University of Baghdad
Al Kindy College of Medicine

Persistent Respiratory Symptoms Post Corona Virus Infection

A research project submitted to the Family & Community medicine Department. Al Kindy College of Medicine as a Partial Fulfillment of Research Module - Year III

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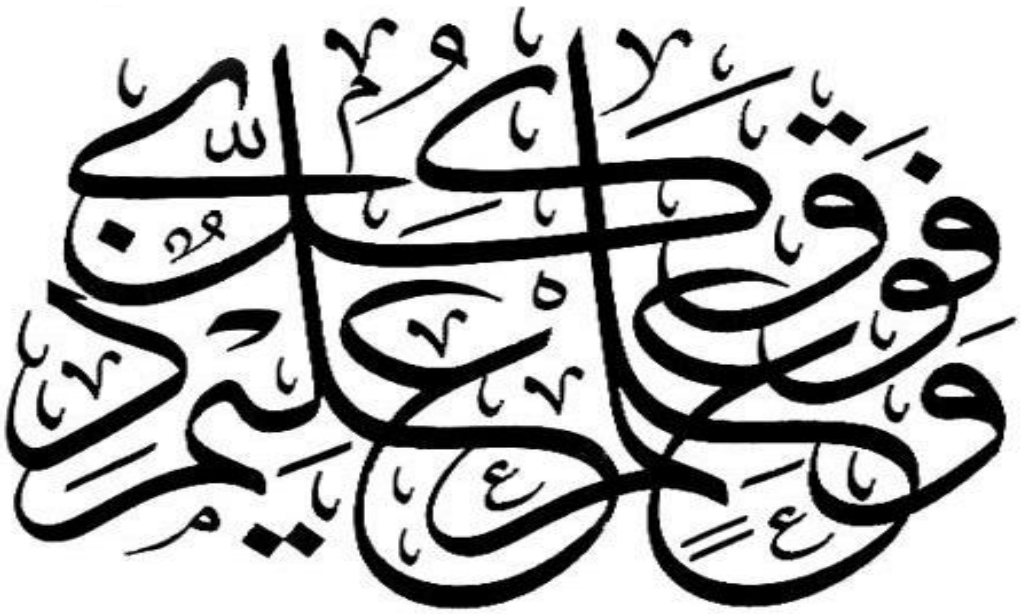

صدق الله العظيم

سورة يوسف (76)

Certification

I certify that this research project was prepared under my supervision, in partial fulfillment Research Module Year III.

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Certification of Committee

We, the examining committee, after reading this research project and examining the candidates

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in its contents, found that it meets the standards in partial fulfillment for Passing the Module.

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Acknowledgment

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Abstract

Background: Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is one of the viruses that was first identified in Wuhan city, Hubei province, China, and is responsible for this pandemic. World Health Organization (WHO) declared Health emergency all over the world in January 30, and a pandemic on March 11, 2020.

Objectives: To determine the frequency of persistent respiratory symptoms after COVID-19 infection.

Patients and Methods: A cross-sectional study was conducted from December 2022 to April 2023 to assess frequency of respiratory symptoms post COVID-19 infection among the Medical and non- medical students who infected with COVID-19 whether vaccinated or not.

Results: The study included 382 medical students at Al-Kindy College of Medicine- University of Baghdad that participated in this study. The majority of them were females (72%) and the rest were males (28%). Most of the students were vaccinated (95.3%) with Pfizer/BioNTech COVID-19 vaccines (71.7%) with two doses (71.2%). The students were infected with COVID-19 and some of them were infected before vaccination (62.6%) and the rest (21.7%) after vaccination. After their recovery from Covid-19 whether vaccinated or not, they had respiratory symptoms and other clinical manifestations. Regarding respiratory symptoms, intermittent (47.4%) dry (46.6%) cough (40.6%) was the most common respiratory symptoms that persist for sixty days. Other symptoms were headache was the most common one (39.5%) followed by fever (22.5%).

Conclusions: The most common respiratory symptoms was intermittent, dry, cough was the most common respiratory symptoms that persist for sixty days.

Keywords: COVID-19; respiratory; symptoms.

