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ORIGINAL RESEARCH

# Rate and Risk Factors of Reinfection, Recurrence, and Hospital Readmission Among SARS-Cov-2 Hospitalized Patients; a National Cohort Study

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**Abstract:** **Introduction:** Reinfection and hospital readmission due to COVID-19 were significant and costly during the pandemic. This study aimed to assess the rate and risk factors of SARS-Cov-2 reinfection, recurrence, and hospital readmission, by analyzing the national data registry in Iran. **Methods:** This study was a retrospective cohort conducted from March 2020 to May 2021. A census method was used to consider all of the possible information in the national Medical Care Monitoring Center (MCMC) database obtained from the Ministry of Health and Medical Education; the data included information from all confirmed COVID-19 patients who were hospitalized and diagnosed using at least one positive Polymerase Chain Reaction (PCR) test by nasopharyngeal swab specimens. Univariate and multivariable Cox regression analyses were performed to assess the factors related to each studied outcome. **Results:** After analyzing data from 1,445,441 patients who had been hospitalized due to COVID-19 in Iran, the rates of overall reinfection, reinfection occurring at least 90 days after the initial infection, recurrence, and hospital readmission among hospitalized patients were 67.79, 26.8, 41.61, and 30.53 per 1000 person-years, respectively. Among all cases of hospitalized reinfection (48292 cases), 38.61% occurred more than 90 days from the initial SARS-Cov-2 infection. Getting infected with COVID-19 in the fifth wave of the disease compared to getting infected in the first wave (P<0.001), having cancer (P<0.001), chronic kidney disease (P<0.001), and age over 80 years (P<0.001) were respectively the most important risk factors for overall reinfection. In contrast, age 19-44 years (P<0.001), intubation (P<0.001), fever (P<0.001), and cough (P<0.001) in the initial admission were the most important protective factors of overall reinfection, respectively. **Conclusions:** Reinfection and recurrence of COVID-19 after recovery and the rate of hospital readmission after discharge were remarkable. Advanced or young age, as well as having underlying conditions like cancer and chronic kidney disease, increase the risk of infection and readmission.

**Keywords:** Reinfection; Recurrence; Patient Readmission; COVID-19; Pandemics

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## 1. Introduction

On 31 December 2019, the World Health Organization (WHO) was informed of the outbreak of a severe pneumonia disease detected in Wuhan City, Hubei Province of China (1). Within a short period, the disease caused by the novel coronavirus (a.k.a COVID-19) spread rapidly, causing a global pandemic. The world faced unprecedented health, economic, social, and political challenges (2,3). On 30 January 2020, the WHO called the 2019 novel coronavirus outbreak a Public Health Emergency of International Concern (4,5).

When a person's body is infected again with a new strain or microorganism, this is called reinfection (6). A 33-year-old man from Hong Kong was reported to be the first con-

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firmed case of SARS-Cov-2 reinfection in August 2020. He was asymptomatic during the second infection, and different strains of SARS-Cov-2 were identified in both infections (7). A study demonstrated that the re-infection rate is 3 per 1000 patients, the earliest day of reinfection is 45 to 172 days after the primary infection, and the latest day is 212 days (8). A study in England demonstrated that a previous history of SARS-CoV-2 infection was associated with an 84% lower risk of infection, with a median protective effect observed 7 months following primary infection (9). The underlying diseases were not common in these patients. However, the most frequent underlying diseases included diabetes, hypertension, immune system deficiencies (e.g., HIV), and the use of immunosuppressive drugs for certain diseases (10,11).

"Recurrence" or "Reactivation" or "Relapse" of SARS-Cov-2 is the return of signs and symptoms of a disease after the recovery (6). The recurrence of positive RT-PCR test results among COVID-19 patients can be ascribed to several reasons, including age, gender, the resistance of the immune system, clinical symptoms, drug treatment, biological features of the COVID-19, the kit used, sampling, false-negative results, medical facilities, nursing care, and the use of throat swabs, necessitating a longer period of observation for recovered COVID-19 patients (12,13).

Hospital readmissions are a major and costly healthcare concern where patient safety may be compromised and hospitals may face periods of resource scarcity. Understanding that COVID-19 is associated with readmissions can have useful policy implications to optimize healthcare delivery (14). Additionally, research from Einstein Medical Center Philadelphia demonstrated that 7.6% of infected patients were readmitted within a month (15). Overall, the most frequent reasons for hospitalization were hypoxia, respiratory distress, thromboembolism, sepsis, psychological disorders caused by the disease, and a recurrent positive PCR test result (16,17). Therefore, reinfection from COVID is not unexpected and increases the economic burden (18). Most current studies on reinfection with COVID-19 are in the form of single-center cohorts and case reports from clinical units. The presence of scientific evidence in the form of a national study, especially in Iran, is limited. Therefore, we decided to investigate the rates of reinfection and re-hospitalization before mass vaccination to have a better understanding of the epidemiological situation of this disease.

# 2. Methods

## *2.1. Study design and setting*

This retrospective cohort study was based on the Iranian COVID-19 registry (The National Medical Care Monitoring Center (MCMC) database) that covers the total hospitalized and confirmed COVID-19 patients from the whole (31 provinces) of Iran. MCMC database includes individual information about 1) demographic characteristics of the admitted patients (age, gender, place and province of living), 2) past medical history of COVID-19 patients, such as comorbidities and history of pregnancy, 3) specific information about COVID-19 disease in admission time, including clinical signs and symptoms, level of consciousness, percentage of Partial Pressure of Oxygen in the blood (PaO2), 4) other information such as the type of hospital, type of ward, results of COVID-19 tests, history of close contacts with a confirmed COVID-19 case, date of admission, date of discharge or death, and length of hospital stay and 5) prognosis of patients, including ICU admission, need to ventilation or intubation, and death.

