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The Prevalence, Clinical Characteristics, Predicting Factors and Impact of Long COVID Syndrome Following Third Wave of Epidemic in Myanmar: Prospective Study

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19), emerged in China at the end of 2019, became a major threat to health around the world by causing acute COVID-19 infection. After recovery, a significant number of patients experience prolonged symptoms, long COVID syndrome. The prevalence of long COVID syndrome, its symptoms, severity and relation between clinical parameters and long COVID syndrome, and its impact were not studied in Myanmar.

Methods: A prospective study was conducted via telecommunication to patients with positive SARS COV 2 PCR from nasopharyngeal swab during the third wave from end of May to August 2021. Data were collected by using standardized forms and analysis was done. A chi-square test of independence was performed to examine the relation between age groups, gender, body mass index (BMI), vaccination status, comorbidity status, severity of initial symptoms, oxygen requirement status, and symptoms of long covid syndrome.

Results: Though initial recruitment included 18,709 patients with PCR confirmed COVID-19 infection, only 853 patients with recovery were analyzed. Long COVID syndrome was recorded in nearly 40% (333/853) of them; sixty percent of them (520/853) did not experienced symptoms following recovery. The common presenting symptoms in order of frequency were fatigue 58.9% (196/333), insomnia 27.3% (91/333), palpitation 17.1% (57/333), poor concentration 15.6% (52/333), anxiety 8.7% (29/333), myalgia 6.6% (22/333), chest pain 5.1% (17/333), persistent cough 4.2% (14/333), rash 3% (10/333), headache 2.7% (9/333), diarrhea 1.8% (6/333), anosmia 1.5% (5/333), sensory symptoms 0.9% (3/333) and dyspnea 0.9% (3/333). The majority 70% described as mild- not disturbing daily activity or job; however, 3% had severe symptoms- disturbing daily activity or job. Minority of cases 3% (10/333) required oxygen therapy for 2 months. Age, sex and BMI were not related with long COVID syndrome. However, initial multiple symptoms more than 2, co-morbidity, vaccination and initial oxygen requirement had significantly relationship with development of long COVID syndrome.

Conclusions: In this study, the prevalence of long COVID syndrome among survivors was 40%; the common presenting symptoms in order of frequency were fatigue, insomnia, palpitation and poor concentration. Most of the cases had mild symptoms- not disturb job or daily routine activity. Nearly 80% of them admitted that their health status was not back to pre-COVID condition. Not only the patients with COVID-19 infection having initial multiple symptoms, co-morbidity, no vaccination and initial oxygen requirement but also their care givers should be warned about

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possible long COVID syndrome; and the necessary for follow up. Vaccination may prevent long COVID syndrome; it should be prioritized to those with comorbidity. It highlighted the need for systematic follow-up after hospitalisation with COVID-19 with multi-disciplinary team, rehabilitation and further investigation.

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KEYWORDS: long COVID syndrome, symptoms, co-morbidity, vaccination

BACKGROUND

Coronavirus disease 2019 (COVID-19), emerged in China at the end of 2019, became a major threat to health around the world. The features of acute COVID-19 infection are usually respiratory symptoms; fever, cough, dyspnoea, loss of smell, sore throat, eye congestion, headache, body aches and pain. Most of the cases usually recover after 2 weeks; the minority require hospitalization. Following recovery, some patients still have symptoms like persistent cough, dyspnoea and appetite loss. On the other hand, some patients experience new symptoms like fatigue, insomnia and anosmia after complete recovery from acute illness. These symptoms are generally labelled as long COVID syndrome; either persistence of symptoms during acute COVID-19 infection more than 2 months or having new symptoms which developed two months after acute COVID-19 infection.

A significant number of patients with COVID-19 experience prolonged symptoms; few studies have reported this population. Long COVID syndrome was reported after first wave in Western countries; and, it became more pronounced after second wave. Long COVID syndrome was reported after first wave in Western countries (Taribagil et al., 2021); more distinct after second wave. The terminology varies; short COVID syndrome and long COVID syndrome depending on duration of symptoms (Raveendran et al., 2021). However, the World Health Organization defines the 'post COVID' condition as one that "occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis" (World Health Organization, 2021).