List of Contents

Introduction:

The world had many epidemics and pandemics throughout past years that have affected millions of populations in different countries. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is one of the viruses that was first identified in Wuhan city, Hubei province, China (1). World Health Organization (WHO) declared Health emergency all over the world in January 30, and a pandemic on March 11, 2020 (2).

It is believed to be a zoonotic disease transmitted from bats and spread through direct contact with respiratory droplets of infected person (3). Thus, Health care workers like are at higher risk group for infection (4). Preventing transmission of this infection is important for reducing morbidity, mortality like wearing masks, gloves and face shield (5). Corona virus is an envelope, positive-sense single-stranded RNA viruses causing respiratory tract infection, enteric, hepatic, and neurologic diseases and divided into subfamilies (α, β, γ, and δ) which human COVID-19 caused by α, and β (6). The virus is mainly transmitted via contact with respiratory droplets and cause viremia through binding to ACE2 receptors(7). Patients may remain asymptomatic while others get respiratory failure (8). The lung of COVID-19 demonstrated bilateral diffuse damage to alveoli which is known as acute respiratory distress syndrome (ARDS). Early diagnosis of the disease is very important using reverse transcriptase-polymerase chain reaction (RT-PCR) and next generation sequencing (NGS) (9). Potential therapy of this disease using drugs like Chloroquine, Ribavirin, convalescent plasma, and monoclonal antibody (10).

Aim of the study:

*To know the frequencies of persistent respiratory symptoms post COVID-19 infection.

Review of literatures

1.1.COVID-19 Phylogeny

Corona viruses are zoonotic viruses cause many diseases like enteritis in cows, pigs, pangolins, birds, and lung diseases in chicken (11). This virus belongs to the order Nidovirales that includes three families: Coronaviridae, Arteriviridae, and Roniviridae. Coronaviridae is divided into two subfamilies: Torovirinae and Coronavirinae. The later Coronavirinae is (HCoV-OC43, Severe Acute Respiratory Syndrome human coronavirus (SARS-HCoV), HCoV-HKU1, and Middle Eastern respiratory syndrome coronavirus (MERS-CoV),

-Gamma(viruses of whales and birds)
-Delta (viruses isolated from pigs and birds) (12).
-Omicron (viruses isolated from South Africa) (13).

Seven types of coronaviruses are causing infections in humans and four of them are endemic human coronaviruses HCoV-229E (alpha), HCoV-NL63 (alpha), HCoV-OC43, and HCoV-HKU1 (beta), that caused mild common cold and the last three are cause severe lower respiratory infections which cause epidemic- coronaviruses SARS-CoV and MERS-CoV, and a third pandemic one causing coronavirus SARS-CoV-2 that belong to the beta coronavirus group. Amazingly, bats could be the natural reservoirs of the three human coronaviruses while palm civet, camels and pangolin acting as intermediate transmitting host that facilitated the transmission of the virus to humans (14,15).

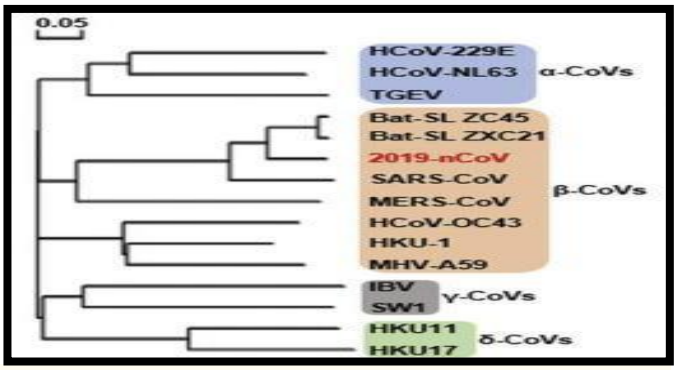

Figure-1- phylogenetic tree of coronaviruses.(16)

1.2.Corona virus Genome, Structure and life cycle

The size of SARS-CoV-2 genome is 30 kb COVID-19 with G+C contents about 43% and its shape is either spherical or pleomorphic enveloped particles encodes a large, non-structural polyprotein (ORF1ab) that cleaved to generate 15-16 proteins, 4 structural proteins (spike (S) surface glycoprotein, the membrane (M) protein, the envelope (E) protein and the nucleocapsid (N) protein), and 5 accessory proteins (ORF3a, ORF6, ORF7, ORF8 and ORF9). The viral genome contains a unique N-terminal fragment within the spike protein. Genes for the major structural proteins in all coronaviruses occur in the 5′–3′ order as S, E, M, and N5(17) (Figure-2-).