This study was performed in accordance with the declaration of Helsinki; this included permission to use anonymized quotations in publications according to the ethics committee. The requirement for informed consent from participants was waived because of the registry-based nature of the study. The ethical approval was granted by the review board of the National Institutes for Medical Research Development (NIMAD), Tehran, Iran (IR.NIMAD.REC.1400.112).

## *2.2. Study duration*

Because the estimation of reinfection, recurrence, and hospital readmission rate before the start of national COVID-19 vaccination was considered, we set the end of the study before April 2021. So, this study was conducted from March 2020 (based on the official announcement of the beginning of the epidemic in Iran) to May 2021.

## *2.3. Outcomes*

This study had four outcomes. The first outcome "overall reinfection" includes all patients who were infected with COVID-19 and hospitalized at least twice regardless of time. The second was inpatient reinfection due to SARS-Cov-2 infection equal to or more than 90 days from the initial laboratory-confirmed infection (19). The third was inpatient recurrence or relapse within 90 days from the initial laboratory-confirmed infection (6) and the fourth was hospital readmission considered as hospitalization due to COVID-19 during one month from the initial discharge (16). The patients whose admission interval (from initial to second admission) was less than seven days were not considered cases of reinfection or re-hospitalization, as these patients may not have fully recovered from the initial infection by the time of the first discharge.

## *2.4. Definitions*

Confirmation of reinfection, recurrence, and hospital readmission due to COVID-19 were based on positive results of PCR tests in the MCMC registry. Since it was not possible to perform genomic sequencing in all patients, the dominant strain in the period of disease was used as an approximation to determine the strain of the disease.

### 2.5. The epidemic waves and variants of concern of SARS-Cov-2

In this study, analyses were conducted based on the epidemic waves. In this specific time period (March 2020 to May 2021), Iran had five large epidemic waves based on the official reports of the Ministry of Health and Medical Education of Iran; the first wave was from February 29, 2020, to April 2, 2020, the second from April 29, 2020, to May 26, 2020, the third from May 27, 2020, to September 1, 2020, the fourth from September 2, 2020, to January 5, 2021, and the fifth from March 30, 2021, to June 25, 2021. The probable circulating variants of SARS-Cov-2 were as follows: Alpha variant (B.1.1.7) from January 2021, Beta variant (B.1.351) from April to May 2021, and Delta variant (B.1.617.2) from April 2021. Alpha and Delta variants correspond to the fourth and fifth epidemic waves, respectively (20).

### 2.6. Data cleaning and quality check

Quality control of data was performed in several steps; missing data were removed and duplicate records were identified based on the patient's national ID codes; the first and last names and ages were checked for people without national ID codes. If a patient was found with the same information based on the date of admission, this case was identified as a duplicate patient and was hence removed from the dataset. But if a patient was found with the same information in two different admissions, we kept the mentioned records and evaluated them about probable reinfection, recurrence, or hospital readmission, according to their standard definitions.

### 2.7. Statistical analysis

Rates of each event were estimated per the 1000 population. Univariate and multivariable Cox's proportional hazards regression model was used to determine the association of the different variables with each event. For selecting the best variables to enter the last multivariable model, a backward stepwise approach with $P < 0.2$ was used. The proportional hazard assumption was evaluated based on the Schoenfeld residuals test. Considering that in this study, death is a competing event and impeding the occurrence of the event of interest, we used a sub-distribution proportional hazard model called "Fine and Gray competing risk regression" as a semiparametric analysis for adjusting the effect of competing events. Lastly, multivariable Cox's regression models were fitted in accordance with the least amount of Akaike Information Criterion (AIC) and with a log-likelihood value closer to zero. A two-sided P-value of lower than 0.05 was considered statistically significant. Hazard Ratio (HR) and Sub-distribution Hazard Ratio (SHR) were reported with a 95% confidence Interval (CI). All of the analyses were performed using STATA software version 16.

## 3. Results

### 3.1. General information

This study was conducted on 1,445,451 patients with COVID-19 in 2020 and 2021. 51.30% of patients were male and 48.70% were female.

The average age of hospitalized patients in the study was 54.44 ± 20.59 years, and the age group of 45-64 years was the majority of them (33.07%). The mean age of people with overall reinfection was 61.85± 20.15 years and the mean age of people without reinfection was 54.18± 20.56 years. The overall death rate among the people under study was 11.36%, and the death rate among people with overall reinfection and people without reinfection was 16.39% and 11.19%, respectively (P <0.001).

### 3.2. Overall reinfection rate

The rate of overall reinfection among the subjects under study was 67.79 per a thousand person-years. This rate was 66.58 in women and 68.94 in men per a thousand person-years. The highest rate of overall reinfection per a thousand person-years was observed in age groups above 80 years (137.30), 65-79 years (111.95), and age group under 5 years (70.32). The lowest rate of overall reinfection per a thousand person-years was observed in the age group of 19-44 years (28.86). The number of reinfections regardless of the period was 48,292 (3.34%). The incidence of reinfection leading to hospitalization in the patients of the first wave of the disease was 16.72 per a thousand person-years. This rate was 33.20, 32.78, 98.17, and 288.98 per a thousand person-years in the patients of the second to fifth waves of the disease, respectively. The distribution of overall reinfection cases by disease waves in Iran is shown in Table 1. Patients with underlying cancer (189.27 per a thousand person-years) and patients with chronic kidney disease (188.18 per a thousand person-years) had the highest overall reinfection rates. The rate of overall reinfection based on other variables is shown in Table 2.