The timing for distinction as well as the pathology between recovery from post–intensive care unit syndrome and ongoing long COVID syndrome pathology were not clearly defined or reported in studies (Brodin et al., 2022).

Although acute COVID-19 infection involves the respiratory, cardiovascular, neurological, gastrointestinal, and musculoskeletal systems, long COVID syndrome involve multiple systems. Patients with 'long COVID' experience a wide range of physical and mental/psychological symptoms. The symptoms of long covid included The symptoms of long covid include fatigue, dyspnoea, cardiac abnormalities, cognitive impairment, sleep disturbances, symptoms of post-traumatic stress disorder, muscle pain, concentration problems, and headache (Crook et al., 2021). One study mentioned that symptoms of long COVID syndrome were more than one hundred (Hayes et al., 2021).

One study reported that patients with long COVID syndrome noticed symptoms at 54 days post discharge; and, the most common was persistent breathlessness and fatigue. They also had elevated biomarkers, elevated d-dimer and C reactive protein, as well as chest radiographs abnormalities (Mandal et al., 2021). Another report mentioned that most prevalent reported symptoms in patients with long COVID were fatigue, shortness of breath, muscle pain, joint pain, headache, cough, chest pain, altered smell, altered taste, diarrhoea, cognitive impairment, memory loss, anxiety and sleep disorders (Aiyegbusi et al., 2021).

The severity of patients with long COVID varied from very mild to severely debilitating disease with objective organ damage (Brodin et al., 2022). Patients with Long COVID syndrome had prolonged, multisystem involvement and significant disability (Davis et al., 2021).

As the impact of Long COVID syndrome was not minor, Munblit et al., (2022) emphasized the requirement for a global initiative; it could not be solved by healthcare professionals, researchers, methodologists, patients, and caregivers (Munblit et al., 2022). It was supported by several studies where patients with long COVID often reported impaired quality of life, mental health and employment issues. They need multidisciplinary care involving the long-term monitoring of symptoms, to identify potential complications, physical rehabilitation, mental health and social services support (Aiyegbusi et al., 2021) (Callard & Perego, 2021).

In Myanmar, long COVID syndrome was noticeable after second wave in Myanmar because the number of cases infected in first wave was less than one hundred. The prevalence of long COVID syndrome, its symptoms, severity and relation between clinical parameters and long COVID syndrome, impact on daily functioning, and return to baseline health were not studied in Myanmar.

METHODS

Study design and population

A prospective study was conducted among patients with confirmed COVID-19 infection during the third wave from end of May to August 2021. They were contacted with either phone or viber two months after the initial infection. Identification of patients done with the records from out-patient department or hospital. Their initial clinical severity

during acute COVID-19 infection as well as long symptoms (2 months after initial symptoms for COVID-19) were clerked; the severity of symptoms of long COVID syndrome was assessed. And duration was recorded too. Comorbidity, BMI, vaccination history/records and oxygen requirement were noted too. At the same time, reassurance of minor symptoms was done. Those with moderate to severe symptoms were given out patient appointment; and, necessary investigations were done. Then, treatment was advised; some patients were referred for chest physiotherapy and pulmonary rehabilitation. They were recorded in proforma; confidentiality was maintained.

Operational definitions

Unvaccinated received no COVID-19 vaccine doses. Vaccinated received at least one dose of COVID-19 vaccine. Body mass index (BMI) was a person's weight in kilo- grams divided by the square of height in meters and it an indicator of body fatness. BMI was categorized as under- weight (<18.5 kg/m^2), normal weight (18.5 to 24.9 kg/m^2), overweight (25.0 to 29.9 kg/m^2) and (≥30.0 kg/m^2) obese. The initial presenting symptom was a symptom or group of symptoms at the time of confirmation of COVID-19 infection by positive nasopharyngeal swab for PCR for COVID-19 (such as runny nose, muscle ache, cough, sore throat, dyspnea, etc.,) and it was categorized as asymptomatic and symptomatic.

