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Estimation of outpatient SARS-CoV-2 reinfection and recurrence rates and associated factors among COVID-19 hospitalized patients over one-year old: a multicenter retrospective cohort study

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Abstract

Introduction Reinfection with SARS-Cov-2 after recovery can occur that most of them don't require hospitalization. The aim of this study is estimation of out-patient COVID-19 reinfection and recurrence rates and its associated factors among Iranian patients with history of confirmed SARS-Cov-2 infection and hospitalization.

Methods This study is a retrospective cohort conducted from May 2021 to May 2022 in Iran. The national Medical Care Monitoring Center (MCMC) database, obtained from the Ministry of Health and Medical Education, includes all information about confirmed COVID-19 patients who are hospitalized and diagnosed during the pandemic. Using probability proportional to size sampling from 31 provinces, 1,532 patients over one years of age with a history of hospitalization in the MCMC data are randomly selected. After that, interviews by phone are performed with all of the selected patients using a researcher-made questionnaire about the occurrence of overall reinfection without considering the time of infection occurrence, reinfection occurring at least 90 days after the discharge and recurrence (occurring within 90 days after discharge). Univariate and multivariable Cox regression analyses are performed to assess the factors associated with each index. All of the analyses are performed using Stata software version 16.

Results In general, 1,532 phone calls are made, out of which 1,095 individuals are willing to participate in the study (response rate ≃ 71%). After assessing the 1,095 patients with a positive history of COVID-19, the rates of non-hospitalized overall SARS-Cov-2 reinfection, reinfection and recurrence are 122.64, 114.09, and 8.55 per 1,000 person-years, respectively. The age range of 19–64 years (aHR:3.93, 95%CI : 1.24–12.41) and COVID-19-related healthcare worker (aHR: 3.67, 95%CI: 1.77–7.61) are identified as risk factors for reinfection, while having comorbidity, being fully

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vaccinated, and having a partial pressure of oxygen (PaO2) ≥ 93 mmHg during the initial infection are identified as factors that reduce the risk of non-hospitalized reinfection.

Conclusion Reinfection due to COVID-19 is possible because of the weakened immune system for various reasons and the mutation of the virus. Vaccination, timely boosters, and adherence to preventive measures can help mitigate this risk.

Keywords SARS-Cov-2, Reinfection, Recurrence, Out-patient, Iran

Introduction

Until January 6, 2024, Coronavirus Diseases 2019 (COVID-19) pandemic, has caused over 700 million infections and 6.9 million deaths worldwide [1]. Almost all global countries fell victim to this disease within a short period and it is currently considered one of the biggest threats to global health [2]. On January 30, 2020, the World Health Organization (WHO) announced COVID-19 was the sixth leading cause of global public health emergencies due to its global and rapid spread, high infectivity, and significant mortality [3]. The infection with COVID-19 can lead to a detectable immune response, but the sensitivity of those previously infected with COVID-19 is unknown. COVID-19 reinfection and recurrence are significant and costly problems in the pandemic [4, 5]. A reinfection occurs when a person's body becomes infected with a new strain or microbe [4]. Recently, a study revealed that the reinfection rate is 3 per 1000 patients. After the primary infection, reinfection often occurs 45 to 172 days later, and it can last as long as 212 days [5]. An increasing number of field studies have estimated SARS-Cov-2 reinfection rates after a primary episode following the first documented case in August 2020 in Hong Kong (6–7). Even though the reported rates have been consistently low, they differ based on the definition of reinfection, the setting, the pandemic period, and the follow-up period, and uncertainties remain about the risk of developing a severe form of COVID-19 disease after reinfection (4, 8–9).

The World Health Organization has provided guidelines for assessing the recovery of COVID-19 patients who have been hospitalized. Generally, this is done after clinical recovery and two negative PCR swabs that are more than 24 h apart [10]. However, many studies have shown that re-positive test for the virus using RT-PCR is very common in recovered patients [10]. Recurrence or relapse means the reappearance of disease symptoms after recovery or the end of the disease [4, 11]. Recurrence may occur due to insufficient treatment of the first course of the disease. Recurrence rates among recovered COVID-19 patients were 133 per 1000 patients according to a meta-analysis [5].