Based on the results of multivariable Cox regression analysis, getting infected with COVID-19 in the fifth wave of the disease compared to getting infected in the first wave (HR: 8.28, CI: 7.93-8.64, P<0.001), having cancer (HR: 2.30, CI: 2.19-2.42, P<0.001), chronic kidney disease (HR: 2.08, CI: 1.99-2.18, P<0.001) and age over 80 years (HR: 2.07, CI: 1.93-2.23, P<0.001) were respectively the most important risk factors for overall reinfection. In contrast, age 19-44 years (HR: 0.59, CI: 0.55 -0.64, P<0.001), the need for intubation (HR: 0.79, CI: 0.75 -0.84, P<0.001), having fever (HR: 0.87, CI: 0.86 -0.90, P<0.001) and cough (HR: 0.89, CI: 0.87 -0.90, P<0.001) in initial admission were the most important protective factors for the overall reinfection of COVID-19, respectively (Table 3).

In the analysis of multivariable Fine and Gray competing risk based on the Sub-distribution Hazard Ratio (SHR), hospitalization in Intensive Care Unit (ICU) (SHR: 3.72, CI: 3.27-4.22, P<0.001) and hospitalization in isolation wards (SHR:

3.42, CI: 3.01-3.88, P<0.001) compared with hospitalization in the emergency ward, getting the disease in the fourth wave (SHR: 2.45, CI: 2.36-2.55, P<0.001) compared with getting the disease in the first wave, and having cancer (SHR: 2.27, CI: 2.17-2.37, P<0.001) and chronic kidney disease (SHR: 2.01, CI: 1.93-2.10, P<0.001) were the most important risk factors, respectively, and need for intubation and the age of 19-44 years were respectively the most important protective factors for overall reinfection with COVID-19 (Table 3(.

### *3.3. Reinfection rate*

The number of reinfection cases (SARS-Cov-2 infection that occurred more than 90 days after the initial infection of COVID-19) was 18,648 (1.29% of all patients with COVID-19 and 38.61% of overall reinfection cases). The rate of reinfection among the subjects under study was 26.8 per a thousand person-years. This rate was 27.55 in women and 24.86 in men per a thousand person-years. The pattern of reinfection is similar to the overall reinfection pattern and the highest rate of reinfection per a thousand person-years was observed in age groups above 80 years (50.67), 65-79 years (41.06), and age under 5 years (28.53). The lowest rate of reinfection per a thousand person-years was observed in the age group of 19-44 years (13.40). Patients with underlying chronic kidney disease (81.93 per a thousand person-years) and cancer (67.33 per a thousand person-years) had the highest reinfection rates. The rate of reinfection based on other variables is shown in Table 2.

In multivariable Cox regression and the analysis of Fine and Gray competing risk, the developed model was the same as the model that was developed for the outcome of overall reinfection, so the details were not provided.

### *3.4. Recurrence (relapse) rate*

The total number of recurrent cases (SARS-Cov-2 infection that occurred less than 90 days after the initial infection of COVID-19) was 29,644 (2.05 % of all patients with COVID-19 and 61.34 % of the overall reinfection cases). The rate of recurrence among the subjects under study was 41.61 per a thousand person-years. This rate was 39.02 in women and 44.08 in men per a thousand person-years. The pattern of recurrence is similar to the overall reinfection and reinfection patterns. The highest rate of recurrence per a thousand person-years was observed in age groups above 80 years (86.63), 65-79 years (70.89), and age under 5 years (41.79). The lowest rate of recurrence per a thousand person-years was observed in the age group of 19-44 years (15.45).

Patients with a history of hospitalization in the emergency ward in initial infection (133.21 per a thousand person-years), patients with underlying cancer (121.93 per a thousand person-years), and chronic kidney disease (106.24 per a thousand person-years) had the highest rates of recurrence. The rate of recurrence based on other variables is shown in Table 2. In the investigation of factors related to recurrence with univariate and multivariable Cox regression and Fine and Gray competing risk, the risk and protective factors for recurrence were exactly identical to the risk and protective factors in reinfection and overall reinfection; therefore, the details were not provided.

### *3.5. Readmission rate*

The total number of readmissions (COVID-19 cases who were readmitted within less than 30 days of the initial infection) was 21,752 (1.50 % of all patients with COVID-19). The rate of readmission among the subjects under study was 30.53 per a thousand person-years. This rate was 27.89 in women and 33.04 in men per a thousand person-years. The highest rate of readmission per a thousand person-years was observed in age groups above 80 years (64.73), 65-79 years (52.24), and 45-64 years (27.09). The lowest rate of readmission was observed in the age group of 19-44 years (11.01 per a thousand person-years).

The highest rate of readmission was related to the fifth (230 per a thousand person-years) and fourth (42 per a thousand person-years) disease waves. Patients with a history of hospitalization in the emergency ward in initial infection (130.37 per a thousand person-years), patients with underlying cancer (80.16 per a thousand person-years), and chronic kidney disease (70.95 per a thousand person-years) had the highest readmission rates. The incidence of readmission based on other variables is shown in Table 2.

Based on the results of the multivariable Cox regression analysis, getting infected with the COVID-19 in the fifth wave of the disease compared to getting infected in the fourth wave (HR: 36.62, CI: 34.77-38.57, P<0.001), age over 80 years compared to age of 1 -5 years (HR: 2.72, CI: 2.42 -3.06, P<0.001), having cancer (HR: 2.23, CI: 2.07- 2.40, P<0.001), and chronic kidney disease (HR: 1.76, CI: 1.63- 1.89, P<0.001) were the most important risk factors for readmission, respectively. In contrast, age 19-44 years (HR: 0.69, CI: 0.61 -0.78, P<0.001), getting infected with COVID-19 in the first wave of the disease (HR: 0.0001, CI: 0.00005-0.0002, P<0.001), the second wave (HR: 0.0004, CI: 0.0001-0.001, P<0.001), and third wave (HR: 0.003, CI: 0.002-0.005, P<0.001) compared to getting infected in the fourth wave were the most important protective factors for readmission, respectively (Table 3).