Comorbidity was a presence of more or additional medical conditions or diseases in physicians like diabetes mellitus, hypertension, chronic kidney disease (early chronic kidney disease to end stage renal disease), cardiovascular disease (ischaemic heart disease, atrial fibrillation, heart failure), obesity (BMI more than 30), chronic lung disease (chronic obstructive airway disease, bronchial asthma), neurological disease (stroke, dementia), chronic liver disease (chronic liver disease with or without portal hypertension), malignancy (cancer, leukaemia, lymphoma). The comorbid associated group was having one or more comorbid disease and comorbid non-associated group did not have comorbid disease. Current smoking was current smokers irrespective of duration of smoking. Alcohol was both current drinker and those who stopped drinking two weeks ago. Immune status was defined as normal or immunocompromised. Immunocompromised status was those not having one of immunocompromised state transplant recipients, those on oral steroids for more than two weeks, those on immunosuppressants, systemic lupus erythematosus, diabetes mellitus, ESRD (eGFR < 30 ml/min), and, hematological malignancy. Normal immune status was those not having immunocompromised state.

The severity of COVID-19 was classified as mild, moderate, severe and critical disease. Mild disease was symptomatic patients without evidence of viral pneumonia or hypoxia. Moderate disease was confirmed patients with clinical signs of pneumonia (fever, cough, dyspnea, and fast breathing). Severe disease was confirmed patient with clinical signs of pneumonia (fever, cough, dyspnea, and fast breathing) adding one of the following: respiratory rate >30 breaths per min, severe respiratory distress, SpO_2 < 93 % on room air, and requirement for oxygen therapy. Critical disease was confirmed patient with severe disease having acute coronary syndrome or stroke or pulmonary embolism.

Long COVID syndrome was defined as either persistence of symptoms during acute COVID-19 infection more than 2 months or having new symptoms which developed two months after acute COVID-19 infection.

Severity of long COVID syndrome (impact on life and job) was classified into 3 categories: (1) mild if symptoms were not disturbing daily routine activities or job; (2) moderate if the patient required rest or help to perform daily activity or could not do job; and, (3) severe if symptoms were disturbing daily activity or job.

Over all patient's comment on 'return to baseline health" was recorded as "yes" or "no'.

The duration of symptoms was defined as follows: (1) for new symptoms- the time of onset of new symptoms to complete disappearance of symptoms; and (2) for old symptoms ie persistence of acute COVID symptoms- two months after the onset of acute COVID to complete disappearance of symptoms with or without treatment.

Data collection and procedure Methods

A prospective study was conducted via telecommunication to patients with positive SARS COV 2 PCR from nasopharyngeal swab during the third wave from end of May to August 2021. Data were collected by using standardized forms and analysis was done. A chi-square test of independence was performed to examine the relation between age groups, gender, BMI, vaccination status, comorbidity status, covid symptom counts, oxygen requirement status, care center categories and symptoms of long covid syndrome.

