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Rehospitalization Incidence in COVID-19 Reinfection: A Retrospective Cohort Study

Mahmoud Abdelgawad Elattar*[1], Samah Ahmed Gad[2], Asmaa Nabil Elgamal[3], Esraa Morshedy Beltagy[3], Taghreed Salah Elsheikh[1], Khaled Ebied Elfeky[2], Amany Mohamed Abd el-azziz[1], Hassan Yousef Elmsri[2]

[1]Clinical Research Department, Kafr El-Sheikh Fever Hospital,
Kafr El-Sheikh Health Affairs, Egyptian Ministry of Health (MOH), Egypt

[2]Therapeutic Medicine Department,

[3]Clinical Research Department, Kafr El-Sheikh Health Affairs, Egyptian Ministry of Health (MOH), Egypt

***Corresponding author**: Mahmoud Abdelgawad Elattar, **Mobile:** (+20) 01005750779,
E-Mail: attarmahmoud83@gmail.com, **ORCID:** 0000-0002-3565-0965

ABSTRACT

Background: The effect of COVID–19 re-infection is not fully clear. Patients may have a benefit or no change in the degree of illness if re-infected with the COVID-19 virus. **Objective:** This study aimed to estimate the incidence of re-hospitalization due to COVID–19 re-infection and to characterize the features of those re-hospitalized patients.

Patients and Methods: A retrospective cohort study from the COVID-19 patients' registration data in Kafr El-Sheikh governorate, Egypt in the period from September 2020 to July 2021. The study population was 1000 patients who had re-infection with the covid-19 disease, at least four months after hospital discharge. The patient presentations included fever, cough, dyspnea, diarrhea, or fatigue plus: polymerase chain reaction confirming infection with SARS-COV2 and/or computed tomography (CT) chest suggesting covid-19 infection. **Results:** Among the study population, there were two (0.2 %), re-hospitalized, due to COVID-19 re-infection. Symptoms with re-hospitalization were fever 100%, cough 100%, tachypnea 100%, and fatigue 50%. **Conclusion:** Once hospitalized; COVID-19 patients significantly have a very low risk of re-admission if re-infected. Clinical approach to COVID-19 patients should consider the history of previous hospitalization due to COVID-19. This history will help in the management including treatment, need for hospital admission, and initial prognosis. All study populations didn't receive the COVID-19 vaccine as the study period was before or just after authorization and availability of the vaccine.

Keywords: COVID-19, Re-infection, Admission, Re-hospitalization, Natural immunity.

INTRODUCTION

The worldwide burden of COVID-19 disease is growing with more than 600 million cases and a mortality of about 1%. By spring 2021, almost a quarter of the world's population had been infected. After the spread of the Delta variant mutation in mid-2021, there was a significant spike in infection rates [(1)].

The new pandemic of COVID-19 had been proven to cause re-infection of the same person [(2,3)]. Risk factors for re-infection were not fully clear. Immune-compromised patients, patients with chronic diseases, and personnel with repeated exposure (e.g. healthcare workers) resemble the riskiest groups for re-infection with the COVID-19 virus. Re-infection should be differentiated from prolonged primary infection.

A suspected COVID-19 re-infection case was defined as positive polymerase chain reaction (PCR) or rapid antigen test (RAT) within ≥ 60 days following a previously confirmed covid-19 infection[(4)]. According to research, people who have recovered from an infection can obtain naturally acquired immunity that appears to be at least as protective as protection brought on by vaccinations [(5)].

Reinfection had a less infectious course if the previous infection was symptomatic. Previous studies showed risk factors for re-admission [(6)], and clinical characteristics of re-hospitalized COVID-19 patients [(7)]. The impact of the previous infection with COVID -19 on patients' hospitalization was not fully known, they may have a benefit or no change. We estimated the association between natural immunity due to COVID-19 reinfection and the need for re-hospitalization.

Our hypothesis; COVID-19 patients who had previous COVID -19 infection will have a mild to moderate form of the disease with a good prognosis if re-infected. In recurrent exposure, Specific immunity will be responsible for fighting the pathogen with the formation of specific antibodies in a short time.