## 4. Discussion

The available evidence has revealed that the immune system begins to produce antibodies after being exposed to COVID-19. Therefore, people are much less likely to be infected again, but in that case, reinfection with Coronavirus is usually not ruled out. Although reinfection, recurrence, and hospital readmission due to COVID-19 are not common, they may happen for some individuals (21). In the present study, according to Iran's national data from March 2020 to April 2021, after 1,445,451 people with a history of hospitalization due to COVID-19 and no history of COVID-19 vaccination were examined, the total reinfection rate was 67.79, the recurrence rate leading to hospital admission was 41.61, and

the rate of readmission due to COVID-19 was estimated to be 30.53 per 1000 person-years. Based on the existing reports, the rate of reinfection has been different due to the facilities available in the diagnosis and patients' follow-up. However, corresponding to the results of the study done by Snezana Medic, et al in the capital of Serbia, the rate of reinfection was reported to be 5.99 per 1000 person-months, which increased to 18.86% after 18 months of follow-up (22). Furthermore, according to a report provided by the state of Rhode Island, the rate of reinfection was reported as 1.9% among the public before vaccination during the alpha and delta variant waves (23). In addition, as the results of meta-analyses show, the recurrence rate due to COVID-19 is in the range of 2.3 to 21.4 percent (8,24,25), and the rate of hospital readmission 30 days after the initial discharge has been reported to be in the range of 4.2 to 20% (8,15) around the world. A single infection with COVID-19 can activate the immune response, but it cannot guarantee the absence of reinfection or the absence of side effects after recovery, such as readmission (26). Some people are likely to be inherently more at risk of reinfection or readmission. After examining the factors related to the occurrence of reinfection leading to hospitalization and hospital admission for COVID-19, it was observed that the risk of reinfection in alive patients and readmission 30 days after the initial discharge increased among the elderly, especially those over 65. However, this rate was less among younger patients compared to children under 5. Therefore, children under 5, possibly due to the weakness and lack of development of the immune system, and the elderly, due to underlying diseases and reduced immune system functions, are at risk of developing various diseases, especially COVID-19. In previous studies, an increase in age, especially over 65 years, was known to be a potential reason for the exacerbation of the disease process and, as a result, the poor prognosis of patients (27,28). Gender has been another influential factor in increasing the risk of reinfection, which leads to hospitalization and an increased risk of readmission 30 days after the initial discharge due to COVID-19. As shown in previously published studies, it has been reported that women naturally produce more interferon type 1; Oestradiol (E2), a female hormone, provides more protection against infection in women. Besides, unlike the estradiol hormone, testosterone can limit the immune response in men. Therefore, it can be assumed that, physiologically, men may be more susceptible to disease-causing agents, especially COVID-19, than women, although the reason is still debatable (29). Nevertheless, in the existing studies, contrary to our results, the risk of reinfection in women was higher than in men (22,30). On the other hand, in pregnant women, the risk of reinfection leading to hospitalization declined, but the risk of readmission 30 days after the initial discharge increased. Pregnancy is known for the change in the state of immune status. Therefore, the immune response during pregnancy may be less efficient. Nevertheless, there is limited evidence concerning reinfection during pregnancy, and it is not identified clearly if the change in immune status during pregnancy is associated with an increased risk of reinfection (31). Because based on the results of our study, pregnancy has been associated with a decline in the risk of reinfection, it can be presumed that since women are more concerned about their health in terms of lifestyle during pregnancy, they may be less exposed to the virus and are therefore less infected and less likely to be hospitalized again. On the other hand, according to the available evidence, being infected with COVID-19 during pregnancy can be associated with an increased risk of complications. Consequently, this factor can be effective in increasing the necessity for readmission of pregnant women (32).

Based on the findings, underlying diseases such as cardiovascular disease, chronic liver and kidney disease, diabetes, blood-borne diseases, inherited blood disorders, cancers, asthma, and psychiatric disorders have been associated with an increasing risk of reinfection, readmission, an overt immune response to pathogens, and poor prognosis. These underlying diseases weaken the immune system, so this may cause people with the mentioned diseases to be more prone, leading to more reinfection with the Coronavirus, readmission, and complications related to the disease (33). Even though the role of underlying diseases in causing severe COVID-19 has been proven, the role and reason for each one of these diseases in the reinfection of SARS-Cov-2 should be separately investigated (34). Patients with a severe form of the disease are those who often have severe symptoms upon entering the hospital, such as a severe drop in blood oxygen saturation and severe pulmonary involvement, which require hospitalization in the ICU or the use of mechanical ventilation (35). In the present study, the presence of symptoms such as fever, low level of consciousness, myalgia, and intubation in alive patients during initial infection are among the factors that reduce the risk of reinfection leading to hospitalization. This could be because those individuals who are hospitalized with symptoms during the initial infection have a severe form of the disease, and as a result, they may produce a stronger immune response to the infection than people with milder forms of the disease and those without symptoms. Therefore, this could be effective in future infections (36,37).

The partial pressure of oxygen in the arterial blood (PaO2 greater than 93) at the time of the initial infection has also played a role in reducing the risk of readmission and reinfection. People with normal oxygen levels in their blood would need pulmonary rehabilitation and therapy less; therefore, it is expected that they will experience fewer complications after the disease and have fewer re-visits to the hospital than other people (38). However, concerning reinfection, it is possible that people who had a lower blood oxygen level during the initial infection were more cautious about their health after discharge and, as a result, were less exposed to infection compared to other people, or the disease has not been serious enough to lead to hospitalization; therefore, the decrease

in the risk of reinfection in these people may be rooted in the lifestyle of these people after the primary infection and the severity of the secondary infection (39). Although, further studies are needed to confirm the underlying reasons for these results. According to the findings, the risk of hospital readmission has increased because of respiratory distress during initial hospitalization due to COVID-19. This clinical sign can be effective in experiencing complications after recovery and may lead to readmission (38).