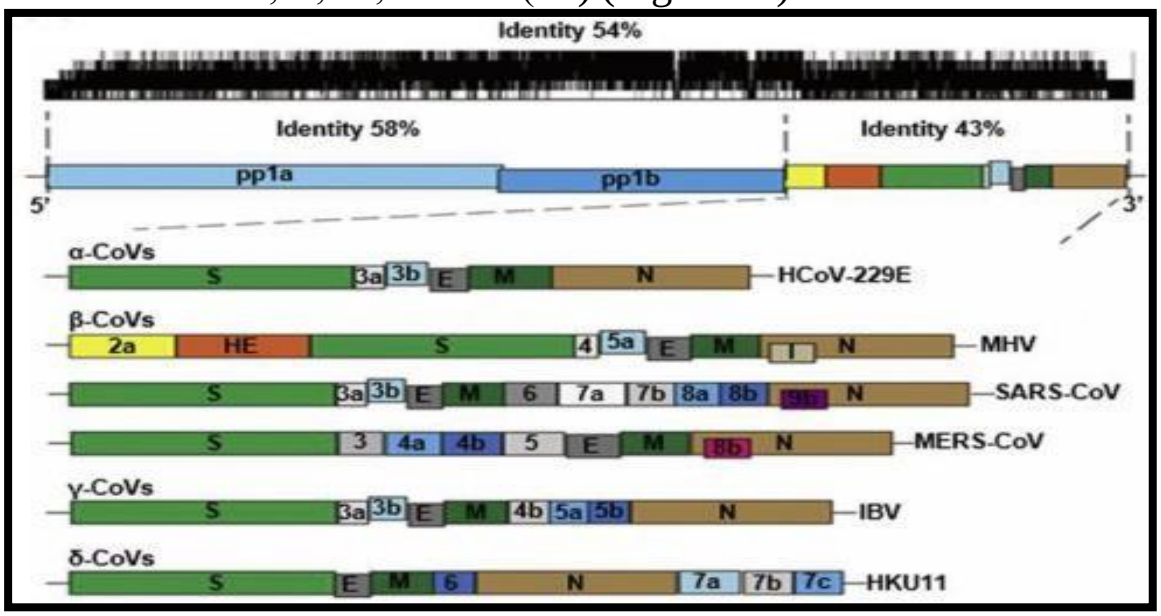

Figure-2- Genomic structure of Corona virus .(16)

The structure of Corona virus consist of single-stranded (positive-sense) RNA genome associated with a nucleoprotein within a capsid included matrix protein. The envelope had a club-shaped glycoprotein spikes or projections (Figure-3-). The spike surface glycoprotein is important in attachment to host cells and help to develop monoclonal antibody drugs and to guide the design and development of vaccines (18).