PATIENTS AND METHODS

A retrospective cohort study from the COVID-19 patients' registration data in Kafr El-Sheikh governorate, Egypt, in the period from September 2020 to July 2021. The study population was 1000 patients who were recorded with hospitalization due to COVID-19 infection and then had COVID-19 re-infection, at least four months after discharge. Data of the study population during hospital admission due to their first COVID-19 infection were collected from recorded data of COVID -19 patients from isolation hospitals in Kafr El-Sheikh governorate (Egypt); Kafr El-Sheikh fever hospital, Kafr El-Sheikh chest hospital, Qilin hospital, Desouq hospital, and Kafr El-Sheikh general hospital. Data of re-infection were collected from home isolation records then history and data collection by contacting participants about COVID-19 re-infection. COVID-19 re-infection was classified as mild, moderate, or severe according to clinical, radiological, and laboratory evaluation [(8)].

Inclusion criteria: Adult patients who was admitted due to COVID-19 infection and had re-infection at least four months after discharge.

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Exclusion criteria: Pregnant females, chronic kidney disease, chronic hepatic disease, cancer, hematologic malignancy, immune deficiency patients, and patients taking immune suppressive medications for long periods.

Study population and Sample size: 1000 patients who were admitted to the isolation hospitals in the period of the study, fit for inclusion and exclusion criteria, and had covid-19 re-infection at least four months after discharge.

Data collection:

Each COVID-19 case report was carefully reviewed from medical records. All the data were collected by two different co-authors independently. An excel sheet was filled with these data.

• History of the previous infection collected from hospital records about the date of the previous infection, period of isolation inward, period of isolation in intensive care unit (ICU) if needed, did he have oxygen therapy or not?

• Patients data (Age, sex, residence, co-morbidities, hospitalization, and discharge dates);

• The days from the appearance of symptoms to hospitalization; days of hospital stay; and if admitted to the intensive care unit.

- Peripheral oxygen saturation, PCR, complete blood count (CBC), C-reactive protein (CRP), serum glutamic pyruvic transaminase (SGPT), serum glutamic-oxaloacetic transaminase (SGOT), and Serum creatinine at the time of hospitalization.

- Clinical evaluation and management plan for patients.

• CT chest evaluation at admission.

Patient's classification as having a mild, moderate, or severe course of the disease according to WHO Classification [8]:

• Mild disease: Symptomatic patients with no pneumonia or hypoxia.

• Moderate disease: patients with pneumonia; (Fever, cough, dyspnea, and tachypnea) with no signs of severe pneumonia and peripheral oxygen saturation >92% on room air.

• Severe disease: patients with pneumonia; (Fever, cough, dyspnea, and tachypnea) plus one of the following; • Tachypnea >30 breaths/minute, and

• Peripheral oxygen saturation <92% on room air.

Case definition: Triaging of patients as suspected, probable, or confirmed covid-19 cases according to the WHO definition [9].

Suspected case:

A person who meets the clinical OR epidemiological criteria:

Clinical criteria: Acute onset of fever AND cough OR acute onset of ANY THREE OR MORE of the following signs or symptoms: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, chorizo, dyspnea, nausea/diarrhea/anorexia.

Epidemiological criteria:

(A) Contact of a probable or confirmed case, or linked to a COVID-19 cluster.

(B) A hospitalized patient with severe acute respiratory illness with onset within the last 10 days.

(C) A person with a positive covid-19 antibody test.

Probable case:

(A) A patient who meets clinical criteria AND is a contact of a probable or confirmed case or linked to a COVID-19 cluster.

(B) Unexplained death in an adult with respiratory distress preceding death AND who was a contact of a probable or confirmed case or linked to a COVID-19 cluster.

Confirmed case:

(A) A person with a positive Nucleic Acid Amplification Test (NAAT).

(B) A person meeting clinical criteria AND/OR epidemiological criteria (suspect case A) with a positive professional use or self-test SARS-CoV-2 Antigen-RDT.

• History and data collection by contacting participants about covid-19 re-infection. Covid-19 re-infection was classified as mild, moderate, or severe according to clinical, radiological, and laboratory evaluation.

Ethical consent: The study protocol had been approved by the Ethics Committee of the ministry of health and population, Egypt (Com.No/Dec.No:24-2021/17). All study participants provided written informed permission after being informed of our research's goals. The Declaration of Helsinki for human beings, which is the international medical association's code of ethics, was followed during the conduct of this study.