According to the available evidence, reinfection with SARS-Cov-2 can be due to an insufficient immune response to the primary infection, a decrease in Neutralizing Antibodies (NAb), or infection with mutated (new) variants of the virus (31). Based on the results of this study, the risk of reinfection in different epidemic waves has been increasing compared to the first wave. Since the leading variant in the first to the third waves in Iran was probably the Wuhan variant, the cause of the fourth wave was probably the alpha variant, and the cause of the fifth wave was probably the delta variant, it is expected that reinfection occurred due to the lack of vaccination; also, with the circulation of mutated variants, the risk of reinfection increased in the fourth and fifth waves. In agreement with the results reached in the present study, the available evidence has also shown that the delta wave, especially among unvaccinated people, accounts for most cases of reinfection (40). In the evaluation of readmission, the risk of hospital readmission increased in the fifth wave compared to the fourth wave, but it decreased in the first to third waves compared to the fourth wave. Clearly, with the emergence of a new wave and a change in the virus variant, it is expected that the number of cases of both infection and hospitalization will increase. The findings of the existing studies are also in agreement with the present study (40,41). Based on our findings, the type of ward during the initial hospitalization for COVID-19 increased the risk of reinfection and hospital readmission. This finding was in accordance with other studies (42,43) that revealed hospitalization, especially ICU admission, can affect reinfection rates due to prolonged hospitalization, recovery, and more exposure to other microorganisms. On the other hand, it is not unexpected for individuals who are severely affected by COVID-19 to experience mild to moderate reinfection or to require hospitalization (44). Concerning infectious diseases, the possibility of reinfection, recurrence after recovery, and hospital readmission due to the complications of the disease is not unlikely, but the important issue is whether the cases that have been reported conform to standard definitions. it should not be forgotten that the exact period of immunity of the patient after contracting COVID-19 and vaccination is not known until today, and there is a likelihood of reinfection or recurrence of the disease, especially during the mutation of the virus, since some studies have revealed that humoral immunity weakens as time passes.

## 5. Limitations

Among the limitations of the present study is the lack of information about the virus variant in patients with COVID-19, which in this study, was divided and reported only based on the time of its occurrence, without considering the criteria of the type of virus variant in the standard definition of reinfection and recurrence. The unavailability of information related to hospital discharge criteria and complete recovery of patients (based on PCR tests) is one of the effective factors in calculating the rates of reinfection, recurrence, and readmission and has caused an overestimation of the rates.

## 6. Conclusions

Advanced age or childhood, as well as having underlying conditions like cancer and chronic kidney disease, increase the risk of infection and readmission. Therefore, the presence of an active surveillance system can be effective in identifying reinfection, re-hospitalization, and a better understanding of the disease and patients' health situations. Also, the widespread vaccination of people, following the principles of prevention, and proper management of the disease can help prevent the frequent occurrence and contracting the disease.

## 7. Declarations

### *7.1. Acknowledgments*

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### *7.2. Ethical Approval*

This study was performed in accordance with the declaration of Helsinki; this included permission to use anonymized quotations in publications according to the ethics committee. The requirement for informed consent from participants was waived because of the registry-based nature of the study. The ethical approval was granted by the review board of the National Institutes for Medical Research Development (NIMAD), Tehran, Iran (IR.NIMAD.REC.1400.112).

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### *7.4. Competing interests*

The authors declare that they have no competing interests.

### *7.5. Availability of data and materials*

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

### 7.6. Authors' contribution

Conceptualization and Methodology: KE, SSHN. Data cleaning: NI, NT, SF, YM, SSHN. Formal analysis: YM, SSHN. Project administration: SSHN, NT, ER. Visualization: FSH, KFB, RF, AM. Writing–original draft: NT, SSGH, SF. Writing and reviewing: SSHN, AS, YM, KE. All authors read and approved the final version of the manuscript.

### 7.7. Using artificial inteligence chatbots

The authors declare that they did not used artificial intelligence chatbots for writing.

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**Table 1:** Frequency of overall reinfection cases in hospitalized patients due to COVID-19 according to epidemic waves in Iran

| Wave | Without* | Wave 1 | Wave 2 | Wave 3 | Wave 4 | Wave 5 | Total |
|---|---|---|---|---|---|---|---|
| 1 | 193061 (98.29) | 33 (0.02) | 9 (0.004) | 24 (0.01) | 1052 (0.54) | 2239 (1.14) | 196418 (100) |
| 2 | 43809 (96.96) | - | 1 (0.002) | 12 (0.03) | 438 (0.97) | 922 (2.04) | 45182 (100) |
| 3 | 272088 (97.57) | - | - | 78 (0.03) | 2199 (0.79) | 4500 (1.16) | 278865 (100) |
| 4 | 431293 (95.51) | - | - | - | 9790 (2.17) | 10477 (2.32) | 451560 (100) |
| 5 | 456908 (96.51) | - | - | - | - | 16518 (3.49) | 473426 (100) |
| Total | 1397159 (96.66) | 33 (0.002) | 10 (0.0006) | 114 (0.01) | 13479 (0.93) | 34656 (2.40) | 1445451 (100) |

The number (percentage) of hospitalized people (regardless of the time period) who had reinfections in the same or subsequent waves of the disease which led to hospitalization. *Cases without reinfection.

