

Isfahan COVID cohort study: Rationale, methodology, and initial results

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Background: The Isfahan COVID Cohort (ICC) study was designed to investigate the short- and long-term consequences of patients with COVID-19 in Iran. This report presents the rationale, methodology, and initial results of ICC. **Materials and Methods:** ICC is a 5-year multicentric prospective cohort study that is ongoing on two groups including 5000 patients hospitalized with moderate or severe and 800 nonhospitalized patients with mild or asymptomatic COVID-19 in Isfahan. The ICC endpoints are morbidity, mortality, incident cases, or worsening of underlying noncommunicable diseases (NCDs) and their risk factors. In the current analysis, we examined the persistent symptoms and incident NCDs or risk factors in 819 previously hospitalized patients who completed 1-year follow-up. **Results:** The two most common symptoms were joint pain/myalgia (19.7%) and dry cough/dyspnea (18.7%). Around 60% of patients had at least one symptom which was more common among women than men and in middle aged than younger or older patients. Female (odds ratio [OR] =1.88, 95% confidence interval [CI]: 1.39–2.55) and highly-educated patients (OR = 2.18, 95% CI: 1.56–3.04) had higher risk of having any symptom in 1-year follow-up. New cases of hypertension followed by diabetes then coronary heart disease (CHD) were the most common incident NCDs. **Conclusion:** During 1-year follow-up after hospital discharge, about 60% of patients experienced persistent symptoms. Incident hypertension, diabetes, and CHD were the most common events seen. Close monitoring and extensive health services with integrative approaches are needed to improve the health status of these patients.

Key words: COVID-19, morbidity, mortality, outcome, prospective cohort study, symptom

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INTRODUCTION

COVID-19 pandemic is a new unexpected health system challenge to our world,^[1] which is encountered with another epidemic of noncommunicable diseases (NCD).^[2] Evidence have shown that NCDs can predict poor prognosis in patients with COVID-19.^[3] Recent meta-analysis indicated that hypertension, chronic respiratory disease (CRD), and cardiovascular disease (CVD) were associated with severe COVID-19.^[3] Another meta-analysis including 3403 COVID-19 patients revealed that the most prevalent comorbidities in patients with COVID-19 were hypertension 16.4%, CVD 12.1%, and diabetes mellitus (DM) 7.9%.^[4]

Previous reports from SARS and MERS infection which shares considerable similarity with COVID-19 have shown that among patients who had recovered from SARS, 68% continued to have abnormalities of lipid metabolism at 12-year follow-up; cardiovascular (CV) abnormalities were present in 40% and altered glucose metabolism in 60%.^[5,6] Similar findings have also been reported in patients recovering from other respiratory tract infections.^[5,6]

Long-term health consequences of COVID-19 remain largely unclear after recovery of this illness. There are not sufficient data available about the immunity after recovery from COVID-19 that might confer immunity against reinfection.^[7] Excess death in a crisis-related period compared to expected death rate in nonpandemic period of time can be attributed to COVID-19, but it has been reported as mortality from ischemic heart disease, stroke, and chronic obstructive pulmonary disease.^[8,9] Moreover, several studies have been reported the many people complaint from the long COVID or postacute COVID symptoms. However, the mechanisms, severity, and duration of sequelae remain largely unknown. Different types of symptoms may occur following COVID such as fatigue, dyspnea, bone and joint pain, arthralgias, physical decline, myalgia, chest pain, hair loss, cough, anosmia, ageusia, difficulty in concentration, decreased appetite, headaches, difficulty in sleeping, smelling disorders, pain with deep breaths, memory loss, confusion, psychological distress, fever, and dizziness. However, these symptoms have been reported in studies with small sample size and short follow-up.^[10-12] Hence, it seems that we are facing the beginning of a new era in public health in which communicable disease and NCDs meet together and we need to gather more data specifically from longitudinal studies with longer follow-up and sufficient sample size to develop new models for best management, diagnosis, treatment, and rehabilitation of patients worldwide.

The Isfahan COVID Cohort (ICC) study has been designed to investigate the short- and long-term morbidity, consequences

occurrence of new or worsening of NCDs and their risk factors, and mortality of patients hospitalized with moderate or severe COVID-19 as well as mild or asymptomatic cases in the community. All patients at any level of severity will be followed for 5 years. The current report aims to present the whole methodology of ICC study and some initial results of hospitalized patients in 1-year follow-up.

MATERIALS AND METHODS

Design and participants

This is a 5-year multicentric prospective, longitudinal cohort study that is ongoing on two groups of patients including hospitalized with moderate and severe COVID-19 in all hospitals and patients with mild or asymptomatic COVID-19 in Isfahan urban and rural areas in Iran. Basically, we designed this cohort study with a 5-year follow-up; however, we got the funds and approval to perform it with 3 years of follow-up; thus, we are continuing our trials to raise fund and extend our follow-up to 5 years. Using consequent sampling method, we are recruiting 5000 hospitalized patients with COVID-19 and 800 mild and asymptomatic subjects. Figure 1 shows the study flowchart.

