



Incidence of post-COVID-19 syndrome and its association with COVID-19 severity in a tertiary private hospital: Prospective cohort study

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ABSTRACT

Objectives: We determined the incidence of post-COVID-19 syndrome and its association with COVID-19 severity among patients discharged in a tertiary private hospital.

Methods: This single-center prospective cohort study included admitted patients 18 years old and older, diagnosed with COVID-19, discharged recovered, and interviewed at least 6 months from onset of COVID-19. Incidence of post-COVID-19 syndrome obtained and its association with COVID-19 severity was analyzed.

Results: Among the 280 patients included in the study, 71.43% were diagnosed with post-COVID-19 syndrome, with higher proportion in men (53%). The median age was 50 (18–92) years old. All severe COVID-19 cases (21%) had post-COVID-19 syndrome. The leading comorbidities were hypertension (25%) and diabetes mellitus (10%). Top three symptoms were shortness of breath (42%), fatigue (38%), and body malaise (36%). Moderate cases had about five times higher odds of post-COVID-19 syndrome than mild cases. Severe cases had 92 times higher odds of having post-COVID-19 syndrome than mild cases. COVID-19 severity at baseline was significantly associated with post-COVID-19 syndrome.

Conclusion: This study found a high incidence of post-COVID-19 syndrome with a higher proportion occurring in men. Severe cases had higher odds of having post-COVID-19 syndrome than mild cases.

Introduction

The strain was first isolated from a patient in Wuhan, China [1]. The incredible speed at which the virus spread has caused a global pandemic that continues to leave much of the world reeling from its effects nearly 3 years later. According to World Health Organization (WHO) [2,3], globally as of August 2023, there have been 768,983,095 confirmed cases of COVID-19, including 6,953,743 deaths. In the Philippines, there have been 4,172,753 confirmed cases of COVID-19 with 66,583 deaths. Most people infected with COVID-19 have mild symptoms [1]. Scientists and researchers are constantly tracking infection and recoveries. Overall, COVID-19 recovery rate is between 97% and 99.5% [2]. Despite the recovery rate of 97–99.5%, some patients experienced persistent symptoms after discharge [3], described using the terms long COVID, long-haul COVID, or post-COVID-19 symptoms [4]. According to the Centers for Disease Control (CDC) [5], post-COVID-19 conditions are wide range of new, returning, or ongoing health problems people can experience 4 or more weeks after first being infected with the virus that causes COVID-19. Common signs and symptoms that linger over time include fatigue, shortness of breath, joint and chest pain, memory, concentration or sleep problems, muscle pain, headache, palpitations, anxiety or depression, and worsened symptoms after physical or mental

activities [6]. Burden of post-COVID-19 syndrome includes functional limitations, poor quality of life, some develop heart, kidney and lung complications, stroke, post-traumatic stress syndrome, depression, and anxiety.

In September 2020, the Classification and Terminologies unit of the WHO created International Classification of Disease (ICD)-10 and ICD-11 codes for the “post-COVID-19 syndrome”. However, with the variety of symptoms associated with post-COVID-19 syndrome and the wide geographical spread of the disease, little is known of its incidence in the Philippines. To date, published literature has been primarily focused on the economic impact or spatio-temporal analysis of COVID-19 within the country.

This study aimed to spearhead research into post-COVID-19 syndrome in the Philippines by determining the incidence of post-COVID-19 syndrome using the WHO definition, and determining its association with COVID-19 severity among patients discharged from a tertiary private hospital.

Methodology

This is a prospective cohort study conducted from June 2022 to August 2022 at the Chinese General Hospital and Medical Cen-

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ter (CGHMC), Blumentritt, Manila, Philippines upon approval of the CGHMC Research Ethics Review Board (RERB, Protocol No. 2022-R-07). The sampling method used is total enumeration. CGHMC is a private tertiary hospital with 592-bed capacity which caters to patients with COVID-19.