Statistical analysis: Data analysis was performed using Statistical Package for the Social Sciences (SPSS) V.23 and a P value less than 0.05 was regarded as statistically significant. Numerical variables were expressed as mean (SD) if normally distributed; and were compared by t-test. Abnormally distributed numerical variables were expressed as median (25-75th percentile) and the Wilcoxon signed-rank test was used. Categorical data were expressed as numbers (Percentage) and compared by chi-square test if normally distributed. Abnormally distributed Categorical data were compared by Fisher's exact test. The risk ratio was used to measure the association between previous COVID -19 infection and hospital re-admission if re-infection occurred.

RESULTS

A total of 1000 COVID-19 patients who were re-infected at least four months after hospital discharge; were selected as the study population. Data from their medical records during hospital admission due to the first covid-19 infection in the period from September

2020 to July 2021. The average age is 50.8 with female predominance (56%). Study participants show main clinical features of fever (81%), cough (73%), fatigue (19%), and muscle ache (14%). Chronic diseases in the study patients are; Hypertension (29.9%), diabetes mellitus (28.9%), and ischemic heart disease (6.5%) (Figure 1).

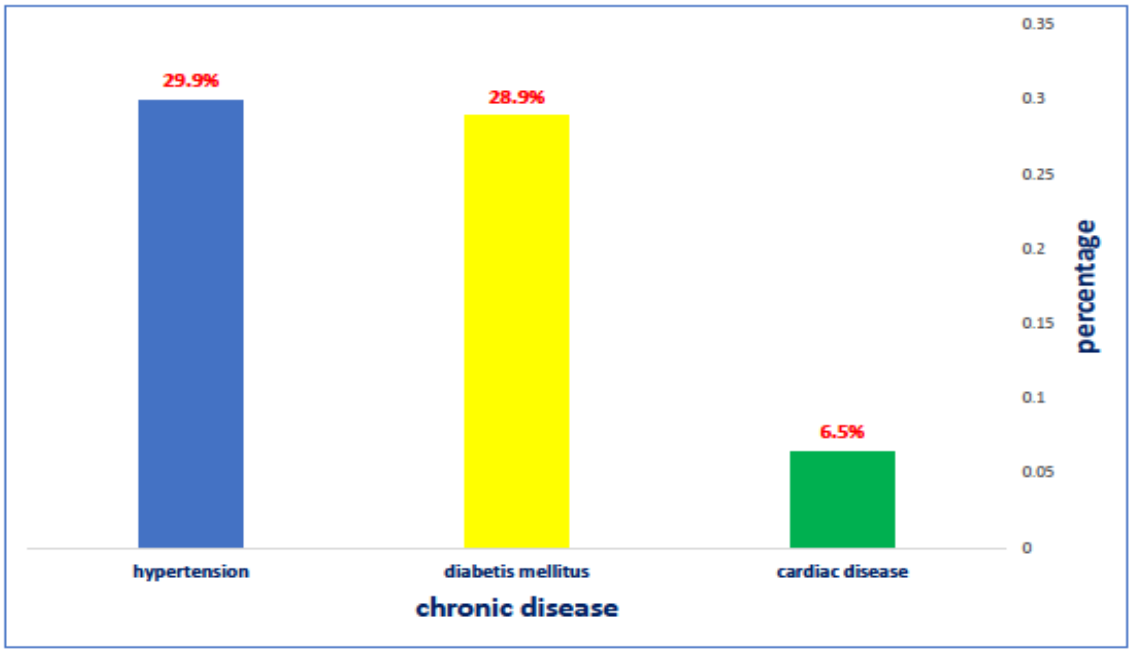

Figure (1): The percentage of hypertension, diabetes mellitus, and ischemic heart disease in study patients.

The patients are classified according to received treatments into; antiviral (79.3%), anti-coagulant (95.2%), steroids (96.2%), and oxygen therapy (78.4%), (Figure 2).