All patients who were discharged from hospitals were invited to 80 health centers located in urban and rural areas in Isfahan. The interim guidance of the World Health Organization (WHO) has been used to diagnose COVID-19^[13] and for hospitalization. Therefore, patients with positive result of reverse transcription-polymerase chain reaction (RT-PCR) and have been hospitalized if they have been diagnosed as having severe or moderate symptoms such as respiratory rate > 30 breaths per minute, oxygen saturation <94% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) <300 mmHg, or lung infiltrates >50%.^[13] Those who died after discharge and before recruitment in our study will undergo verbal autopsy Figure 1.

In addition, we are recruiting those who have been referred to health centers because of a new experience of mild symptoms of COVID-19 or have been exposed to someone with COVID-19 and are asymptomatic but have positive results of RT-PCR test for coronavirus.^[13] We did not consider limitations such as age, sex, pregnancy, or lactation and our recruitment started since March 10, 2020. Our exclusion criteria were hospitalized patients before March 10, 2020, and patients who did not have a RT-PCR test for COVID-19 or negative test results of RT-PCR.

To date, we have recruited 3040 hospitalized patients in our cohort study but followed 819 of them for 1 year by

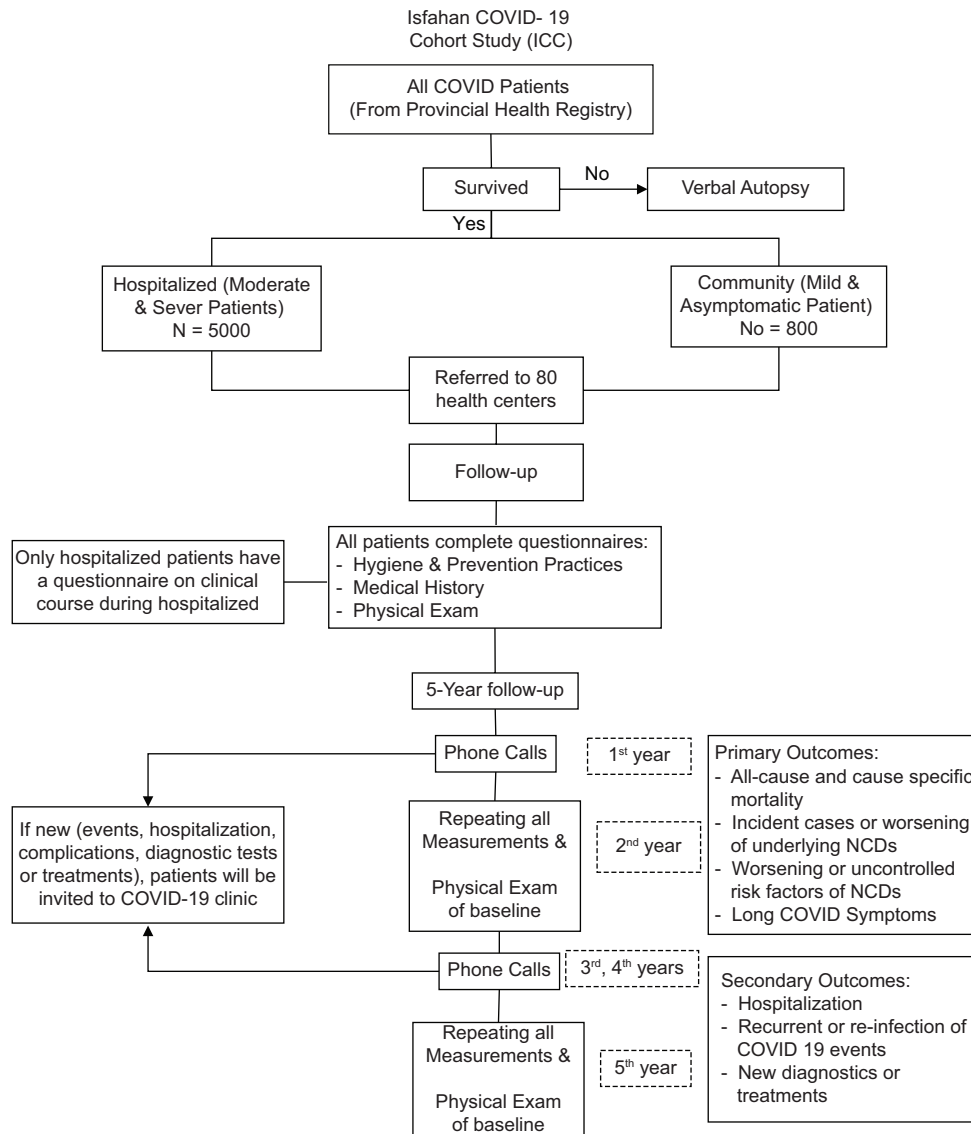


Figure 1: Flowchart of study in both hospitalized and mild

phone calls. We will continue recruiting until reaching our complete samples in both groups. For the baseline phase of this cohort study, we obtained patients' address and phone numbers from the Integrated Health System (SIB) dataset in health centers and contacted them to attend health centers with all their previous medical documents related to the period of time before and after their hospitalization for COVID-19. Upon arrival to the health centers, we explained the whole study and follow-up and obtained consent forms from all patients. Then, we completed three types of questionnaires including demographic and socioeconomic, prevention, and hygiene; lifestyle behaviors and practices; and clinical course during hospitalization. In addition, we completed medical history and did complete physical examination for each patient during their presence in health centers. This study was approved by the Ethics Committee of Isfahan University of Medical Sciences (IUMS) (No: IR.MUI.MED.REC.1399.223).

Data collection

Demographic, socioeconomic, hygiene and prevention practice questionnaires

First, data regarding demographic and socioeconomic status were collected. Other questions in our first questionnaire were on participants' knowledge and practice before and after hospitalization for COVID-19 regarding quarantine, social distance, wearing masks, disinfecting surfaces, cloths, and methods of disinfection. We also asked patients on their considering hygiene recommendations in work place and shopping, as well as their information on the source of COVID-19 transmission and how they were infected, etc. Trained staff of health center have completed our online questionnaire.

Lifestyle behavior questionnaire

Using a valid and reliable questionnaire as ICC second questionnaire, we examined lifestyle characteristics including