In general, various studies have been conducted regionally or nationally, to raise awareness of the rate of reinfection and recurrence of COVID-19. For example, a national study in Kuwait in 2023, which examined 232,103 individuals with prior COVID-19 infection, reported a reinfection rate of 0.52%. It was found that the reinfection among older patients occurred in a shorter time frame following the initial infection [12]. The results of another study conducted in South Korea indicate that the incidence rate of reinfection is 346.2 per 100,000 individuals, equivalent to 0.3%. According to the results of this study, the rate of reinfection was higher among individuals who had received only one dose of the vaccine compared to others. Additionally, the highest rates of reinfection were observed during the circulation of the Delta and Omicron variants [13]. However, in our study that conducted in Iran [14], it was observed that the results regarding reinfection, recurrence, and re-hospitalization rates among individuals with a history of hospitalization due to COVID-19 differed from the findings in other countries in the region. Specifically, the incidence rates of reinfection, recurrence, and re-hospitalization in Iran were estimated to be 26.8, 41.61, and 30.53 per 1,000 person-years, respectively. It was also identified that having a history of cancer, chronic kidney disease, and being over 80 years old were recognized as risk factors for reinfection. Furthermore, the rate of reinfection during the circulation of the Delta variant (the fifth wave of the epidemic in Iran) was higher compared to other epidemic waves [14]. Finally, due to the limited studies conducted at national level, especially in Iran, to investigate the epidemiology of reinfection and recurrence of COVID-19, particularly in mild and outpatient cases, this study was designed. This study can help by providing detailed data on the epidemiology of reinfection in a national level, which contributes to the global understanding of COVID-19 and aids in formulating effective public health responses, enhancing vaccination efforts, and optimizing healthcare resources.

Materials and methods

Study design

This study was a retrospective cohort that conducted based on information from all hospitalized patients due to COVID-19 that the infection was confirmed based on respiratory symptoms and positive nasopharyngeal PCR or CT scan of the lungs in whole of the country (31 provinces). We used from patients' information

(1,505,567 cases) that recorded in the national Medical Care Monitoring Center (MCMC) database with supervision of ministry of health and medical education of Iran from the March 2020 to May 2021. The available database included demographic information, medical history about underlying diseases, specific information related to signs and symptoms of SARS-Cov-2 infection at the time of admission to the hospital, and information related to patients' hospitalization and prognosis. Therefore, we extracted the basic information of the patients over one years of age from the national database over a specific time period and conducted interviews from March 20, 2022, to May 11, 2022, to collect data on the occurrence of out-patient reinfection after discharge. This study was approved by the ethics committee and review board of National Institutes for Medical Research Development (NIMAD), Tehran, Iran (IR.NIMAD.REC.1400.112).

Patients' information and data extraction

After extracting the data, for sampling and understanding of the population under study were carried out in order to estimate out-patient reinfection and recurrence rates (without hospitalization in subsequent periods) in patients with a history of hospitalization due to initial SARS-Cov-2 infection.

In the first stage, all discharged and alive patients over one years of age who, according to the MCMC data, had not been re-hospitalized after their last discharge were selected and placed under a separate database for follow-up regarding the occurrence of out-patient reinfection or recurrence. In this stage, the correctness of individuals' contact numbers (mobile phone numbers) was checked, ensuring they were 11 digits long. In addition, outliers in the variables were assessed and any non-reliable or erroneous data was excluded.

Sampling method

After data cleaning, a stratified random sampling was conducted. In this study was considered 31 provinces in the country, including those in the north, south, east, west, and central regions. Sampling of alive cases with a history of at least one hospitalization due to COVID-19 in the MCMC database was then randomly conducted using the Probability Proportional to Size (PPS) sampling method from each of the 31 provinces in the country. Therefore, the overall sample size was determined by dividing and sampling according to the number of patients in each province. In other words, if a province had a higher number of COVID-19 cases, a larger sample size was consequently allocated to it. In each province, simple random sampling was conducted using a list of eligible individuals with accessible mobile phone numbers, which were registered in the MCMC dataset as the sampling population. The entire sampling process was carried out using Stata software version 16 commands.

Sample size estimation

Based on our previous meta-analysis study [5], and considering the probability of SARS-Cov-2 recurrence as 0.15, an error type I of 5% ($\alpha=0.05$), margin of error as 2% ($d=0.02$) and a 20% probable attrition rate, the estimated sample size was 1532 patients.

Interview and questionnaire

The telephone interview started with an explanation of the study's objectives, and verbal consent was obtained from the patients or their guardian/close relatives (in children or patients with low ability to explain or patients who died) to participate in the study by the trained research team on March 20, 2022 to May 11, 2022. The interview lasted approximately 3 to 4 min.