**Table 2:** The rate of overall reinfection, reinfection, recurrence and hospital readmission among studied cases

| Variable | Overall reinfection | Reinfection > 90 days | Recurrence < 90 days | Readmission < 30 days |
|---|---|---|---|---|
| **Age (years)** | | | | |
| 1 – 5 | 70.32 (66.7 -74.8) | 28.53 (25.8- 31.4) | 41.79 (38.5- 45.3) | 25.82 (23.3- 28.6) |
| 5 – 18 | 54.87 (51.9- 58.1) | 22.22 (20.3- 24.2) | 32.65 (30.3- 35.1) | 19.78 (18- 21.7) |
| 19 – 44 | 28.86 (28.2- 29.6) | 13.40 (12.9- 13.8) | 15.45 (14.9- 15.9) | 11.01 (10.5- 11.4) |
| 45 – 64 | 58.52 (57.5- 59.5) | 22.30 (21.7- 22.9) | 36.21 (35.4- 36.9) | 27.09 (26.4- 27.7) |
| 65 – 79 | 111.95 (110.3- 113.7) | 41.06 (40.0- 42.1) | 70.89 (69.5- 72.2) | 52.24 (51.1- 53.4) |
| ≥ 80 | 137.30 (134.5-140.2) | 50.67 (48.9- 52.4) | 86.63 (84.4 -88.9) | 64.73 (62.8- 66.7) |
| **Gender** | | | | |
| Male | 68.94 (68.1- 69.8) | 24.86 (24.3- 25.3) | 44.08 (43.4- 44.7) | 33.04 (32.4- 33.6) |
| Female | 66.58 (65.7 – 67.4) | 27.55 (27.0- 28.1) | 39.02 (38.3- 39.6) | 27.89 (27.3- 28.4) |
| **Asthma** | | | | |
| Yes | 111.15 (105.8- 116.7) | 51.59 (48.0- 55.4) | 59.55 (55.7 63.6) | 37.66 (34.6- 40.9) |
| No | 66.89 (66.28- 67.5) | 25.64 (25.2- 26.0) | 41.24 (40.7- 41.7) | 30.38 (29.9- 30.7) |
| **Pregnancy in admission** | | | | |
| Yes | 30.54 (26.7-35) | 8.95 (6.9- 11.5) | 21.58 (18.36- 25.3) | 16.73 (13.9- 20.1) |
| No | 68.15 (67.5-68.8) | 26.34 (25.9- 26.7) | 41.81 (41.3- 42.3) | 30.66 (30.2- 31.1) |
| **Chronic heart disease** | | | | |
| Yes | 124.77 (122.2-127.4) | 48.36 (46.7- 50.0) | 76.40 (74.4- 78.4) | 54.04 (52.3- 55.7) |
| No | 61.40 (60.8-62) | 23.68 (23.3- 24.0) | 37.71 (37.2- 38.1) | 27.89 (27.5- 28.3) |
| **Chronic liver disease** | | | | |
| Yes | 113.46 (102.2 -126) | 41.49 (34.8- 49.3) | 71.96 (63.1- 82.1) | 49.92 (42.6- 58.4) |
| No | 67.59 (67 -68.2) | 26.11 (25.7- 26.4) | 41.48 (41- 41.9) | 30.45 (30- 30.8) |
| **Blood diseases** | | | | |
| Yes | 137.73 (126.7- 149.7) | 59.45 (52.3- 67.5) | 78.27 (70.05- 87.4) | 53.93 (47.1- 61.6) |
| No | 67.40 (66.7- 68) | 25.99 (25.6- 26.3) | 41.41 (40.9- 41.9) | 30.40 (30- 30.8) |
| **Chronic kidney disease** | | | | |
| Yes | 188.18 (180.9-195.7) | 81.93 (77.2- 86.9) | 106.24 (100.8- 111.9) | 70.95 (66.5- 75.6) |
| No | 65.52 (64.9- 66.1) | 25.12 (24.7- 25.5) | 40.39 (39.9- 40.8) | 29.77 (29.4- 30.2) |
| **Any type of cancer** | | | | |
| Yes | 189.27 (181.4- 197.4) | 67.33 (62.7- 72.2) | 121.93 (115.6- 128.5) | 80.16 (75.1- 85.5) |
| No | 65.835 (65.2- 66.4) | 25.51 (25.1- 25.8) | 40.32 (39.8- 40.7) | 29.73 (29.3- 30.1) |
| **Diabetes** | | | | |
| Yes | 112.40 (110.1- 114.7) | 40.38 (39.0- 41.7) | 72.01 (70.2- 73.9) | 52.98 (51.4- 54.6) |
| No | 62.03 (61.4- 62.6) | 24.34 (23.9- 24.7) | 37.69 (37.2- 38.1) | 27.63 (27.2- 28.0) |
| **Mental illness** | | | | |
| Yes | 115.78 (109- 123) | 44.28 (40.1- 48.8) | 41.23 (40.7- 41.7) | 49.24 (44.8- 54.0) |
| No | 67.174 (66.5-67.8) | 25.94 (25.5- 26.3) | 71.49 (66.2- 77.2) | 30.29 (29.8- 30.7) |