smoking, dietary habits, alcohol use, psychological factors, physical activity, and drug abuse. We assessed dietary habits using a validated food frequency questionnaire,^[14] mental health status using a validated Persian version of hospital anxiety and depression scale^[15] and perceived stress scale,^[16] tobacco smoking habits using global adult tobacco survey questionnaire which was designed by the Centers for Disease Control and Prevention and WHO,^[17] drug abuse using a validated questionnaire in Iran,^[18] and physical activity using international physical activity questionnaires.^[19] All questionnaires were completed online by interviewers who were trained on how to complete online questionnaires.

Medical history and physical examination questionnaire

In our third questionnaire, all medical history related to the time before or after hospitalization for COVID-19 on the existence of NCDs including CVD such as coronary heart disease (CHD), hypertension, CRD, DM, cancers, and chronic kidney disease (CKD) as well as previous history of all medicines used for these NCDs and their risk factors have been obtained by interviewing patients in health centers. If patients indicate any other NCD or medicines used that have not been included in our questions, it was added to the questionnaire. In addition, persistent COVID symptoms or any new symptoms were asked during follow-ups. The medical history was completed by trained health centers' general practitioners (GPs).

GPs in health centers performed general physical examinations and completed our checklists. If patients develop new sign and symptoms after discharge from hospitals, they were referred by GPs to our COVID-19 clinic and internal medicine specialist visited them. GPs in health centers have informed all patients to attend this clinic if they face any problem after their baseline examination and during the 5 years of follow-up.

Anthropometric and blood pressure measurements

Trained staff in health centers measured anthropometric variables that consist of height, weight, waist, hip, and neck circumferences (NCs), while GPs measured the patients' blood pressure. Body weight was measured using a standard digital scale and recorded to the nearest 0.5 kg. Height was measured using an inelastic tape measure and recorded to the nearest 0.5 cm.^[20] Body mass index was calculated by dividing weight (Kg) to height (m) square. Waist circumference was measured at the approximate midpoint between the lower margin of the last palpable rib and the top of the iliac crest, and hip circumference measurement was taken around the widest portion of the buttocks using an inelastic tape to the nearest 0.1 cm, respectively.^[21] The NC was measured below the cricoid cartilage, at the level of the midcervical spine.^[22]

For blood pressure measurements, participants have been asked to avoid any severe physical activity, eating and drinking any type of liquids (except for water), smoking, and consuming any medicine which affects blood pressure at least 1 h before the measurement. Using an OMRON barometer, the blood pressure was measured by trained nurses while participants were sitting and rested at least for 5 min before measurement. Measurements were done twice from each arm, and the mean value of all measurements was recorded as the final value for blood pressure.^[23]

Questionnaire on clinical course during hospitalization

Another questionnaire which is the 4th one in ICC study was developed to study the hospitalization clinical course and was completed using the patients' medical records in hospitals. There have been questions that cover all clinical findings, patients' outcomes and signs of severity, need for mechanical ventilation and transfer to intensive care unit, medicines used, lab tests, comorbidities such as underlying NCDs, length of hospitalization in different units, and reasons for transferring patients to different units. These data were collected by trained nurses in each COVID-19 referral hospital.