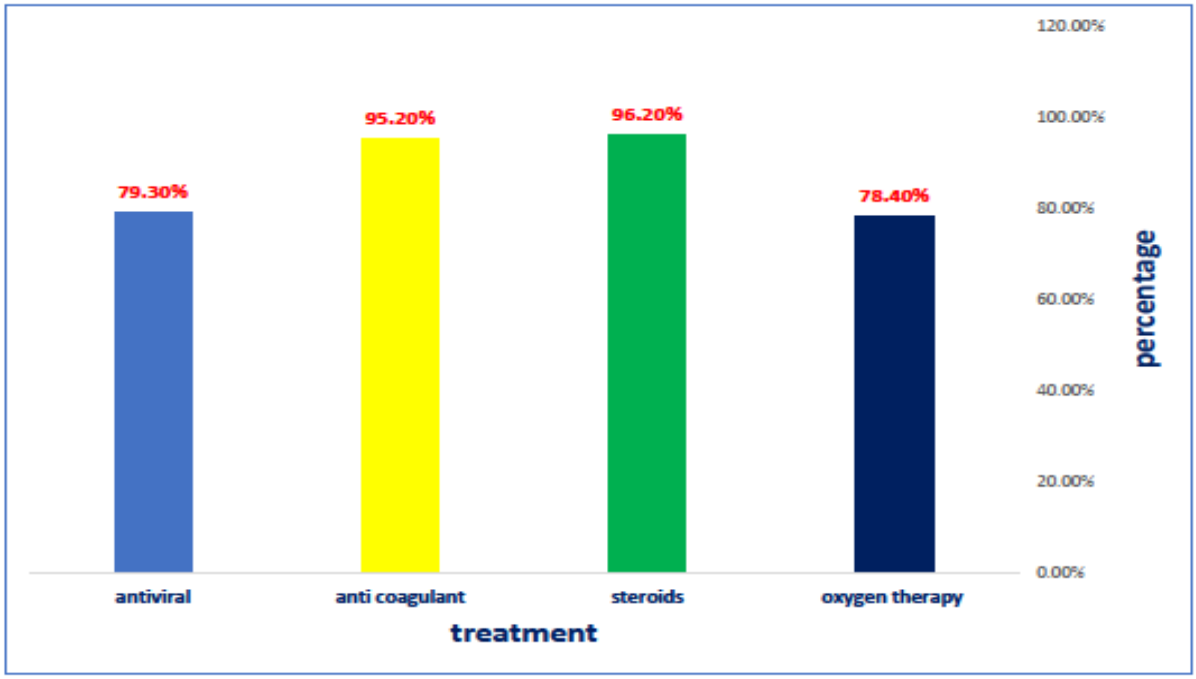

Figure (2): The percentage of treatment received in study patients (antiviral, anticoagulant, steroids, and oxygen therapy).

All patients were not vaccinated against COVID -19 diseases.

Only two patients (0.2 %) of COVID-19 were re-hospitalized due to re-infection. Clinical presentations, laboratory findings, and treatment of the two patients on both admissions were summarized in (Table1).

The average age of the two patients was 31.5 years and both were females. Both are healthcare workers; nursing staff. According to the epidemiological history, patients mentioned symptoms during infection times, fever, tachypnea, and cough in both patients and both times of infection. Sore throat occurred in one patient during the first attack and fatigue in the second patient during the second infection. One patient received oxygen therapy in both admissions

while the other did not receive oxygen in either of her admissions. On the first admission, there was one patient (50%) receiving antiviral drugs while on the second admission, both had anti-viral drugs.

Table (1): Shows data of the two patients on the first and second admissions about clinical presentations, laboratory findings, and treatment.

Variables	Patient A		Patient B	
	1st admission	2nd admission	1st admission	2nd admission
Fever	yes	yes	yes	yes
Tachypnea	yes	yes	yes	yes
Cough	yes	yes	yes	yes
Fatigue	no	no	no	yes
Period of hospitalization	2 days	13 days	18 days	11 days
Hemoglobin (mg/dl)	13	12.8	10.2	10.5
Neutrophils (thousand/c.mm)	3700	3100	10200	7800
Lymphocytes (thousand/c.mm)	1800	1200	1600	2400
Platelets (thousand/c.mm)	248000	196000	311000	275000
SGOT (unit/litre)	30	40	50	50
SGPT (unit/litre)	35	40	79	75
Urea (mg/dl)	35	42	33	40
Creatinine (mg/dl)	0.8	0.6	1.1	0.8
Oxygen therapy	no	no	yes	yes
Antibiotics	yes	yes	yes	yes
Antiviral	no	yes	yes	yes
Anticoagulants	yes	yes	yes	yes
Steroids	yes	yes	yes	yes