We included patients aged 18 years old and above at the time of admission, admitted and discharged recovered from CGHMC between July 2021 to January 2022, diagnosed with COVID-19 using reverse transcription-polymerase chain reaction assay of nasopharyngeal and/or oral swab samples, and interviewed at least 6 months from time of onset of COVID-19.

The following were excluded: deceased patients, patients re-hospitalized for any reason aside from COVID-19 pneumonia, vulnerable patients such as those mentally disabled, and children under 18 years of age.

OpenEpi Sample Size calculator for proportion and PASS15 software was used to calculate the minimum sample size requirement. Parameters were based on a previously published study, post-COVID-19 syndrome among symptomatic COVID-19 patients by Mahmud et al. [7], April 2021. Specifying a proportion of post-COVID-19 syndrome equal to 46%, a maximum tolerable error of 5%, and alpha set at 0.05, and finite population of 1000 patients, a minimum of 277 patients is required.

The investigator identified the list of patients from hospital records and then secured consent from the attending physician before contacting the selected patients. The mobile number of each eligible patient was retrieved from the medical charts. Each patient was invited to participate in the study via text and phone call. The investigator attempted to invite the patient up to three times before considering as a non-respondent.

After explaining study objectives, procedures, risks, and benefits to each patient, an implied consent was obtained before conducting the interview. A standardized interview tool (Appendix A) was used to determine the symptoms experienced by patients after hospital discharge, and patients were classified into with or without post-COVID-19 syndrome groups based on the WHO case definition that defines post-COVID 19 syndrome as individuals with a history of a probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis.

Patient charts were reviewed and the following admission data were obtained: age, sex, comorbidities, date of admission, and date of discharge. COVID-19 severity was determined using the Disease Severity Classification of Adult Patients with probable confirmed COVID-19 [8].

Mild cases are defined by the following symptoms, fever, cough, fatigue, anorexia, myalgias. Other non-specific symptoms such as sore throat, nasal congestion, headache, diarrhea, nausea, vomiting, anosmia, and loss of taste preceding the onset of respiratory symptoms. Additionally, there must be no signs of pneumonia or hypoxia for a case to be considered mild.

COVID-19 cases are considered moderate if a patient presents with non-severe pneumonia (fever, cough, dyspnea, or difficulty of breathing) with a respiratory rate of 21–30/min and oxygen saturation at >92% on room air.

COVID-19 cases are classified as severe if a patient presents with severe pneumonia or severe acute respiratory infection presenting as fever, cough, dyspnea, respiratory rate >30 breaths per minute, and oxygen saturation of <92% on room air.

Finally, COVID-19 cases are classified as critical; if onset is within 1 week of known clinical insult (pneumonia) or new or worsening respiratory symptoms, the presence of progressing infiltrators on chest x-ray or chest computed tomography, with respiratory failure not fully explained by cardiac failure of fluid overload. Additional symptoms include sepsis, signs of organ dysfunction and septic shock.

The primary outcome measured in the study was the incidence of post-COVID-19 syndrome and association of COVID-19 severity to post-COVID-19 syndrome.

Table 1

Demographic and clinical characteristics of patients (n = 280).

Characteristics	N (%)
Age (in years), median	50 (interquartile range: 34–63)
<60 years old	186 (66)
≥60 years old	94 (34)
Sex	
Female	142 (51)
Male	138 (49)
COVID-19 severity	
Mild	113 (41)
Moderate	124 (44)
Severe	43 (15)
Comorbidities, %yes	
Hypertension	71 (25)
Diabetes mellitus	29 (10)
Chronic obstructive pulmonary disease	0
Asthma	7 (3)
Chronic kidney disease	8 (3)
Liver disease	4 (1)
Malignancy	0

Stata MP version 16 software was used for data processing and analysis. Continuous variable (i.e., age) was presented as median (interquartile range) while categorical variables were presented as frequencies and percentages. Mann-Whitney U test was used to compare continuous variables. Categorical variables were compared using chi-square test or Fisher's exact test.