Blood sample collection

A blood sample was obtained to from each participant to test immunoglobulin (Ig) G and IgM. All blood samples were transferred to the Isfahan Cardiovascular Research Institute laboratory, which is a WHO Collaborating center in the Eastern Mediterranean Region (EMR). In addition, we collected whole blood samples and stored it in -80°C freezers for future studies including genetic or epigenetic ones.

Follow-ups

At the end of 6 months of basic visits to health centers, patients were contacted, then on annual basis until 5 years. Our staff had called all participants asking for their symptoms, new events or worsening of the underlying NCDs or risk factors that they had during their hospitalization, new diagnostics or treatment approaches, and reinfection. If participants report any of the above, they were invited to our COVID-19 clinic for further investigations. Patients are visited by an internal medicine specialist in this clinic, if the internist needs further investigation by other subspecialty, he could refer them to different subspecialty physicians to perform complementary diagnostic tests such as electrocardiography, echocardiography, fitness test, spirometry, renal or liver function tests or ultrasound among others. Furthermore, all patients were provided by the COVID-19 clinic phone numbers to contact our staff if they face any medical problem, hospitalization, new diagnostic tests, or treatments in the period of time between our 5 annual follow-ups [Figure 1].

At the end of the 5th year of follow-up, all baseline measurements will be repeated using the same tools such as questionnaires and the same process as of the baseline study. If any new event happens during the 5-year follow-up, a panel including 3 specialists in the field of the event and related fields would examine and study the patient documents and decide on final diagnosis.

Outcomes

Primary outcomes

They include all-cause and cause-specific mortality, incident cases or worsening of underlying NCDs and their risk factors, as well as persistent symptoms or any new symptom following COVID-19.

Secondary outcomes

Any hospitalization and new diagnostic or treatment prescribed to the patients will be investigated. Furthermore, reinfection of COVID-19 or the occurrence of other infectious diseases, will be considered [Figure 1].

Statistical analysis

We utilized SPSS Statistics for Windows, version 25 (SPSS Inc., Chicago, Ill., USA). We presented continuous variables as means and standard deviations (SDs) and categorical variables including as frequency and percentages. The logistic regression was used to estimate the odds ratio (OR) (95% confidence interval [CI]) (OR [95% CI]) of long COVID symptoms by adjusting for age (year), sex (male/female), education (middle school or lower/high school or university), and smoking (ever smoker/nonsmoker). $P < 0.05$ was considered statistically significant.

RESULTS

General characteristics of the patients based on sex are shown in Table 1. The mean age was 56.7 ± 14.3 years. The majority of subjects (almost 80%) aged over 45 years and this proportion was almost identical between men and women. Women had lower educational level compared to men. The prevalence of smoking was 3.9%, 6.1%, and

Table 1: Basic characteristics according to sex

	Overall (n=819), n (%)	Men (n=489), n (%)	Women (n=330), n (%)
Age (years), mean±SD	56.7±14.3	57.5±14.1	55.6±14.6
Age group (years)			
<45	168 (20.5)	91 (18.6)	77 (23.3)
45–60	317 (38.7)	189 (38.7)	128 (38.8)
>60	334 (40.8)	209 (42.7)	125 (37.9)
Education			
Middle school or lower	464 (56.7)	249 (50.9)	215 (65.2)
High school or university	355 (43.3)	240 (49.1)	115 (34.8)
Smoking status			
Never smoker	728 (88.9)	403 (82.4)	325 (98.5)
Current smoker	32 (3.9)	30 (6.1)	2 (0.6)
Former smoker	59 (7.2)	56 (11.5)	3 (0.9)
Alcohol use	27 (3.3)	24 (4.9)	3 (0.9)
Underlying NCD			
DM	226 (27.6)	136 (27.8)	90 (27.3)
Hypertension	316 (38.6)	172 (35.2)	144 (43.6)
CHD	152 (18.6)	98 (20.0)	54 (16.4)
CRD	63 (7.7)	40 (8.2)	23 (7.0)
Cancer	24 (2.9)	13 (2.7)	11 (3.3)
CKD	36 (4.4)	21 (4.5)	15 (4.2)
Any NCD	359 (56.2)	216 (55.8)	143 (56.7)
Hospitalization			
Length of hospitalization (days)			
Mean±SD	6.7±5.2	7.0±5.1	6.4±5.3
Median (minimum–maximum)	5 (2–21)	6 (2–18)	5 (2–21)
ICU admission	81 (9.9)	49 (10.0)	32 (9.7)
Length of ICU stay (days)			
Mean±SD	5.5±3.7	5.8±3.9	5.1±3.6
Median (minimum–maximum)	5 (2–12)	5 (2–12)	5 (2–11)
Mechanical ventilation	13 (1.6)	8 (1.6)	5 (1.5)
O ₂ saturation<93%	515 (62.9)	314 (64.2)	201 (60.9)