In this study, general and baseline information of patients was extracted from the MCMC dataset, which included age, gender, clinical symptoms and signs at the time of hospitalization, date of discharge and underlying diseases. Other necessary information for this study, was obtained by questionnaire during interviewing. The researcher-made questionnaire included 8 questions, covering topics such as the job types, frequency and timing of confirmed or suspected COVID-19 infection after the last discharge from the hospital due to COVID-19, confirmation of infection using diagnostic tests such as chest x-ray or CT-scan, Reverse Transcription-Polymerase Chain Reaction (RT-PCR) result, rapid test or serological tests, the patient's signs and symptoms at the time of secondary infection, history of COVID-19 vaccine injections, and contact history with a confirmed SARS-Cov-2 cases (supplementary file). In this study, the combination of effects from similar predictors, such as underlying diseases, was considered using the comorbidity score. This index reflects the summation of comorbidities in patients, regardless of the type of disease.

After obtaining verbal consent from participants, the patients were assured that they can withdraw the interview or refuse to answer to any of the questions freely at any phase of the interview. If a person refused to participate in the study, they were removed from the study population. If the research subject did not respond, they were followed up to three times, and if they were unresponsive after three attempts, they were excluded from the study population. After completing the questionnaire, all collected information was entered into statistical software to analysis.

Outcomes' definitions

According to the following definitions, the occurrence and timing of SARS-Cov-2 recurrence or reinfection

have been investigated as suspected or confirmed cases and their frequency:

The first outcome "overall reinfection", includes all outpatients' cases who were reinfected with SARS-Cov-2 after last discharge from hospital due to COVID-19, without considering the time of infection occurrence. If a study participant experiences an infection within 90 days after the last discharge due to SARS-Cov-2 infection, it is considered a case of COVID-19 recurrence (relapse) [4, 5]. If the infection occurs more than 90 days after the last discharge due to SARS-Cov-2 infection, it is considered a case of reinfection [5, 15].

The confirmation of reinfection or relapse was based on self-reporting of positive clinical signs and symptoms and RT-PCR test result or CT scan of the lungs or rapid test or serology tests results. If an interviewee had not undergone clinical tests and examinations, we assessed the possibility of reinfection or recurrence based on the patient's clinical signs and symptoms and their exposure history to suspected or probable cases.

Statistical analysis

In this study continuous and categorical data reported as mean ± standard deviation (SD) and frequency and percentages (%), respectively. The incidence rate for each index is calculated based on the total number of new cases of an event (reinfection or recurrence) divided by the sum of the person-time of the at-risk population. Reinfection and recurrence rates estimated per 1000 person-year. The univariate and multivariable Cox's proportional hazards regression model were used to determine the association of the variables with each event. The important assumption of Cox analysis (the assumption of proportional hazards over time) is examined through the Schoenfeld residuals test. In this test, the assumption of proportional hazards holds for variables with a P_value greater than 0.05. For selection of potential variables for predicting the outcomes we used from stepwise selection method with forward and backward approaches with a P_value ≤ 0.2. Models' goodness-of-fit was assessed using the lowest value of Likelihood ratio, Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). Hazard Ratio (HR) with 95% Confidence Interval (CI) was reported as effect size of each variable. All of the analysis performed using Stata software version 16.

Results

In this study, we sampled 1,532 individuals out of 1,397,159 patients with history of hospitalization due to COVID-19. In general, 1,532 phone calls have been made at this stage, out of which 1095 individuals have willingness to participate in the study (a response rate of approximately 71%).

In this study the total analysis time at risk and under observation was 1,402.376 years. The minimum and maximum follow-up duration in this study has been 12 and 15 months, respectively (on average, it lasts for about one year and three months).

Overall reinfection was reported for 183 cases (17.28%, 95% CI: 15 − 19%) over the one-year old, that 171 (16.15%, 95%CI: 13 − 18%) and 12 (1.13%, 95%CI: 0.6 − 2%) of non-hospitalized cases occurred more than 90 days after discharge and within 90 days, respectively.

Females accounted for 50.32% of total cases. The total mean age was estimated as 52.86 ± 21.11 years. Mean ages for people with and without reinfection were calculated as 53.15 ± 21.56 and 50.34 ± 18.63 years, respectively ($P = 0.100$).

The study identified a total of 125 deaths, accounting for 11.63% of the cases, and among these, reinfection was reported in one patient, which represents 0.80% of the total deaths.