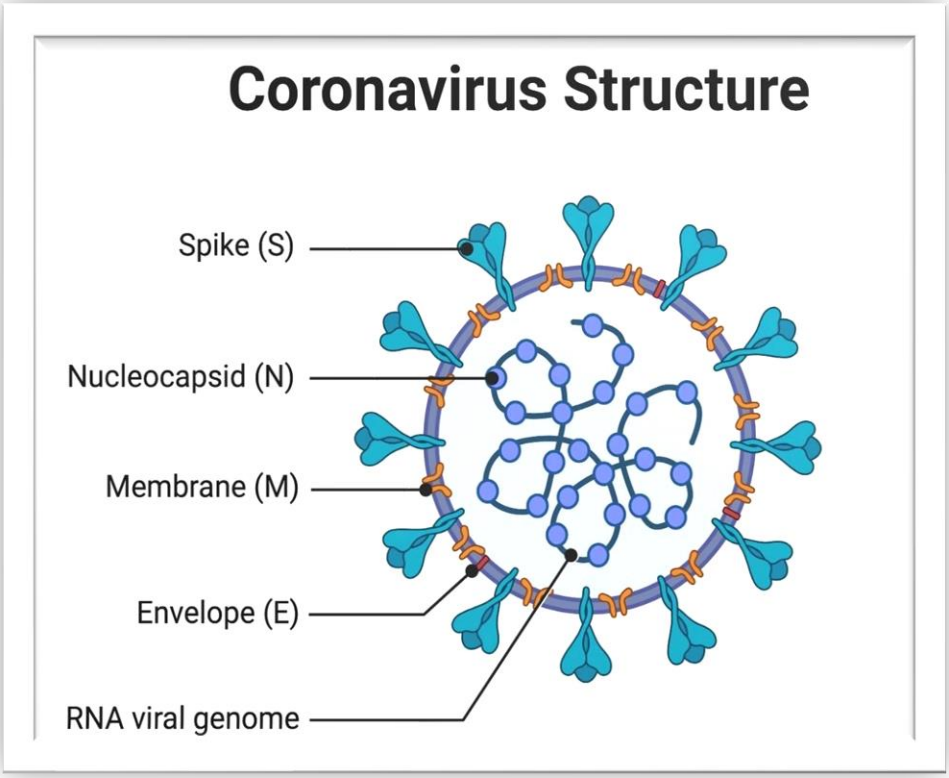

Figure-3- Structure of COVID-19 (19).

The life cycle of this virus started by infecting human cells by binding to the cell surface protein angiotensin-converting enzyme 2 (ACE2) through the Receptor Binding Domain (RBD) of its spike (S) protein (Figure-4-). Adding together, SARS-CoV-2 may utilize receptor CD147 that expressed in high levels in the brain to infect cerebral nervous system. After binding, the clathrin mediated endocytosis and release of genomic RNA and viral protein will be synthesized in free endoplasmic reticulum that attached to ribosomes then vesicle mediated exocytosis will release new viruses (19). This virus leads to a variety of symptoms started from sore throat, fever, cough, dyspnea, pneumonia, respiratory failure, and extral pulmonary symptoms like gastrointestinal symptoms (20,21).