SD=Standard deviation; ICU=Intensive care unit; DM=Diabetes mellitus; CHD=Coronary heart disease; CRD=Chronic respiratory disease; CKD=Chronic kidney disease; NCD=Noncommunicable disease

0.6% in total, men, and women, respectively. Alcohol was consumed by 3.3% of participants, particularly in male patients (4.9%). The distribution of underlying NCDs during hospitalization was similar between men and women. The first prevalent disease was hypertension (35.2% in men and 43.6% in women), followed by DM (27.8% in men and 27.3% in women), CHD (20.0% in men and 16.4% in women), and CRD (8.2% in men and 7.0% in women). Cancer and CKD were present in a smaller fraction of our study population.

On average, the duration of hospitalization was 6.7 ± 5.2 days, which did not differ considerably between men and women. Although the need for mechanical ventilation was similar between men and women, suffering from low O_2 saturation was higher among men.

Table 2 reveals the prevalence of various postdischarge symptoms after 1-year follow-up of hospitalized patients with COVID-19. The first and second most common symptoms were joint pain or myalgia and dry cough or dyspnea, with a prevalence of 19.7% and 18.7%, respectively. In addition, 14.7% reported hair loss and either

fatigue or muscle weakness (11.7%). The prevalence of other symptoms was around of 6% or less. The order of prevalent symptoms in men was dry cough or dyspnea followed by joint pain or myalgia. In women, however, the first symptom was hair loss, which affected almost one-fourth of the total sample followed by joint pain or myalgia then dry cough or dyspnea and the last was fatigue or muscle weakness. Around 40% of patients had no symptoms in 1-year of follow-up, of which a larger proportion of men experienced no symptoms compared to women (45.8% vs. 33.6%).

Further analysis for the prevalence of various symptoms according to the age groups revealed that middle-aged patients experienced any of the reported symptoms more than younger (≤ 45 year) and older (> 60 year) patients. In other words, two-thirds of middle-aged subjects had at least one symptom in 1-year follow-up, while this figure was 60% and 50% in young and older patients, respectively [Table 2]. Having two symptoms or more was similar in all three age groups. The first two prevalent symptoms in middle-aged were dry cough or dyspnea and joint pain or myalgia which affected almost one in four and they were 14.1%,

Table 2: Occurrence of symptoms in 1 year follow-up of hospitalized patients with COVID-19 according to sex and age groups

Symptom	Overall (n=819), n (%)	Gender		Age group (years)		
		Men (n=489), n (%)	Women (n=330), n (%)	<45 (n=168), n (%)	45-60 (n=317), n (%)	>60 (n=334), n (%)
Fatigue or muscle weakness	96 (11.7)	38 (7.8)	58 (17.6)	21 (12.5)	47 (14.8)	28 (8.4)
Dry cough or dyspnea	153 (18.7)	88 (18.0)	65 (19.7)	27 (16.1)	79 (24.9)	47 (14.1)
Sleep difficulties	2 (0.2)	1 (0.2)	1 (0.3)	1 (0.6)	1 (0.3)	0 (0)
Hair loss	120 (14.7)	42 (8.6)	78 (23.6)	39 (23.2)	52 (16.4)	29 (8.7)
Smell disorder	11 (1.3)	6 (1.2)	5 (1.5)	3 (1.8)	7 (2.2)	1 (0.3)
Palpitations	42 (5.1)	19 (3.9)	23 (7.0)	17 (10.1)	17 (5.4)	8 (2.4)
Joint pain or myalgia	161 (19.7)	86 (17.6)	75 (22.8)	29 (17.3)	79 (24.9)	53 (15.9)
Decreased appetite	10 (1.2)	6 (1.2)	4 (1.2)	1 (0.6)	4 (1.3)	5 (1.5)
Taste disorder	5 (0.6)	2 (0.4)	3 (0.9)	3 (1.8)	2 (0.6)	0
Dizziness	26 (3.2)	17 (3.5)	9 (2.7)	4 (2.4)	15 (4.7)	7 (2.1)
Ear problems	9 (1.1)	5 (1.0)	4 (1.2)	0	4 (1.3)	5 (1.5)
Ocular problems	22 (2.7)	14 (2.9)	8 (2.4)	4 (2.4)	10 (3.2)	8 (2.4)
Chest pain	21 (2.6)	11 (2.2)	10 (3.0)	3 (1.8)	13 (4.1)	5 (1.5)
Sore throat, difficult to swallow, xerostomia or sputum production	10 (1.2)	8 (1.6)	2 (0.6)	2 (1.2)	8 (2.5)	0
Skin rash and pruritus	18 (2.2)	11 (2.2)	7 (2.1)	6 (3.6)	7 (2.2)	5 (1.5)
Headache	47 (5.7)	29 (5.9)	18 (5.5)	9 (5.4)	24 (7.6)	14 (4.2)
Gastrointestinal disorders	58 (7.1)	33 (6.7)	22 (7.6)	9 (5.4)	26 (8.2)	27 (6.9)
Renal disorders	11 (1.3)	8 (1.6)	3 (0.9)	1 (0.6)	3 (0.9)	7 (2.1)
Low grade fever	30 (3.7)	14 (2.9)	16 (4.8)	4 (2.4)	14 (4.4)	12 (3.6)
Mental health problems	51 (6.2)	24 (4.9)	27 (8.2)	14 (8.3)	20 (6.3)	17 (5.1)
Body tremor or tingling	11 (1.3)	6 (1.2)	5 (1.5)	4 (2.4)	4 (1.3)	3 (0.9)
Any one of the following symptoms	484 (59.1)	265 (54.2)	219 (66.4)	104 (61.9)	213 (67.2)	167 (50.0)
Number of symptoms						
0	335 (40.9)	224 (45.8)	111 (33.6)	64 (38.1)	104 (32.8)	167 (50)
1	219 (26.7)	133 (27.2)	86 (26.1)	49 (29.2)	112 (35.3)	58 (17.4)
≥ 2	265 (32.1)	132 (27)	133 (40.3)	55 (32.7)	101 (31.8)	109 (32.6)