Based on the results of Table 1, most of the participants in this study had unrelated to healthcare and medical occupations ($n = 1053$). Among the fully vaccinated patients the prevalence of reinfection was 10.03% ($n = 63$). In addition, the distribution of gender, job types, vaccination status, initial signs and symptoms such as low consciousness and cough, history of diabetes, and frequency of comorbidity among the two study groups were significantly different ($P < 0.05$) (Table 1).

Overall re-infection rate and associated factors

According to the results, overall reinfection rate (without considering the time of occurrence) was estimated as 122.64 (per 1000 person-year). This figure was reported 139.22 for females and 105.94 for males. The highest reinfection rate was reported in 19–44 age group (156 per 1000 person-year) and 45–64 age group (135.97 per 1000 person-year). The lowest overall reinfection rate was estimates for 5–18 age group (69.77 per 1000 person-year), children under 5 years old (76.09 per 1000 person-year) and adults more than 80 years old (76.24 per 1000 person-year). Cox regression proportional hazard model indicated that 19–44 age group compared to 1–19 age group (HR: 3.93, 95% CI: 1.24–12.41) and 45–64 age group (HR: 3.40, 95% CI: 1.08–10.68); and COVID-19 related healthcare worker compared to unrelated to healthcare and medical (HR: 3.67, 95% CI: 1.77–7.61) are risk factors for reinfection; while fully-vaccination compared to lower than two doses is a preventive factor for reinfection (HR: 0.21, 95% CI: 0.15–0.30). None statistical association between reinfection with age, gender, and medical history was observed ($P > 0.05$) (Table 2).

Table 1 Characteristics of non-hospitalized patients over than one-year old with a history of hospitalization due to COVID-19 by overall reinfection occurrence

Variables	Reinfection *N* = 183 (16.71%)*	Non- reinfection *N* = 912 (83.29%)*	*P*_value
Age (years)	50.33 ± 18.63	53.15 ± 21.56	0.100
Gender			
Female	105 (19.06)	446 (80.94)	**0.036**
Male	78 (14.34)	466 (85.66)	
Job types			**0.001**
Unrelated to healthcare and medical	169 (16.05)	884 (83.95)	
Healthcare worker	4 (21.05)	15 (78.95)	
COVID-19 related health care worker	10 (45.45)	12 (54.55)	
Vaccination status			**< 0.001**
Lower than two doses	120 (25.70)	347 (74.30)	
Two or more than two doses	63 (10.03)	565 (89.97)	
Muscular pain**			0.190
No	118 (15.71)	633 (84.29)	
Yes	65 (18.90)	279 (81.10)	
Respiratory distress**			0.155
No	111 (18.14)	501 (81.86)	
Yes	72 (14.90)	411 (85.09)	
Low Consciousness**			**0.026**
No	182 (17.17)	878 (82.83)	
Yes	1 (2.86)	34 (97.14)	
PaO2 ≥ 93 (mmHg)**			0.120
No	99 (18.50)	436 (81.50)	
Yes	84 (15.00)	476 (85.00)	
Intubation**			0.576
No	180 (16.81)	891 (83.19)	
Yes	3 (12.50)	21 (87.50)	
Cough**			**0.012**
No	80 (14.26)	481 (85.74)	
Yes	99 (20.12)	393 (79.88)	
Fever**			0.106
No	106 (15.61)	573 (84.39)	
Yes	73 (19.52)	301 (80.48)	
Comorbidities			
Immunosuppress disease[1]			0.207
No	182 (16.65)	911 (83.35)	
Yes	1 (50)	1 (50)	
Mental illness			0.649
No	181 (16.77)	898 (83.23)	
Yes	2 (12.50)	14 (87.50)	
Diabetes			**0.030**
No	164 (17.77)	759 (82.23)	
Yes	19 (11.05)	153 (88.95)	
Any type of cancer			0.334
No	182 (16.84)	899 (83.16)	
Yes	1 (7.14)	13 (92.86)	
Chronic kidney disease			0.238
No	181 (16.92)	889 (83.08)	
Yes	2 (8)	23 (92.00)	
Blood disease[2]			0.437
No	183 (16.76)	909 (83.24)	
Yes	0 (0.00)	3 (100.00)	

Table 1 (continued)