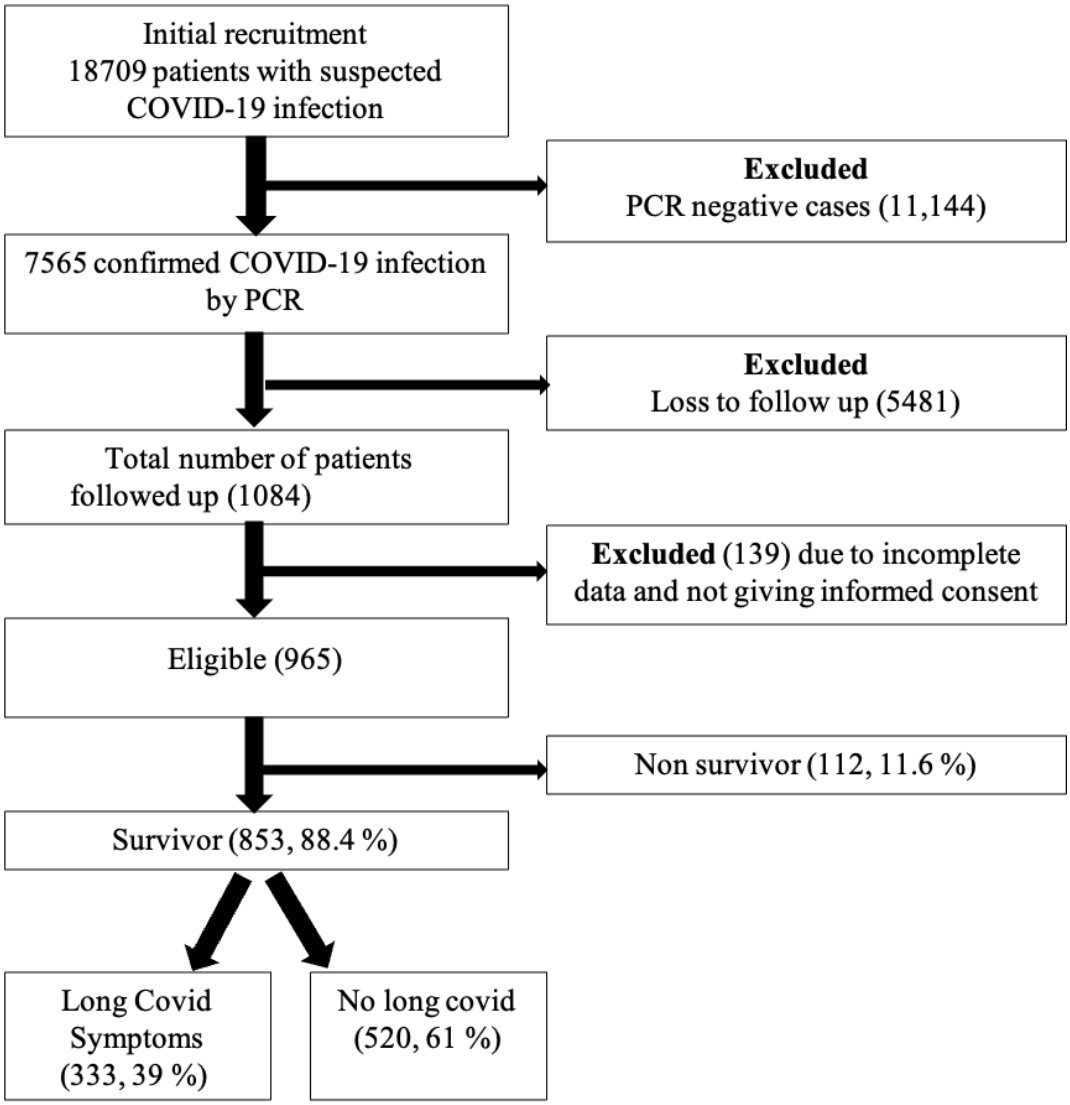
Demographic characteristics (sex, age, height, weight, BMI), severity of COVID-19 infection (mild, moderate, severe and critical disease), vaccination status (unvaccinated or vaccinated), symptoms of long COVID syndrome (fatigue, insomnia, palpitation, poor concentration, anxiety, myalgia, chest pain, persistent cough, rash, headache, diarrhea, anosmia, sensory symptoms, fever, appetite loss and dyspnea), comorbidity (hypertension, diabetes mellitus, chronic kidney disease) and severity of long COVID syndrome (mild, moderate, and severe) were collected using a standardized case report form. The data were checked by two medical officers and then, supervision, completeness, and consistency of collected data were performed by the principle investigator.

Statistical analysis

The collected data were entered into Microsoft Excel 2016 and exported to IBM SPSS Statistics for Windows, Version

26.0 (Armonk, NY: IBM Corp) for analysis. Descriptive statistics were presented as frequency and percentages for categorical variables and mean (standard deviation, SD) for continuous variables. A chi-square test of independence was performed to examine the relation between age groups, gender, BMI, vaccination status, comorbidity status, covid symptom counts, oxygen requirement status, care center categories and long covid.

FLOW CHART



RESULTS

Though initial recruitment included 18,709 patients with PCR confirmed COVID-19 infection, only 853 patients with recovery were analyzed. Long COVID syndrome was recorded in nearly 40% (333/853) of them; sixty percent of them (520/853) did not experienced symptoms following recovery.