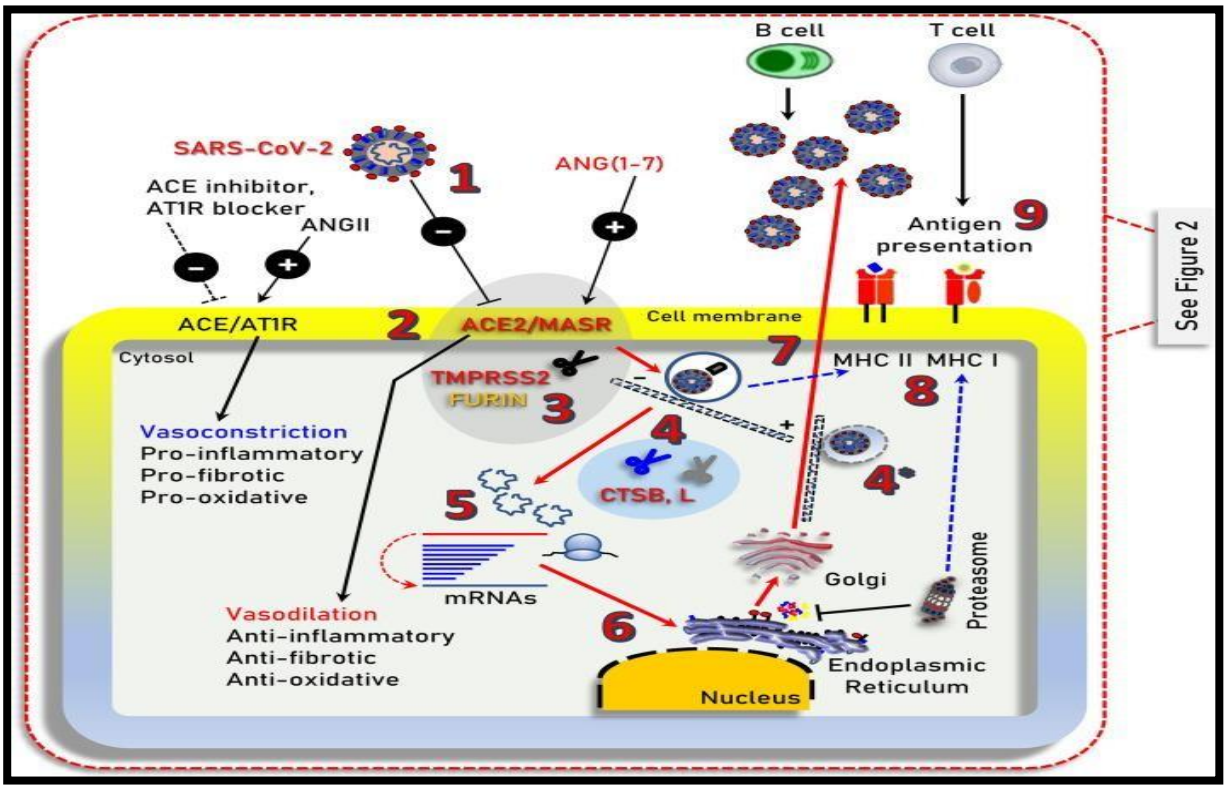

Figure-4- Life cycle of Corona virus.(22)

1.4.Epidemiology of Corona virus

Epidemiology is a discipline that study the emergence of new diseases and analyses the evolution of it like COVID-19.

1.4.1. Global COVID-19 epidemiology

The first reported case of COVID-19 in Wuhan, China, at the end of 2019 then rapidly spread throughout China and by the end of January 2020, COVID-19 had already been reported in Europe and USA and in many other countries in spite of global efforts to prevent its spread. The infection was declared as an international public health emergency by the WHO on 30 January 2020 (23). As of 10 March, COVID-19 was spread to many countries in Europe and more than 48,000 confirmed cases and about 3000 deaths were reported across the globe. Finally, the WHO declared COVID-19 as a pandemic on 11 March 2020 (24). Notably, after 15 March, a sharp rise in the number of infected cases and death rate was observed, and by the end of March, the number of infected individuals increased to more than 640,000 and the death rate crossed more than 18% (25).

1.5. Immunopathogenesis

The immunopathogenesis has not been completely understood and with aid of autopsy and biopsy studies would be the key to understand the disease. Viral infection stimulates the host immune response which is initiated by entrance of the virus through binding to ACE1 receptor and start multiplication then stimulate innate immune cells and failure of the innate immune responses in removal of viruses' leads to the activation of adaptive immune system by presentation of viral antigenic peptides via major histocompatibility complex (MHC) or human leukocyte antigen (HLA) on antigen presenting cells (macrophage, dendretic cell, and B cells) to specific cytotoxic T lymphocytes (CTLs) that leads to secretion of cytokines and chemokines suggesting that the cytokine storm was associated with disease severity and respiratory failure (figure -10-) (26,27).

