal factors, and gender differences in the biological pathways associated with COVID-19 [50]. These results were in line with our study.

In the current study increased NLR levels were positively correlated with incomplete resolution. NLR plays a prognostic role in several inflammatory diseases and it can be a useful marker for predicting poor prognosis in hospitalized patients [53-55]. According to the study by Jimeno *et al*., endothelial damage that activates the pro-inflammatory cascade and releases cytokines can increase the chemotaxis of inflammatory cells, including neutrophils, which leads to increased NLR. Therefore, the higher the NLR, the more severe the disease [53].

Kalil *et al.* reported that the combination of interferon beta-1a and Remdesivir was not superior to Remdesivir alone in hospitalized COVID-19 patients. However, in the subgroup of patients who initially required high-flow oxygen, treatment with interferon beta-1a was associated with more side effects and worse outcomes than the placebo [18], which is in line with our study.

In multivariable logistic regression, age, gender, percentage of O_2Sat, and the score of lung involvement at baseline were significantly associated with imaging resolution of COVID-19 patients. The results show that for each year increase in age, the probability of complete recovery of patients with COVID-19 decreases by 6.4%. In line with this, several studies show bilateral lung involvement to be more common in older adults [23,56,57].

The present study demonstrates a significant difference in the imaging resolution of COVID-19 patients with gender differences so that women are 2.079 times more likely to recover completely than men. The reasons for these gender differences seem to stem from genetic, immunologic, and social differences between men and women [58]. Higher expression of the angiotensin-converting enzyme 2 (ACE2) gene in men, possibly due to the gene being located on chromosome X, makes men more susceptible to SARS-CoV-2 virus infection, since ACE2 receptor is the entry point for the SARS-CoV-2 coronavirus [59]. Although we did not assess the distribution of lesions across the lung space, our findings are compliant with Moradi *et al.* on related issues [60].

For each percentage increase of primary O_2Sat in patients, they were 15.4% more likely to fully recover. A study by Aalinezhad *et al.* showed that there was a significant reverse relationship between CT severity score and oxygen saturation which is in line with our findings of higher CT severity scores in patients with hypoxia [60].

In our study, as the patients' shortness of breath increased, the probability of recovery decreased by 9.8%. We also investigated shortness of breath after 60 days and its relationship with lung involvement. The results indicate that persistent shortness of breath after 60 days can be considered a clinical sign associated with pulmonary involvement. On the other hand, patients who had higher O_2Sat at baseline and discharge time had significantly higher odds of a better clinical status resolution on chest CT scan evaluation. Patients with a higher grade of MMRC at baseline were significantly more likely to not have complete resolution. The lower the pulmonary involvement at baseline, the more likely the patients were to fully recover. We recommend that during the follow-up of patients, shortness of breath be considered as a clinical criterion for performing a CT scan and further evaluation of lung involvement.

One of the study's limitations was that critical patients in ICU wards were not included. Another limitation of the study was that due to the prevalence of different variants during the study period and the impossibility of accessing and evaluating patient samples in terms of variants in Iran, it was not possible to investigate the effect of the type of variant on the severity of the disease and its long-term complications.

Conclusions

In conclusion, this study has demonstrated that significant imaging abnormalities are still observed two months after discharge. Some clinical and paraclinical factors including gender, age, percentage of O_2Sat, and score of lung involvement can be used to predict the improvement of patients' imaging. Thus, in patients with COVID-19, especially those with alterations of specific factors at the baseline, a long-term follow-up in terms of clinical evaluation and imaging is necessary.

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Authors' contributions

FS and MGJ: conception and design of the study; MN and SM: collected the data; SM and MM: worked on the statistical analysis. All authors helped with the preparation of the manuscript. All authors read and approved the final manuscript.

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