Variables	Reinfection *N* = 183 (16.71%)*	Non- reinfection *N* = 912 (83.29%)*	*P*_value
Chronic liver disease			0.437
No	183 (16.76)	909 (83.24)	
Yes	0 (0.00)	3 (100)	
Chronic heart disease			0.945
No	161 (16.68)	804 (83.32)	
Yes	22 (16.92)	108 (83.08)	
Pregnancy**			0.896
No	181 (16.70)	903 (83.30)	
Yes	2 (18.18)	9 (81.82)	
Asthma			0.138
No	182 (16.95)	892 (83.05)	
Yes	1 (4.76)	20 (95.24)	
Chronic respiratory disease except asthma			0.063
No	183 (16.98)	895 (83.02)	
Yes	0 (0.00)	17 (100.00)	
Other chronic disease[3]			0.461
No	172 (16.95)	843 (83.05)	
Yes	11 (13.75)	69 (86.25)	
Comorbidity score			**0.042**
0	140 (18.79)	605 (81.21)	
1	28 (11.86)	208 (88.14)	
2	14 (14.58)	82 (85.42)	
3	1 (5.56)	17 (94.44)	

*All percentages have been calculated row-wise

**At the time of first hospitalization and initial infection

PaO2: partial pressure of oxygen

[1] Such as rheumatoid arthritis, lupus, inflammatory bowel disease, celiac disease, etc.

[2] Such as anemia, thalassemia, bleeding disorders such as hemophilia, blood clots and etc.

[3] Such as musculoskeletal disease, central nervous system diseases and etc.

Re-infection rate (occurred more than 90 days from discharge) and associated factors

According to the results, total reinfection rate more than 90 days after discharge was estimated as 114.09 (per 1000 person-year). These figure were reported 127.85 for females and 100.22 per 1000 person-year for males. The highest reinfection rate was reported in 19–44 age group (145.77 per 1000 person-year). The lowest reinfection rate was estimates for age group of 1–18 years old (73.86 per 1000 person-year).

Cox regression proportional hazard model indicated that 19–44 age group compared to 1–19 age-group (HR: 3.26, 95% CI: 1.02–10.42) and COVID-19 related healthcare worker compared to unrelated to healthcare and medical (HR: 4.07, 95% CI: 1.93–8.60) are risk factors for reinfection; however, fully-vaccination compared to lower than two doses (HR: 0.26, 95% CI: 0.18–0.36), PaO2≥93 compared to PaO2<93 (HR: 0.62, 95% CI: 0.44–0.87), and one medical history compared to none (HR: 0.60, 95% CI: 0.38–0.94) are preventive factors. No statistical significant association about reinfection with gender and clinical symptoms during hospitalization due to COVID-19 was observed ($P>0.05$) (Table 3).

Recurrence rate (occurred within 90 days from discharge)

Total recurrence rate has been estimated as 8.55 per 1000 person-year ($n=12$). These figures were calculated as 11.36 for females and 5.72 per 1000 person-year for males. The maximum and minimum recurrence rate were showed in adults more than 65 years old (10.88 per 1000 person-year) and children under 18 years old (none), respectively (Table 4).

Discussion

In this retrospective cohort study the reinfection and recurrence rates of COVID-19 among patients who previously tested positive for this infection were investigated. Our analysis revealed that the rates of non-hospitalized overall SARS-Cov-2 reinfection, reinfection occurring at least 90 days after the discharge and recurrence were 122.64, 114.09, and 8.55 per 1,000 person-years, respectively. Which is equivalent to 16.71%, 15.61% and

Table 2 Univariate and Multivariable analysis of overall reinfection in non-hospitalized patients over one-year old with a history of hospitalization due to COVID-19