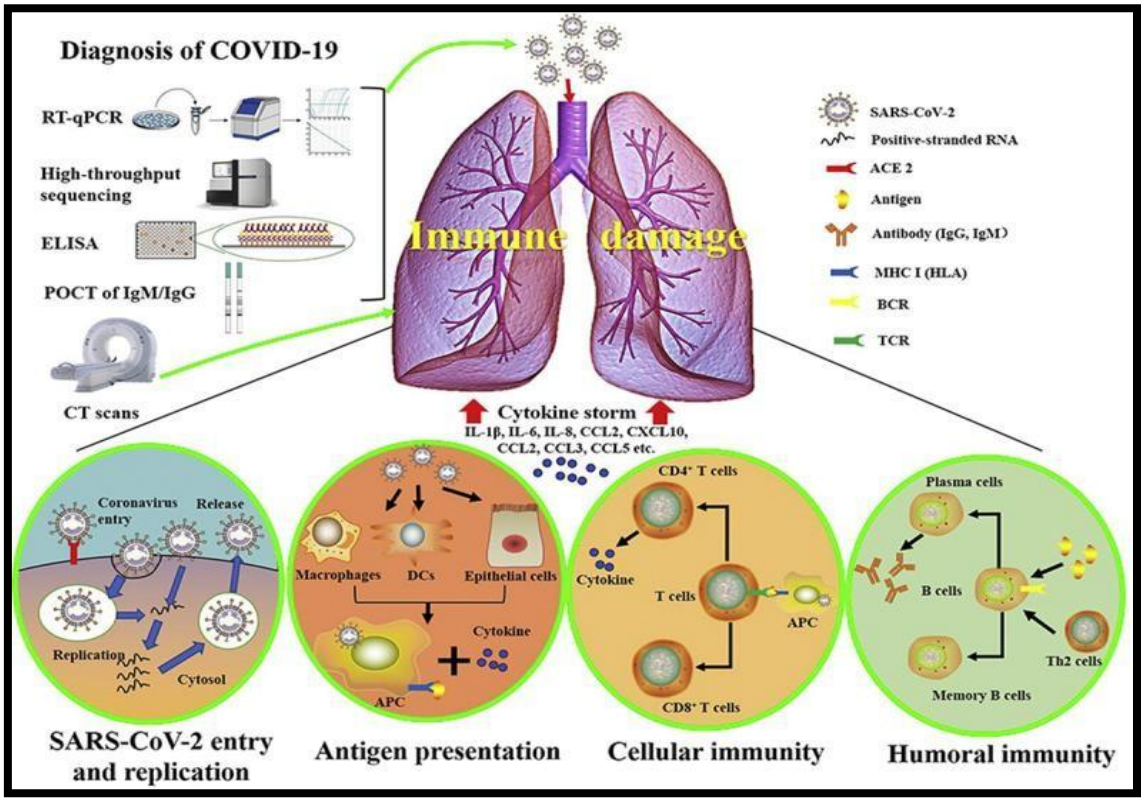

Figure-10- Immune pathogenesis of COVID-19 (27)

These cytokines stimulate the influx more monocytes, macrophages and neutrophils from the blood to the site of infection (28). However, COVID-19 infection also activates Th2 cells that secrets antibodies and memory B cells. Thus, corticosteroids used in treatment of patients with severe illness for reducing inflammatory induced lung injury (29).

1.6. Diagnosis

Clinical diagnosis of COVID-19 made by detection of viral genome using RT-PCR nucleic acid from nasal or pharyngeal swabs and increased level of serum IgM in acute stage and IgG in chronic phase. Other laboratory tests like increased number of neutrophils, decreased number of lymphocytes, high level of C-reactive protein, increased LDH, elevated d-Dimer, thrombocytopenia, elevated ALT, and high HS- troponin level and IL-6, IL-2, TNF-α, and IL-10(30,31). Other medical tests are chest X-ray and chest CT scan that demonstrated bilateral ground glass opacity (32).

1.7. Treatment

There are many types of drugs were used to treat this disease depend on the severity and clinical course of COVID-19 illness like antiviral drugs, antibody based treatments (Monoclonal antibodies), corticosteroids, and immunomodulating drugs (33). Other drugs like Hydroxychloroquine, Remdesivir, Lopinavir, and Ivermectin (34,35,36,37,38).

1.8. Prevention Of COVID-19 and vaccination

The major preventive tools against COVID-19 are using surface disinfectant, antiseptics, detergents, personal protective equipment (39). Inorganic surfaces and contaminated hands are the most horizontal site for the transmission of CoVID-19.Thus using hydrogen peroxide, ethanol (75%), isopropyl alcohol (70%) are the key ingredient responsible for the virucidal activity (40). Prevention occurred by vaccination with different manufactured type (41). Three doses of vaccine was advisable for adult and children to enhance immunity against the Omicrone variant of COVID-19 (42,43).

Patients and methods

Study design and period

A cross-sectional study was conducted from December 2022 to April 2023 to assess frequency of respiratory symptoms post COVID-19 infection among the Medical and non- medical students.

Study setting

This study was conducted among medical students in Al-Kindy Medical College, University of Baghdad, Baghdad -Iraq and other non-medical students.

Samples

Some of Medical students at different stages studied at Al-Kindy medical college-University of Baghdad and non -medical students were included in this study.

Inclusion criteria: Medical and non-medical students who had been studying in the college for the study period and infected with COVID-19.

Exclusion criteria: Staffs, lecturers, teachers and other administrative in the college were excluded.