**Table 2:** The rate of overall reinfection, reinfection, recurrence and hospital readmission among studied cases (continue)

| Variable | Overall reinfection | Reinfection > 90 days | Recurrence < 90 days | Readmission < 30 days |
|---|---|---|---|---|
| **HIV/AIDS** | | | | |
| Yes | 110.31 (82.1- 148.2) | 35.09 (20.7- 59.2) | 75.20 (52.5- 107.5) | 40.11 (24.5- 65.4) |
| No | 67.77 (67.2- 68.4) | 26.17 (25.8- 26.5) | 41.59 (41.1- 42.1) | 30.53 (30.1- 30.9) |
| **Immune suppress disease** | | | | |
| Yes | 98.53 (84.6- 114.6) | 43.66 (34.7- 54.8) | 54.87 (44.7- 67.2) | 35.99 (28- 46.2) |
| No | 67.72 (67.1- 68.3) | 26.137 (25.7- 26.5) | 41.58 (41.1- 42.0) | 30.52 (30.1- 30.9) |
| **Other chronic diseases** | | | | |
| Yes | 99.95 (97.1- 102.8) | 35.39 (33.7- 37.1) | 64.56 (62.3- 66.8) | 47.19 (45.2- 49.1) |
| No | 65.50 (64.9- 66.1 | 25.52 (25.1- 25.9) | 39.98 (39.5- 40.4) | 29.34 (28.9- 29.7) |
| **Cough** | | | | |
| Yes | 57.29 (56.5 58.1) | 21.72 (21.2- 22.2) | 35.57 (34.9- 36.2) | 27.10 (26.5- 27.6) |
| No | 76.60 (75.7- 77.5) | 29.92 (29.3- 30.4) | 46.68 (46- 47.3) | 33.41 (32.8- 33.9) |
| **Fever** | | | | |
| Yes | 54.12 (53.3- 54.9) | 22.64 (22.1 23.2) | 31.47 (30.8- 32.1) | 23.377 (22.8- 23.9) |
| No | 76.68 (75.8- 77.5) | 28.47 (27.9- 28.9) | 48.20 (47.5- 48.8) | 35.19 (34.6- 35.7) |
| **Need to Intubation** | | | | |
| Yes | 69.66 (66.2- 73.3) | 23.84 (21.8- 26.0) | 45.82 (43.0 48.8) | 33.70 (31.3- 36.3) |
| No | 67.74 (67.1- 68.3) | 26.25 (25.8- 26.6) | 41.48 (41- 41.9) | 30.44 (30.0- 30.8) |
| **PaO2 > 93/hour (mmHg)** | | | | |
| Yes | 55.34 (54.6- 56.1) | 24.19 (23.7- 24.6) | 31.14 (30.6- 31.7) | 21.58 (21.1- 22.0) |
| No | 83.53 (82.5- 84.5) | 28.68 (28.1- 29.2) | 54.83 (54.02- 55.6) | 41.84 (41.1- 42.5) |
| **Low consciousness** | | | | |
| Yes | 106.90 (102.8- 111.1) | 36.88 (34.5- 39.4) | 70.02 (66.7- 73.4) | 48.32 (45.6-51.2) |
| No | 66.44 (65.8- 67.1) | 25.81 (25.4- 26.2) | 40.63 (40.16- 41.1) | 29.92 (29.5- 30.3) |
| **Respiratory distress** | | | | |
| Yes | 79.01 (78.1- 80.1) | 27.98 (27.4- 28.5) | 51.10 (50.3- 51.8) | 38.42 (37.7- 39.1) |
| No | 58.71 (57.9- 59.5) | 24.72 (24.2- 25.2) | 33.98 (33.4- 34.5) | 31.37 (30.6- 32.1) |
| **Muscular pain** | | | | |
| Yes | 63.82 (62.7- 64.9) | 22.86 (22.2- 23.5) | 40.95 (40.1- 41.8) | 31.37 (30.6- 32.1) |
| No | 69.37 (68.6- 70.1) | 27.49 (27.0- 27.9) | 41.87 (41.3 42.4) | 30.20 (29.7- 30.6) |
| **Type of ward in first admission** | | | | |
| Emergency | 133.12 (117.4 150.9) | 0.000 | 133.12 (117.3-150.9) | 130.37 (114.7-148) |
| Isolate | 64.26 (63.3- 65.1) | 24.31 (23.7- 24.8) | 39.95 (39.2- 40.6) | 30.32 (29.6- 30.9) |
| ICU | 97.11 (94.7- 99.5) | 32.76 (31.4- 34.2) | 64.34 (62.4- 66.3) | 47.30 (45.6- 48.9) |
| Other | 64.8 (64.1 65.7) | 26.59 (26.1- 27.1) | 38.28 (37.6- 38.9) | 27.10 (26.5- 27.6) |

All rates are presented in per thousand person-years scale with 95% confidence interval.
PaO2: Partial pressure of oxygen; HIV/AIDS: Human Immunodeficiency Virus/ Acquired immunodeficiency syndrome.