In order to determine the association between COVID-19 severity and post-COVID-19 syndrome, logistic regression analysis using Firth bias correction was performed. Screening of potential confounders was done using simple logistic regression analysis and criteria of $P < 0.20$ (Statistical foundations for Model-Based Adjustments). Model building was performed using multiple logistic regression analysis, and confounders that satisfied that change-in-estimate criterion of 10% was retained. P -values ≤ 0.05 were considered statistically significant.

Results

A total of 280 patients were included in the study. Table 1 represents the characteristics of patients included in the study. Median age was 50 years old and ranged from 18–92 years old. Most were <60 years old ($N = 186$, 66%). Fifteen percent had severe COVID-19 pneumonia. The leading comorbidity was hypertension ($N = 71$, 25%) followed by diabetes mellitus ($N = 29$, 10%).

A total of 200 patients were diagnosed with post-COVID-19 syndrome with incidence of 71.43% (95% CI: 65.83–76.44%). Top three most commonly cited symptoms were shortness of breath ($N = 84$, 42%), fatigue ($N = 76$, 38%), and malaise ($N = 71$, 36%).

Table 2 compares the characteristics of patients with and without post-COVID-19 syndrome. No significant difference between the two groups in terms of age. Compared to those without post-COVID-19 syndrome, a higher proportion of patients with post-COVID-19 syndrome were men and had moderate-to-severe COVID-19. All severe cases developed post-COVID-19 syndrome. A higher proportion of patients with post-COVID-19 syndrome have hypertension than those without post-COVID-19 syndrome.

COVID-19 severity at baseline was significantly associated with post-COVID-19 syndrome (Table 3). Compared to mild cases, moderate cases had about five times higher odds of post-COVID-19 syndrome. Furthermore, severe cases had about 92 times higher odds than mild cases.

It is important to note that the wide 95% CI for the severe category is due to the low number of severe cases, and none of the severe cases were classified as “without post-COVID”. Due to sparse data bias, this led to “separation” phenomenon. We addressed this bias by using Firth's bias logistic regression instead of the usual binary logistic regression.

Table 2
Demographic and clinical characteristics of patients with and without post-COVID-19 syndrome (n = 280).

Characteristics	Post-COVID-19 syndrome		P-value
	With (n = 200) n (%)	Without (n = 80) n (%)	
Age (in years), median	50 (interquartile range: 34–64)	45 (interquartile range: 33–62)	0.2170 ^a
<60 years old	131 (66)	55 (69)	0.603 ^b
≥60 years old	69 (34)	25 (31)	
Sex			
Female	93 (47)	49 (61)	0.026 ^b
Male	107 (53)	31 (39)	
COVID-19 severity			
Mild	55 (28)	58 (73)	<0.0001 ^c
Moderate	102 (51)	22 (27)	
Severe	43 (21)	0	
Comorbidities, %yes			
Hypertension	64 (32)	7 (9)	<0.0001 ^b
Diabetes mellitus	24 (12)	5 (6)	0.154 ^b
Chronic obstructive pulmonary disease	0	0	-
Asthma	6 (3)	1 (1)	0.677 ^c
Chronic kidney disease	8 (4)	0	0.110 ^c
Liver disease	4 (2)	0	0.581 ^c
Malignancy	0	0	-

^a Mann-Whitney U test was used

^b Chi-square test was used

^c Fisher's exact test was used

Table 3
Association between COVID-19 severity and post-COVID-19 syndrome (n = 280).

	Crude odds ratio (95% CI)	P-value	Adjusted odds ratio (95% CI) ^a	P-value
Mild	Ref	Ref	Ref	Ref
Moderate	4.80 (2.67–8.63)	<0.0001 ^a	4.43 (2.44–8.04)	<0.0001 ^a
Severe	91.70 (5.51–1525.89)	0.002 ^a	64.13 (3.82–1076.66)	0.004 ^a

Ref, reference category.

^a Controlled for the confounding effects of hypertension and chronic kidney disease.