Questionnaire

An online questionnaire by Google forms was used to collect the data and utilized as screening instrument examining frequency of respiratory symptoms post COVID-19 infection. The questionnaire contains many questions regarding symptoms and other information's. Sociodemographic questions like stage, age, gender was added to the original questionnaire. Adequate explanation concerning the purposes of the study was provided to the participants and informed consent was obtained to utilize their data for research purposes.

Statistical analysis

The data were analyzed using SPSS-version- 25. Descriptive statistics including frequencies, percentages.

Results

The study included 382 medical students at Al-Kindy College of Medicine- University of Baghdad that participated in this study. The majority of them were females (72%) and the rest were males (28%)as shown in Table -1-. The mean age was 21years (SD ±0.7) as demonstrated in Table-2-.

Gender	Frequency	Percent
Female	275	72.0
Male	107	28.0
Total	382	100.0

Table -1- Distribution of gender among participations.

Years	Frequency	Percent
16-20	247	64.65
21-25	135	35.34
Total	382	99.99

X ±SD=21±0.7

Table-2- Distribution of age among participants.

The majority from medical college (96.3%) and the rest from non-medical college (3.7%) as shown in figure -1-.

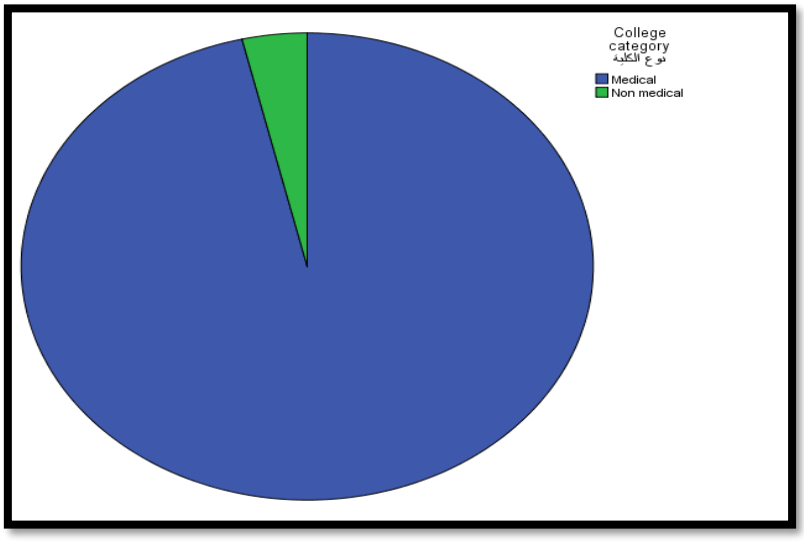

Figure-1- Medical and non-medical distribution of the students.

Table-3- illustrated that most of the students were vaccinated (95.3%) with Pfizer/BioNTech COVID-19 vaccines (71.7%) with two doses (71.2%).

COVID-19 Vaccine	Frequency	Percent
Unvaccinated	18	4.7
Vaccinated	364	95.3
Moderna COVID-19 vaccine	13	3.4
Oxford, AstraZeneca vaccine	37	9.7
Pfizer/BioNTech COVID-19 vaccines	274	71.7
Sinopharm(Chinese) vaccine	40	10.5
First dose	81	21.2
Second dose	272	71.2
Third dose	13	3.4
Total	382	100.0

Table-3- Frequency of vaccinated students with different types of vaccines and doses.

The students were infected with COVID-19 and some of them were infected before vaccination (62.6%) and the rest (21.7%) after vaccination (table-4-).

State of infection with COVID-19	Frequency	Percent
After vaccination	83	21.7
Before vaccination	239	62.6
Total	382	100.0

Table -4- state of COVID-19 infection regarding vaccination.

After their recovery from Covid-19 whether vaccinated or not, they had respiratory symptoms and other clinical manifestations. Regarding respiratory symptoms, intermittent (47.4%) dry (46.6%) cough (40.6%0 was the most common respiratory symptoms that persist for sixty days as shown in the table -5-.

Respiratory symptoms	Frequency	Percent
Common Cold	77	20.2
Difficulty breathing	80	20.9
Cough	155	40.6
Dry type	178	46.6
Reproductive type	73	19.1
Diurnal	6	1.6
Intermittent	181	47.4
Nocturnal	30	7.9
Persistent	84	22.0
30 days	213	55.75
60 days	120	31.41
120 days	25	6.54
240 days	24	6.28
Total	382	100.0

Table-5- frequencies of respiratory symptoms after recovery fro COVID-19 infection.