and 15.9% in older patients, respectively. The figure for the young age group were 16.1% and 17.3%, respectively. In contrast, the first common symptom in the young was hair loss, affecting around one-fourth, and 16% and 9% of middle-aged and older patients, respectively. Older patients than that of for two other age groups was more susceptible renal disorders (2.1% in the old, 0.9% in the middle-aged, and 0.6% in the young). In men, the frequency of one and at least two symptoms was approximately equal (27%). However, in women, the proportion of patients with two symptoms and over was higher and about 40%.

The occurrence of various outcomes during 1 year of follow-up in hospitalized patients with COVID-19 stratified by sex is shown in Table 3. New incident cases of CHD, DM, and hypertension were seen in 2.4%, 3.2%, and 4.4% of patients in 1-year follow-up, respectively. A smaller proportion of our studied population developed CRD (1.1%) or stroke (0.1%). In addition, while 1.2% of women were hospitalized due to any reason, only 0.2% of men and 0.5% in total were hospitalized due to any reason.

Figure 2 presents the OR (95% CIs) of the association of COVID-19 with the presence of any of the examined symptoms according to some of general characteristics. Our results revealed that females (OR = 1.88, 95% CI: 1.39, 2.55) and highly-educated patients (OR = 2.18, 95% CI: 1.56, 3.04) had higher risk of having any of the examined symptoms compared with men and lower educated patients. However, age (OR = 1.00, 95% CI: 0.98, 1.01) and having any of the NCDs as underlying disease during hospitalization (OR = 1.16, 95% CI: 0.83, 1.61) could not predict the risk of the presence of any of the reported symptoms in 1-year follow-up.

DISCUSSION

To our knowledge, the ICC study is the largest ongoing prospective cohort study with long follow-up of patients and wide range of COVID-19 severity including asymptomatic and mild at community level as well as moderate and

severe hospitalized cases to investigate the short- and long-term morbidity, mortality symptoms, incident cases, or worsening of NCDs and its risk factors in the EMR. In this article, we present the methodology and initial results of symptoms and some incident NCDs of only hospitalized patients with COVID-19 during the 1st year of follow-up. We found that about 60% of participants had at least one COVID-19 persistent or new symptom in the 1st year of follow-up, which indicates a probable multisystem involvement. These symptoms are more frequent in women than men and highest in 45–60 years' age group. Myalgia or joint pain, dry cough or dyspnea, hair loss and fatigue, or muscle weakness are the four most common symptoms in 1-year follow-up, which mostly terrified our patients. As we have completed additional questions on prehospitalization, we are able to present pre-COVID data for comparison in future reports.