Patient characteristics	Reinfection Rate (per 1000)	Crude Hazard Ratio (95%CI)	*P*_value	Adjusted Hazard Ratio (95%CI)	*P*_value
Age (years)					
1–18	73.86	Reference	-	Reference	-
19–44	156.002	2.33 (1.02–5.32)	**0.043**	3.93 (1.24–12.41)	**0.030**
45–64	135.97	1.97 (0.86–4.50)	0.104	3.40 (1.08–10.68)	**0.046**
≥ 65	89.23	1.30 (0.56–3.02)	0.537	1.82 (0.56–5.83)	0.359
Sex					
Female	139.22	Reference	-	Reference	-
Male	105.94	0.75 (0.55- 1.00)	0.054	0.77 (0.56–1.05)	0.065
Job types					
Unrelated to healthcare and medical	118.82	Reference	-	Reference	-
Healthcare worker	77.89	0.74 (0.18–2.98)	0.678	0.93 (0.22–3.95)	0.846
COVID-19 related health care worker	345.16	3.49 (1.89–6.43)	**< 0.001**	3.67 (1.77–7.61)	**< 0.001**
Cough*					
No	109.25	Reference	-	Reference	-
Yes	141.11	1.33 (0.99–1.80)	0.056	1.26 (0.93–1.71)	0.109
Fever*					
No	116.86	Reference	-	Reference	-
Yes	136.86	1.23 (0.91–1.67)	0.178	1.14 (0.83–1.56)	0.358
PaO2 (mmHg)*					
< 93	138.30	Reference	-	Reference	-
≥ 93	108.52	0.80 (0.59–1.08)	0.149	0.65 (0.47–0.91)	**0.007**
Respiratory distress*					
No	128.99	Reference	-	Reference	-
Yes	114.44	0.84 (0.62–1.14)	0.266	0.82 (0.59–1.14)	0.235
Muscular pain*					
No	116.32	Reference	-	Reference	-
Yes	136.91	1.15 (0.85–1.57)	0.351	1.06 (0.76- 1.47)	0.660
Comorbidity score					
0	138.12	Reference	-	Reference	-
1	88.34	0.62 (0.41–0.94)	**0.025**	0.58 (0.38–0.91)	**0.012**
2	102.54	0.74 (0.42–1.29)	0.298	0.67 (0.37–1.21)	0.207
3	46.38	0.30 (0.04–2.20)	0.239	0.49 (0.07–3.65)	0.423
Vaccination status					
Lower than two doses	195.97	Reference	-	Reference	-
Two or more than two doses	70.67	0.33 (0.24–0.45)	**< 0.001**	0.21 (0.15–0.30)	**< 0.001**

*At the time of first hospitalization and initial infection

PaO2: partial pressure of oxygen

Table 3 Univariate and Multivariable analysis of reinfection more than 90 days after discharge in non-hospitalized patients over one year old with a history of hospitalization due to COVID-19

Patient characteristics	Reinfection Rate (per 1000)	Crude Hazard Ratio (95%CI)	*P*_value	Adjusted Hazard Ratio (95%CI)	*P*_value
Age (years)					
1–18	73.86	Reference	-	Reference	-
19–44	145.77	2.20 (0.96–5.05)	0.169	3.26 (1.02–10.42)	**0.046**
45–64	129.60	1.89 (0.83–4.34)	0.702	3.02 (0.95–9.58)	0.060
≥ 65	78.35	1.15 (0.49–2.70)	0.861	1.50 (0.46–4.87)	0.500
Sex					
Female	127.85	Reference	-	Reference	-
Male	100.22	0.76 (0.56–1.04)	0.075	0.76 (0.55–1.05)	0.215
Job types					
Unrelated to healthcare and medical	109.91	Reference	-	Reference	-
Healthcare worker	77.89	0.81 (0.20–3.28)	0.629	0.91 (0.20–3.96)	0.400
COVID-19 related health care worker	345.16	3.85 (2.06–7.20)	**< 0.001**	4.07 (1.93–8.60)	**< 0.001**
Cough*					
No	98.18	Reference	-	Reference	-
Yes	134.77	1.42 (1.04–1.94)	**0.028**	1.35 (0.98–1.86)	0.522
Fever*					
No	108.76	Reference	-	Reference	-
Yes	126.64	1.23 (0.89–1.69)	0.187	1.15 (0.83–1.59)	0.253
PaO2 (mmHg)*					
< 93	129.28	Reference	-	Reference	-
≥ 93	100.38	0.79 (0.58–1.08)	0.231	0.62 (0.44–0.87)	**0.006**
Respiratory distress*					
No	121.40	Reference	-	Reference	-
Yes	104.63	0.81 (0.59–1.11)	0.055	0.78 (0.56–1.10)	0.080
Muscular pain*					
No	109.11	Reference	-	Reference	-
Yes	125.31	1.12 (0.81–1.55)	0.297	1.02 (0.72–1.44)	0.106
Comorbidity score					
0	127.57	Reference	-	Reference	-
1	85.07	0.65 (0.42–0.99)	**0.048**	0.60 (0.38–0.94)	**0.026**
2	94.66	0.74 (0.41–1.32)	0.312	0.70 (0.38–1.29)	0.256
3	46.38	0.32 (0.04–2.38)	0.276	0.49 (0.06–3.69)	0.498
Vaccination status					
Lower than two doses	175.34	Reference	-	Reference	-
Two or more than two doses	70.67	0.36 (0.26–0.50)	**< 0.001**	0.26 (0.18–0.36)	**< 0.001**

*At the time of first hospitalization and initial infection

PaO2: partial pressure of oxygen

Table 4 Recurrence rate in non-hospitalized over the one-year patients with a history of hospitalization due to COVID-19