Only two symptoms, persistent cough and dyspnoea were the persistence of symptoms during acute COVID-19 infection more than 2 months. The remaining symptoms were new symptoms which developed two months after acute COVID-19 infection.

The common presenting symptoms in order of frequency were fatigue 58.9% (196/333), insomnia 27.3% (91/333), and palpitation 17.1% (57/333), poor concentration 15.6% (52/333), anxiety 8.7% (29/333), myalgia 6.6% (22/333), chest pain 5.1% (17/333), persistent cough 4.2% (14/333), rash 3% (10/333), headache 2.7% (9/333), diarrhea 1.8% (6/333), anosmia 1.5% (5/333), sensory symptoms 0.9% (3/333) and dyspnea 0.9% (3/333).

The majority 78.3% (47/60) described the impact on life/job as mild- not disturbing daily activity or job; however, 3% (10/333) had severe symptoms- disturbing daily activity or job. The overall patient's comment on 'return to baseline health" was responded as "no" in nearly 80% of respondents. The duration of symptoms ranged from one months to 6 months. Minority of cases 3% (10/333) required oxygen therapy for 2 months.

A chi-square test of independence was performed to examine the relation between age groups, gender, BMI, vaccination status, comorbidity status, number of covid symptoms, oxygen requirement status, care center categories and symptoms of long covid syndrome. There was no significant relationship between age and long covid status $X^2(2, 853) = 2.16$, $p = .766$. The long covid status was not differed by gender $X^2(1, 853) = .09$, $p = .340$. The BMI status didn't associate with long covid status $X^2(3, 774) = 3.40$, $p = .333$. Age, sex and BMI were not related with long COVID syndrome.

Nevertheless, there was significant relationship between vaccination status and long covid status $X^2(1, 853) = 25.67$, $p < .001$. And it was related with increased number of comorbidities $X^2(2, 853) = 23.64$, $p < .001$. Moreover, there was significant association with increased number of symptoms during covid illness $X^2(2, 853) = 140.84$, $p < .001$ though 16 % of asymptomatic individuals were having long covid symptoms. Furthermore, there was significant association with oxygen requirement (severity) during acute covid illness $X^2(1, 853) = 24.96$, $p < .001$. There was no association between hospitalization and long covid status $X^2(2, 853) = 5.46$, p = .065. In summary, initial symptoms more than 2, co-morbidity, vaccination and initial oxygen requirement had significantly relationship with development of long COVID syndrome.

DISCUSSION

Long COVID syndrome for this study was defined as either persistence of symptoms during acute COVID-19 infection more than 2 months or having new symptoms which developed two months after acute COVID-19 infection. The persistence of symptoms during acute COVID-19 infection more than 2 months were persistent cough (5%) and dyspnoea (1%). They were found to be initial severe cases by WHO definition, requiring oxygen therapy. They had received antiviral therapy (Remdesivir), Tocilizumab and convalescent plasma therapy. The remaining symptoms were new symptoms which developed two months after acute COVID-19 infection.

Regarding the prevalence of long COVID syndrome, almost 60% reported one or more features of long Covid during a median follow-up period of six months. In this study, nearly 40% of survivors had at least one features of long COVID syndrome; the median follow-up being 4 months (Davis et al., 2021).

Although acute COVID-19 infection involves the respiratory, cardiovascular, neurological, gastrointestinal, and musculoskeletal systems, long COVID syndrome involve multiple systems, the systems of long covid include fatigue, dyspnoea, cardiac abnormalities, cognitive impairment, sleep disturbances, systems of post-traumatic stress disorder, muscle pain, concentration problems, and headache (Crook et al., 2021)

The onset of symptoms of long COVID syndrome was 54 days (median) post discharge in one report (Mandal et al., 2021). In this study, it was difficult calculate definite onset of symptoms for several reasons. The symptoms like persistent cough and dyspnoea were the continuation of symptoms of acute COVID infection which were not resolved. On the other hand, systems like insomnia, palpitation, anxiety, anosmia and diarrhea were noticeable during acute illness; they were not persistent and difficult to memorize the exact date of onset. Moreover, some symptoms like fatigue and appetite loss were more prominent after recovery. In addition, symptoms like myalgia and poor concentration were not recognized during acute illness; and, they became pronounced after recovery.