Even after controlling for the effects of confounders, the association remained significant. Compared to mild cases, moderate cases had about four times higher odds of post-COVID-19. Furthermore, severe cases had about 64 times higher odds than mild cases.

Discussion

The results of our study provide valuable insights into the incidence of post-COVID-19 syndrome and its association with COVID-19 severity in the Philippines. Firstly, we observed that age did not have a significant difference in the development of post-COVID-19 Syndrome. This suggests that individuals of all age groups, including those younger than 60 years old, may be at risk of experiencing long-term symptoms after recovering from COVID-19. Healthcare providers should be vigilant in recognizing and managing post-COVID-19 Syndrome across different age groups.

In terms of comorbidities, hypertension was the leading comorbidity in patients with post-COVID-19 Syndrome. This finding highlights how healthcare providers should be particularly vigilant in monitoring and managing pre-existing conditions, especially hypertension, in individuals who have recovered from COVID-19 to potentially reduce the risk of developing long-term symptoms. The study further supports the findings of current research that patients with comorbidities such as hypertension and diabetes mellitus have a higher risk of developing post-COVID-19 syndrome compared to patients without these disorders [4,9,10].

Results of this study are consistent with findings in current literature on post-COVID-19 syndrome with the most prevalent symptoms being shortness of breath (N = 84, 42%), fatigue (N = 76, 38%), and malaise (N = 72, 36%) [4]. Outside of the three most prevalent symptoms, other symptoms such as insomnia, cough, depression, and headache, are also

in line with findings from medical research across the globe [9,10,11]. Healthcare providers should be aware of these frequent symptoms and consider them when evaluating patients who present with persistent or new symptoms after COVID-19 recovery.

One interesting finding from this study was the higher incidence of post-COVID-19 syndrome in men. Multiple studies have found that women are significantly more likely to suffer from post-COVID-19 syndrome than men [9,10,12,13]. However, the findings are still highly varied with some studies indicating that women are 22% more likely to experience post-COVID-19 syndrome while other literature suggests that they are twice as likely to experience it [10,12,13]. Why this particular result of the study goes against the current body of literature could be attributed to several factors, such as the study being conducted in a single healthcare institution, biological factors, or factors that are unique to the Philippine population. Further research into potential gender-specific risk factors or biological factors that could contribute to long-term symptoms is warranted.

Results of the study show a high incidence of post-COVID-19 syndrome at 71.43% in the studied population. This suggests that a substantial proportion of patients who recover from COVID-19 may experience lingering symptoms, however, generalizations about the overall population should be made with caution, as the incidence rate may vary in different regions and among diverse populations.

Additionally, severity at baseline shows a strong association with post-COVID-19 syndrome with moderate cases having five times higher odds of post-COVID-19 syndrome and severe cases experiencing 92 times higher odds of developing the syndrome. Patients with more severe COVID-19 infections had significantly higher odds of experiencing long-term symptoms. This association can be generalized to suggest that more severe acute COVID-19 cases may require increased attention in post-recovery care.

This study made use of total enumeration sampling and was centered on a single healthcare institution but can serve to support further studies into post-COVID-19 syndrome across the nation. It is recommended that a multi-center study be conducted to compare the findings of post-COVID-19 syndrome across a wider range of populations. Moreover, to make broader and more accurate generalizations, further research involving larger and more diverse populations is required. Additionally, as the field of COVID-19 research is evolving rapidly, continuous monitoring and evaluation of new findings will be necessary to inform clinical practice effectively.

Declarations of competing interest

The authors have no competing interests to declare.

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Author's contribution

EAM collected data; both authors contributed to research design, data analysis, and discussion.

Ethical approval

This study was conducted from June 2022 to August 2022 at Chinese General Hospital and Medical Center (CGHMC), Blumentritt, Manila, and has been approved by the ethics board of Chinese General Hospital and Medical Center Research Ethics Review Board (CGHMC RERB Protocol No. 2022-R-07).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijregi.2023.08.005.

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