Other clinical manifestation that persists after COVID-19 infection as demonstrated in table-6-, headache was the most common one (39.5%) followed by fever (22.5%).

Clinical manifestations	Frequency	Percent
Abdominal pain	17	4.5
Bad mouth smell	20	5.2
Diabetes	1	3.0
Fever	86	22.5
Headache	151	39.5
High heart rate	27	7.1
Hypertension	1	3.0
Hyperthyroidism	3	8.0
Vomiting	5	1.3

Table-6- Clinical manifestations after recovery fromCOVID-19.

Discussion

Coronavirus disease 2019 (COVID-19) caused severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) and there is a limited data on long-term effects and lingering symptoms of post COVID-19 recovery. This study deals with a sample of college students with long term symptoms after recovery from this disease. Most of them were females (72%) from medical college (96.3%), their ages were from 16-20 years (64.65%). Regarding vaccination state, 95.35% of them were vaccinated with Pfizer/BioNTech COVID-19 vaccine (71.7%) with two doses (71.2%). They infected with COVID-19 virus before vaccination (62.6%).

After their recovery from Covid-19 whether vaccinated or not, they had intermittent (47.4%), dry (46.6%), cough (40.6%) was the most common respiratory symptoms that persist for sixty days followed by difficulty in breathing (20.9%) and the least one is common cold (20.2%). Other study done by Sonnweber T *etal*. 2021 who reported that 41% of COVID-19 patients had dyspnoea (shortness of breath) after 100 days after infection due to lung pathology in 63% of them that improved over time (44) while another study reported 74% of the recovered patients had shortness of the breath (45). Regarding nearby country like Saudi Arabia illustrated chronic cough (56.8%), dyspnea (11.2%), headache (64%), abdominal pain (26%), palpitation (25%), and Diabetes mellitus (41%) in post COVID-19 recovery period (46,47). Concerning Indian patients with minimal COVID-19 symptoms, they showed dry cough (0.6%), headache (4.5%), and hypertension (4.5%) (48).

This difference with other studies may be due to type of patients' selection, severity of the disease that patients had, type of the drugs that prescribed to them, sample size, period of follow-up to those patients. Moreover, 54.3% of recovered sever COVID-19 infected patients had abnormal CT findings and 75.4% had an abnormal pulmonary function compared to the non-sever cases while others had sleep apnoea as a predictor of lung fibrosis (49,50).

SARS-CoV-2 has been a pan-systemic disease affecting multi-organ beyond the acute phase of infection and recovery. This study reported other extra pulmonary manifestations include headache (39.5%) and fever (22.5%) while others like diabetes (3%),

hypertension (3%), tachycardia (7.1%), hyperthyroidism (8%). Other studies illustrated different organ manifestations like myocardial inflammation and pericarditis (40%) in recovered patients, acute kidney injury with greater dialysis requirement after recovery and discharge in 32% of patients (51,52). Long-term effects on the liver during the path of recovery showed elevated liver enzymes and liver damage in 39% of the patients while in sever hospitalized patients was 86% (53). The long-term effect of COVID-19 on fertility was 20% of women had decrease sex hormones and 19% had prolonged cycle while testosterone, follicle-stimulating hormone and luteinising hormone levels were normal in patients recovered from COVID-19 (54). Concerning endocrine system, thyroid function did not affect after recovery but some developed new onset of diabetes mellitus (55). About 4.72% who had encephalopathy or psychiatric diseases (56). This differences with other studies due to severity of diseases of the patients, sample size, and management and drugs used. Thus COVID-19 infection needs a proper follow-up and management of the disease post recovery.

Conclusions: The most common respiratory symptoms were intermittent, dry, cough was the most common respiratory symptoms that persist for sixty days.

Limitation of this study:

-Small sample size.

-Poor response of students in this study.

Recommendations:

- Extended the sample size to involve more population with different occupation.
- Discriminate the symptoms whether the role of vaccine had an effect in decreasing symptoms.

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