**Table 3:** Factors associated with overall reinfection and hospital readmission

| Factors | †Overall reinfection | P-value | †Readmission | P-value | *Overall reinfection | P-value |
|---|---|---|---|---|---|---|
| **Age (year)** | | | | | | |
| 1 – 5 | Reference | - | Reference | - | Reference | - |
| 5 – 18 | 0.90 (0.82 -0.99) | 0.043 | 1.08 (0.93-1.26) | 0.265 | 0.97(0.89- 1.06) | 0.524 |
| 19 – 44 | 0.59 (0.55 -0.64) | <0.001 | 0.69 (0.61-0.78) | <0.001 | 0.58(0.54- 0.62) | <0.001 |
| 45 – 64 | 0.97 (0.91 - 1.04) | 0.453 | 1.29 (1.15-1.45) | <0.001 | 0.92(0.86- 0.98) | 0.013 |
| 65 – 79 | 1.66 (1.55- 1.79) | <0.001 | 2.19 (1.95-2.46) | <0.001 | 1.46(1.37 - 1.56) | <0.001 |
| ≥ 80 | 2.07 (1.93- 2.23) | <0.001 | 2.72 (2.42-3.06) | <0.001 | 1.68(1.57- 1.80) | <0.001 |
| Gender (male) | 1.07 (1.05 -1.09) | <0.001 | 1.24(1.20- 1.27) | <0.001 | 1.06(1.04- 1.08) | <0.001 |
| **Epidemic wave** | | | | | | |
| First | Reference | - | 0.0001 (0.00005-0.0002) | <0.001 | Reference | - |
| Second | 1.53 (1.44 -1.63) | <0.001 | 0.0004 (0.0001-0.001) | <0.001 | 1.59(1.49- 1.69) | <0.001 |
| Third | 1.34 (1.28 -1.40) | <0.001 | 0.003 (0.002-0.005) | <0.001 | 1.33(1.27- 1.38) | <0.001 |
| Fourth | 2.5 (2.41- 2.60) | <0.001 | Reference | - | 2.45(2.36- 2.55) | <0.001 |
| Fifth | 8.28 (7.93 -8.64) | <0.001 | 36.62 (34.77-38.57) | <0.001 | 1.97(1.90- 2.05) | <0.001 |
| **Underlying diseases** | | | | | | |
| Asthma | 1.50 (1.42 - 1.59) | <0.001 | 1.13(1.03- 1.23) | 0.006 | 1.62(1.54- 1.70) | <0.001 |
| Pregnancy | 0.91 (0.79- 1.05) | 0.199 | 1.35(1.11- 1.64) | 0.002 | 0.87(0.75- 0.99) | 0.041 |
| CHF | 1.23 (1.20- 1.27) | <0.001 | 1.11(1.06- 1.15) | <0.001 | 1.27(1.24- 1.31) | <0.001 |
| Chronic liver disease | 1.32 (1.16 - 1.47) | <0.001 | 1.42(1.20- 1.69) | <0.001 | 1.26(1.13 - 1.40) | <0.001 |
| Blood diseases | 1.65 (1.50 - 1.81) | <0.001 | 1.63(1.41- 1.90) | <0.001 | 1.71(1.56- 1.86) | <0.001 |
| CKD | 2.08 (1.99 - 2.18) | <0.001 | 1.76(1.63- 1.89) | <0.001 | 2.01(1.93 -2.10) | <0.001 |
| Cancer | 2.30 (2.19- 2.42) | <0.001 | 2.23(2.07- 2.40) | <0.001 | 2.27(2.17- 2.37) | <0.001 |
| Diabetes | 1.20 (1.16 - 1.23) | <0.001 | 1.20(1.16- 1.25) | <0.001 | 1.18(1.15- 1.21) | <0.001 |
| Mental illness | 1.28 (1.21 - 1.37) | <0.001 | 1.18(1.06- 1.30) | 0.001 | 1.35(1.27-1.43) | <0.001 |
| HIV /AIDS | 1.15 (0.82 - 1.60) | 0.413 | 1.13(0.68- 1.88) | 0.610 | 1.18 (0.86- 1.61) | 0.293 |
| Immune suppress disease | 1.46 (1.23 - 1.73) | <0.001 | 1.25(0.94- 1.66) | 0.116 | 1.48(1.26 -1.73) | <0.001 |
| Other chronic disease | 1.16 (1.12 -1.19) | <0.001 | 1.14(1.09- 1.20) | <0.001 | 1.14(1.11-1.18) | <0.001 |
| **Having sign and symptoms in first admission** | | | | | | |
| Cough | 0.89 (0.87 - 0.90) | <0.001 | 0.95(0.92- 0.98) | 0.003 | 0.88(0.87 - 0.90) | <0.001 |
| Fever | 0.87 (0.86 -0.90) | <0.001 | 0.91(0.89- 0.94) | <0.001 | 0.87(0.85 -0.89) | <0.001 |
| Need to Intubation | 0.79 (0.75 - 0.84) | <0.001 | 0.74(0.68- 0.80) | <0.001 | 0.30(0.28 -0.31) | <0.001 |
| PaO2 > 93 (mmHg) | 0.93 (0.92 -0.95) | <0.001 | 0.79(0.77- 0.82) | <0.001 | 1.03(1.01 – 1.05) | <0.001 |
| Low consciousness | 1.00 (0.95 -1.05) | 0.978 | 1.001(0.93- 1.07) | 0.962 | 0.89(0.86- 0.93) | <0.001 |
| Respiratory distress | 1.02 (1.0 -1.04) | 0.034 | 1.12(1.09 1.16) | <0.001 | 0.99(0.97- 1.00) | 0.182 |
| Muscular pain | 0.92 (0.90 - 0.94) | <0.001 | 0.98(0.95- 1.02) | 0.507 | 0.90(0.88- 0.92) | <0.001 |
| **Type of Ward in first admission** | | | | | | |
| Emergency | Reference | - | Reference | - | Reference | - |
| Isolate | 1.34 (1.17 - 1.53) | <0.001 | 1.08(0.94 -1.23) | 0.247 | 3.42(3.01- 3.88) | <0.001 |
| ICU | 1.43 (1.25 -1.63) | <0.001 | 1.21(1.05- 1.39) | 0.006 | 3.72(3.27- 4.22) | <0.001 |
| Other | 1.58 (1.38 - 1.81) | <0.001 | 1.04(0.91- 1.19) | 0.483 | 3.13(2.75- 3.56) | <0.001 |

† Based on multivariate cox regression and presented as Adjusted Hazard Ratio (HR) with 95% confidence interval.
* Based on Fine and Gray competing risk model and presented as Sub-distribution Hazard Ratio (SHR). PaO2: Partial pressure of oxygen; HIV/AIDS: Human Immunodeficiency Virus/Acquired immunodeficiency syndrome; ICU: intensive care unit; CHF: Chronic heart disease; CKD: Chronic kidney disease.