ICC study advantages compared to other long COVID cohort studies in the UK, USA, Netherland, France, Russia, and China are its large sample size of 5800 from the community and hospitals with annually follow-up until 5 years. In addition, we completed wide range of questionnaires to collect data on demographic, socioeconomic, prevention, and hygiene practices and lifestyle habits such as dietary, smoking, addiction, physical inactivity, and psychological

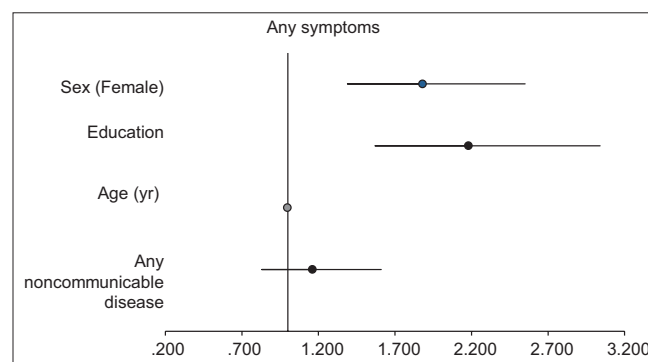


Figure 2: Odds ratio (95% confidence interval) of any long COVID symptoms occurrence with age, sex, education and any underlying noncommunicable disease

Table 3: Outcomes occurrence at 1 year follow-up of hospitalized patients with COVID-19 according to sex

Outcomes	Overall (n=819), n (%)	Men (n=489), n (%)	Women (n=330), n (%)
NCD			
CHD	20 (2.4)	10 (2.0)	10 (3.0)
Stroke	1 (0.1)	1 (0.2)	0 (0.0)
CRD	9 (1.1)	5 (1.0)	4 (1.2)
NCD risk factors			
New case of DM	15 (3.2)	8 (3.0)	7 (3.4)
Uncontrolled DM	11 (7.2)	6 (7.3)	5 (7.1)
New case of hypertension	21 (4.4)	12 (4.5)	9 (4.4)
Uncontrolled hypertension	10 (5.3)	5 (5.4)	5 (5.3)
Any hospitalization	5 (0.5)	1 (0.2)	4 (1.2)

DM=Diabetes mellitus; CHD=Coronary heart disease; CRD=Chronic respiratory disease; NCD=Noncommunicable disease

factors. Medical history, general health and symptoms, medication use, anthropometrics, and physical examination were done by GPs in health centers. All hospital information was completed in another questionnaire. Our 5-year follow-ups and actions taken each year or when patients develop problems are shown in Figure 1. We have developed an evidence-based multidisciplinary team approach for follow-up and caring of patients.

Similar to our study, various long COVID cohort studies in the US, European countries, and China reported the existence of at least one symptom in 30%–88% with an average of 50% of patients who were hospitalized with COVID-19 during a postdischarge follow-up of 1–6 months.^[10-12,24-34] About 50% of the patients reported at least one GP visit during their postinfection period in Germany.^[28] However, most of mild COVID-19 cases have returned to their normal health status after 1 or 2 months.^[26] In contrast to our findings, an early report from Wuhan, China, showed that persistent postdischarge symptoms of COVID-19 have been recovered in 86% before the end of the 1st month.^[35] Our results showed that to be free of any symptom or to return to normal health and life might take more than 1 year after discharge in moderate and severe COVID-19 cases.

In the Consultation Multi-Expertise de Bicêtre Après COVID-19 study in France, fatigue cognitive symptoms, and new-onset dyspnea were reported after 4 months in 31%, 21%, and 16% of patients, respectively.^[24] Another study showed that in 23% of noncritical COVID-19 patients had complaints from anosmia/ageusia, 30% from dyspnea, 40% from asthenia and 15% from chest pain in 40% of patients during 2-months of follow-up. Consistent to our study, the follow-up evaluation after 1 month of discharge was declarative over a phone call without physical examination in various long COVID studies.^[24,25] Similarly, former studies of SARS, H1N1, and Ebola revealed that fatigue, myalgia, and breathlessness were persistent for long time after discharge in more than half of patients even after 1 year.^[36-38] A Canadian study reported that 40% of SARS survivors still had a chronic fatigue problem for a mean period of 41.3 months of follow-up.^[39] Various studies had inconsistent results about the determinants of persistent symptoms such as age and sex.^[12,33,40] Keeping in line with our study, several studies found that persistent symptoms of COVID-19 were associated with female gender, but Petersen *et al.* could not find any association with sex.^[33] Similar to our study, the persistent symptoms were seen more in 40–60 years' age group. While our findings did not show age as a predictor of persistent symptoms, in contrast, in the UK study, age was the main risk factor for persistent symptoms.^[11,41,42] Preexisting chronic disease had with long COVID symptom in Petersen *et al.*' study, which is in agreement to our study.^[33] Few

studies evaluated the association of education with persistent symptom occurrence, though we found the positive strong relationship between education and any symptom incidence. Owing to our self-reported approach first in the 1-year follow-up, it might be due to their more attention and worriedness about their health status, hence their over reporting compared to lower educated patients.