DISCUSSION

In this retrospective cohort study involving hospitalized covid-19 patients in the period from September 2020 to July 2021, we observed the risk of hospital re-admission with COVID-19 re-infection is 0.2%. Only two of the 1000 study participants need re-hospitalization due to covid-19 re-infection. The two re-admitted patients were females, in their fourth decade, and both were nurses. This suggests as middle age and repeated exposure to covid-19 patients are risk factors for severe covid-19 infection, they are also a risk for re-hospitalization with covid-19 re-infection. This high protection for most study patients with covid-19 repeated infection from severe infection and re-hospitalization gives a clue about the conversion of the covid-19 pandemic to an endemic state.

This was as protection gained after infection with other endemic human coronaviruses; repeated infections are less in severity [(10)]. The study was designed on covid-19 patients who were hospitalized to confirm that they had a moderate course of the disease with pneumonia or a severe course with pneumonia and hypoxemia. Patients who have Pregnancy, chronic renal disease, chronic liver disease, cancer, hematologic malignancy, immune deficiency, or taking immune suppressive medications for long periods were excluded as these conditions interfere with the immune response to infection.

Previous studies found that natural infection gives protection against re-infection and serious disease [(10-13)]. The severity of re-infection is affected by the severity of the first infection [(14)]. This was explained by the presence of specific antibodies and cellular immunity. A quick drop in antibodies within four months after infection was linked to previous, mild, or asymptomatic COVID-19 infections.

On the other hand; T-cell immunity is robust and is associated with long-lasting immunity. Several other studies had shown that asymptomatic infections may result in a lesser immune response than symptomatic infections and that people with severe disease mounted a greater antibody titer than those with mild disease [(15)]. In our study; hospitalized patients on the first admission had a moderate or a severe degree of the disease. So, they had a higher immune response with a higher antibody titer and T cell immunity. This immune response especially memory cells gives a rapid immune response against re-infection leading to less severity of the disease on recurrent illness.

We estimated protection against serious disease by the number of patients who needed re-hospitalization due to COVID-19 re-infection. Specific immunity with re-exposure to infection provides protection helping to overcome the disease with a mild to moderate course in most cases. All study patients were not vaccinated against COVID -19; as the study period was before or shortly after authorization and availability of the vaccine, so the protection is due to immunity from natural infection. Despite the high protection after natural infection, we can't encourage personnel to expose to infection or not to take the available vaccine. Personnel who had a natural covid-19 infection and then take the vaccine will gain hybrid immunity. Both

vaccine-induced immunity and natural immunity give protection but hybrid immunity is superior.

The time, schedule, and adverse effects of vaccination of previously infected individuals are important items for future research about hybrid immunity in covid-19. Herd immunity in parallel with vaccination will be the way to overcome the pandemic. Management of COVID-19 patients should stress in history of the previous admission due to COVID-19 infection to make medical and financial priorities according to the expected course of the disease. This study had limitations: genomic PCR for COVID -19 and antibody titer was not done for all patients, no available electronic medical records for all data of the patients, and some laboratory testing such as serum ferritin and D-dimer was not done for most patients.

CONCLUSION

Natural immunity gained from covid-19 infection gives high protection against re-infection, the need for re-hospitalization, and serious outcomes. The incidence of re-hospitalization with COVID-19 re-infection is very low (0.2 %). Hybrid immunity gives stronger protection but more studies are needed for its best schedule. The management of COVID -19 patients should focus on previous infection and previous hospitalization. Additionally, we should pay more attention to genome sequencing to identify whether all variants are the same or different in giving immunity protection. Personalized treatment should be scheduled to treat patients with recurrent COVID-19 infections.

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Data Availability: Due to ethics committee regulations, the datasets created and analyzed during the current investigation are not publically accessible; however, they are available from the corresponding author upon request.

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