Patient characteristics	Recurrence Rate (per 1000 person-year)
Age (years)	
1–18	0
19–44	10.22
45–64	6.37
≥ 65	10.88
Sex	
Female	11.36
Male	5.72
Job types	
Unrelated to healthcare and medical	8.91
Healthcare worker	0
COVID-19 related health care worker	0
Cough*	
No	11.06
Yes	6.34
Fever*	
No	8.09
Yes	10.21
PaO2 (mmHg)*	
< 93	9.01
≥ 93	8.13
Respiratory distress*	
No	7.58
Yes	9.80
Muscular pain*	
No	7.20
Yes	11.60
Comorbidity score	
0	10.54
1	3.27
2	7.88
3	0
Complete vaccination	
Lower than two doses	20.62
Two or more than two doses	0

*At the time of first hospitalization and initial infection

PaO2: partial pressure of oxygen

1.09% from 1095 participants with a history of SARS-Cov-2 infection, respectively.

The evidences regarding the rate of reinfection and recurrence of COVID-19 vary across different regions of the world. For instance, in a cohort study conducted in Israel with 1,280,649 participants, 8.7% of individuals experienced a recurrence during the circulation of the Omicron variant [16]. In another study conducted in Serbia in 2022, considering the 251,104 participants with a history of SARS-Cov-2 infection, the prevalence of reinfection occurring more than 90 days after the initial infection was 5.49%, that hospitalizations due to reinfection were uncommon [17]. Meanwhile, in Pakistan, among 29,617 cases, the prevalence of reinfection was reported as 0.22% [18]. It seems that outpatient reinfection is more common in Iran, which may be due to differences in the socio-economic factors of each region, demographic transition, diagnostic and therapeutic protocols, access to accurate diagnostic tools, the timing of the start of mass vaccination, and the type of circulating variant of the virus. These factors could influence the variation in rates [19].

In our study, it was observed that adults aged 19 to 64 years, COVID-19 related health care worker, and patients with a partial pressure of oxygen (PaO2) level less than 93 mmHg were at a higher risk of overall reinfection and recurrence rates. On the other hand, having comorbidity, receiving a full dose of the COVID-19 vaccine (two doses and higher), were protective factors for non-hospitalized reinfection and recurrence rates of COVID-19.

Based on our findings, the reinfection and recurrence rates of COVID-19 in the adult was higher than in children. To justify this issue, the following points can be mentioned: With increasing age, the immune system weakens and its ability to suppress infections decreases, so the background is provided for many types of reinfections [20, 21]. Also, therapeutic interventions in the elderly may be less effective, which causes the presence of untreated infection to cause recurrence and reinfection. Finally, the COVID-19 infection in the elderly is often asymptomatic [22], while their viral load is similar to those with symptoms, so their initial infection may not be completely treated and false reinfection may be seen in them [23].

Regarding the effect of gender on the rate of reinfection, our study indicated that women had a higher rate for both reinfection and relapse which not compatible with some previous studies [24]. Although in our study, its association with the occurrence of reinfection was not statistically significant. The study conducted by Tavakoli, et al. in Shiraz found that men had a 28% higher rate of reinfection compared to women [25]. However, a study by Adrielle and colleagues in Brazil revealed that women included 78.8% of the reinfection cases [26]. Also based on the results from a systematic review and meta-analysis the male/ female ratio was 9558/12,499 (0.8 with 60.0% female patients) from 24 studies with 22,057 re-infected patients [27]. This observation may be a result of lower screening rates in males and higher occupational exposure among females. On the other hand, biological differences in the immune systems of women and men can affect their abilities in fighting infections, especially COVID-19 [24].

In terms of job's type, COVID-19 related health care worker had the highest overall recurrence and reinfection rates. These people are vulnerable as the pandemic frontline and the lack of special personal protective equipment

among them causes more recurrence and reinfection in them. workers who are in direct contact with infected patients are exposed to excessive psychological stress for reasons such as overcrowding of the intensive care unit, overcrowding of the emergency department, long working hours to compensate for the absence of colleagues, wearing personal protective equipment, the fear of transmitting the disease to their own families, and use of poor protective services. This psychological stress leads to the weakening of the immune system and subsequently to repeated infections of COVID-19 [28–31].