Various reported long-term postdischarge symptoms among COVID-19 patients such as fatigue, dyspnea, bone and joint pain, arthralgias, physical decline, myalgia, chest pain, hair loss, cough, anosmia, ageusia, difficulty concentrating, decreased appetite, headaches, sleep disorders, memory loss, confusion, psychological distress, fever, and dizziness.^[10-12,24-28,33-35,40,43-45] In contrast to our findings, the most prevalent symptom in several studies was fatigue or muscle weakness by 31%–72%;^[11,12,24,27,28,40,43] however, in some reports, it was fever up to 87% followed by cough, fatigue, and dyspnea, particularly in patients with severe COVID-19.^[35,37,46] This inconsistency might be due to our longer follow-up, which is about 1 year compared with up to 6 months in former reports. In addition, most of these symptoms are multidimensional health problems that can overlap with each other.^[11]

The potential mechanisms are unknown; however, like other viral infections, the long COVID symptoms might be linked with the sequela of central nerve system injury by SARS-CoV-2.^[47] Recent evidence stated that COVID-19-prolonged outcomes might be attributed to the mast cell activation syndrome 32 and the The-2 biased immunological response in allergic diseases. Moreover, inflammatory response related to symptomatic COVID-19 and posttraumatic stress disorder after COVID-19 might cause long-term symptoms.^[48,49] Neurological COVID-19 sequelae can prove involvement of central and peripheral nervous system, which leads to expressing angiotensin-converting enzyme 2 (ACE2) receptor in muscle and neural tissue, thus causing the speculation of potential neurotropism.^[50] Hence, COVID-19 can promote a large care burden after the pandemic is ended. It requires more attention and efforts of health system. However, the frequency of patients with CVD in this cohort is fairly low, since self-reported by patients might lead to underestimation.^[12]

To date, most studies have provided data on long COVID symptoms, rather than multiorgan dysfunction, and a few studies have reported the incidence of NCDs such as CHD, stroke, and CRD as well as new cases of hypertension and DM. During 1-year follow-up, a remarkable proportion of new cases and uncontrolled DM as well as hypertension have been occurred in the current study. Similarly, a prospective cohort study in UK on more than 47,000 discharged patients

with the mean follow-up of about 5 months had new onset of DM and major adverse CV events by 2.5% and 7%, respectively.^[51] Some researchers proposed that diabetes may indirectly result from severe COVID-19 illness. The coronavirus could promote development of Type 2 diabetes or more uncontrolled state in high-risk patients like those with prediabetes, obesity, and hypertension. In agreement to our study, a cohort study in Italy revealed that uncontrolled hypertension was extremely prevalent, which may be due to the association of that SARS-CoV-2 infection and CV injury.^[52] SARS-CoV-2 pass cell membrane by leveraging the ACE2 receptor, a leading regulator of the renin-angiotensin system. The most spike glycoprotein of the virus binds to ACE2; however, proximal serine proteases cleave the viral spike protein and ACE2, to stimulate virus entrance. Cell death due to infection activates inflammatory cytokine production, inflammatory immune cell recruitment, circulation of immune cells, stimulation of lymphocyte apoptosis, and inflammatory cytokine secretion, known as “cytokine storm.” It can develop multiorgan failure, raise blood pressure, disrupt endocrine signaling, and consequently induce hyperglycemia.^[53] Acute kidney injury COVID-19 infection can prompt renal failure and hence elevated blood pressure in those with prior normotensive.^[54] Therefore, using effective strategies such as lifestyle modification and proper medication can be applied to manage CVD and its risk factors and subsequently reduce the burden of COVID-19 pandemic.

Strength and limitation

This report which is a part of the ICC study has some strengths that include the multicentric design with a large sample size of postdischarged patients with COVID-19. Another strength is the long follow-up of these patients for 1 year. However, the absence of pre-COVID-19 assessments in this article is one of our limitations and similar to other studies, but we will report it in our future articles. Another limitation is we have not reported the psychological and psychosomatic variables in this paper.

CONCLUSIONS

So far, the ICC study has been the largest ongoing prospective cohort study with the longest follow-up of patients with wide range of COVID-19 severity from asymptomatic to severe cases to investigate the persistent symptoms, short- and long-term morbidity, incident and worsening NCDs and their risk factors, and mortality of COVID-19 in Iran and the EMR.

Following 1 year of our patients discharge, about 60% experienced persistent symptoms with the most common being myalgia or joint pain, dry cough or dyspnea, hair loss, fatigue, or muscle weakness. It was more frequent in women

than men and most common in 45–60 years’ age group. New cases of hypertension then diabetes followed by CHD were the most incident NCDs seen in our 1-year follow-up, with higher prevalence in women compared to men. Therefore, our findings showed that extensive health services and integrative approaches are needed to improve health status of patients with COVID-19 after their discharge. Along with effort to control the spread of COVID-19 infection, it is critical to plan for human and financial resources to diminish the burden from long COVID. Although the management of acute phase of COVID-19 is still challenging, its long-term symptoms and events may create major problems for survivors, their families, and the society.

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Conflicts of interest

There are no conflicts of interest.

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