According to the findings of this study, the partial pressure of oxygen less than 93mmHg increases the recurrence and reinfection hazard ratio. PaO2 levels have been associated with many adverse outcomes in COVID-19 patients and is considered a relevant index in the management of acute respiratory failure from COVID-19 [32]. Low PaO2 levels are an indicator of acute lung injury and may lead to adverse outcomes such as death and reinfection/recurrence. In justification of this issue and consistent with similar studies, the need for pulmonary resuscitation in people with normal PaO2 is less than in people with low PaO2 levels, so complications after the disease, including returning to the hospital, are less in these people. On the contrary, regarding reinfection, it is possible that people who had a lower blood oxygen level during the initial infection were more careful about their health after discharge and were less exposed to infection than other people, or catch mild forms of the disease that it does not lead to hospitalization [33]. Therefore, the reduced risk of reinfection in these people may be attributed to the lifestyle of these people after the primary infection and the severity of the secondary infection.

According to the results of our study, the risk of outpatient reinfection and recurrence in those who had comorbidity was lower than those who did not have comorbidity. Based on the evidences, underlying diseases cause the severity of COVID-19 [34].In order to justify this issue, it should be said that people who have comorbidities have a higher risk perception than people who did not have these features, therefore, they will take more individual care measures than others to prevent reinfection and re-hospitalization [34, 35] The second assumption is that these patients may be more susceptible to a reinfection that would lead to hospitalization (severe form of the disease). Therefore, the reduction in the risk of non-hospitalized reinfection in this individuals may be influenced by these two assumptions. Although, the second hypothesis is more plausible because, according to our previous study, the rate and risk of reinfection leading to hospitalization is higher in individuals with various underlying diseases compared to others [14]. Finally, different comorbidities have varying effects on the immune system [36]. For instance, while controlled diabetes may not significantly affect immune responses, uncontrolled diabetes can lead to more severe outcomes. This variability can explain differing rates of reinfection. To understand the reasons for this issue, more studies and evidences are needed.

Finally, the risk of reinfection and recurrence in fully-vaccinated people who had received two or more doses of the vaccine was lower than those who had either not received the vaccine or had received only one dose of the vaccine. Recent studies showed that complete vaccination was effective against SARS-Cov-2 even for emerging variants; and infection was significantly lower among vaccinated individuals than non-vaccinated. Based on the previous literature, vaccination after SARS-Cov-2 infection increased T-cell immunity, antibody-secreting memory B-cell response to the spike protein, and neutralizing antibodies effectivity even after the first dose of mRNA-based vaccines. Molecular evidence from other studies showed that receiving fully vaccination or natural infection confers immunity against genetically distinct strains or new variants of COVID-19 virus [37].

The present study has several limitations, which are as follows:

Participant attrition and lack of access to them for participation in the study, probable information bias such as recall bias and response bias that may have led to underestimation in the estimation of each indicator, failure to detect and report asymptomatic cases, lack of information regarding the type of virus strain at the time of reinfection and the lack of information about socioeconomic status, access to healthcare, and treatment adherence after discharge as confounding factors significantly impacts the estimation of reinfection and recurrence rates.

We hope that in future studies, by addressing the existing limitations, a more thorough examination of the issues will take place, and also consider the burden of reinfection and strategies related to reducing costs and infections.

Conclusion

Our study shows that it is possible for patients to be reinfected by COVID-19 without being hospitalized. Overall, adult patients (ages 19 to 64), COVID-19-related healthcare workers, and patients with a PaO2 level of less than 93 mmHg during initial infection are at a higher risk of reinfection and recurrence rates. Considering the protective effect of full vaccination in reducing the rates of reinfection and recurrence of COVID-19, the public should be fully vaccinated, and susceptible individuals should pay attention to maintaining social distance to avoid reinfection with the virus.

Supplementary Information

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Supplementary Material 1

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Conceptualization and Methodology: KE, SSHN. Data cleaning: NI, NT, SF, YM, SSHN. Formal analysis: YM, SSHN. Project administration: SSHN, NT. Interview monitoring: FSH, AM, KFB, RF, ER. Writing–original draft: YM, FSH, NT, SSGH, SF. Writing and reviewing: SSHN, AS, KE.

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Data availability
The individual data are confidential and cannot be shared according to the ethic committee decision.

Declarations

Ethical approval
Ethical approval was granted by the National Institutes for Medical Research Development (NIMAD), Tehran, Iran (IR.NIMAD.REC.1400.112). The recruitment of all patients for interviews was voluntary and based on verbal informed consent from participants or their legal guardians.

Clinical trial number
Not applicable.

Competing interests
The authors declare no competing interests.

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