In the study by (Aiyegbusi et al., 2021), ten most prevalent reported symptoms were fatigue, shortness of breath, muscle pain, joint pain, headache, cough, chest pain, altered smell, altered taste and diarrhoea; they were similar to findings of present study (Aiyegbusi et al., 2021). It was also supported by findings of meta-analysis; the symptoms of long covid include fatigue, dyspnoea, cardiac abnormalities, cognitive impairment, sleep disturbances, symptoms of post-traumatic stress disorder, muscle pain, concentration problems, and headache (Crook et al., 2021).

Fatigue was the most common symptoms reported in several studies (Mandal et al., 2021) (Arjun et al., 2022). It was confirmed by this study; nearly 60% of patients had fatigue. The reasons for having fatigue may be multifactorial. Those having severe fatigue in this study had normal sodium level, normal potassium level, normal blood urea and serum creatinine level, normal thyroid function and normal glycemic status. Although serum cortisol level was normal in one case, the electrolytes level in the remaining cases were not compatible with hypoadrenalism.

They found that half of their patients had dyspnoea (Aiyegbusi et al., 2021); it was supported by (Davis et al., 2021) where one in four breathlessness (Davis et al., 2021). However, only 1% of patients in this study required home oxygen therapy for dyspnoea. Females were prone to have features of long COVID; and, they were also at higher risk for neurological or cardiovascular features (Davis et al., 2021). Nonetheless, this study did not reveal significant difference in sex regarding prevalence of long COVID syndrome.

Initial symptoms more than 2 during acute illness, presence of co-morbidity, vaccination and initial oxygen requirement had significantly relationship with development of long COVID syndrome in this study.

It was reported that old age group and female sex were prone to long COVID syndrome (Sudre et al., 2021) (Jones et al., 2021). Nevertheless, they were not statistically related with it.

Presence of multiple symptoms and severity of acute illness in terms of oxygen requirement were associated with long COVID in this study as well as other studies (Jones et

al., 2021) (Arjun et al., 2022). It was likely that they might probably have high viral load to have severe symptoms though viral load was not easy to perform in poor resource setting.

In the previous report, increasing body mass index was associated with long COVID (Sudre et al., 2021); however, this study did not support it. Frailty was related with prevalence of long COVID syndrome (Jones et al., 2021). Presence of comorbidity was associated with it in this study. Reports in early 2022 mentioned that presence of previous Epstein Barr virus infection, high SARS CoV2 viral load, presence of autoantibodies, diabetes mellitus and vaccination status were linked with it (Su et al., 2022). Diabetes mellitus was top common comorbid diseases in this study as well as other studies. Statistically significant predictors of Long COVID were comorbidity, multiple symptoms during acute phase of COVID-19 disease, two doses of COVID-19 vaccination, the severity of illness and requirement for admission to hospital (Arjun et al., 2022).

Not having booster vaccination (two doses of COVID-19 vaccination) was related with long COVID syndrome (Arjun et al., 2022); it was supported by this study where non-vaccination status was found to be a risk for it. Therefore, vaccination program should be extended in every country.

Regarding the magnitude of problem of long COVID syndrome, impaired quality of life, mental health and employment issues were reported by some study (Aiyegbusi et al., 2021). In this study, majority of respondents described as mild- not disturbing daily activity or job; however, 3% had severe symptoms- disturbing daily activity or job. Minority of cases 3% required oxygen therapy for 2 months. The overall patient's comment on 'return to baseline health" was responded as "no" in nearly 80% of respondents in this study; it highlighted the important issues for the whole community. The severity of patients with long COVID as well as significant disability were pointed out in several studies (Brodin et al., 2022) (Davis et al., 2021).

The requirement for a global initiative with multidisciplinary care was recommended by (Munblit et al., 2022) (Aiyegbusi et al., 2021) (Callard & Perego, 2021).

CONCLUSIONS

Less than half of the survivors from acute COVID-19 infection had long COVID syndrome. The top common symptoms were fatigue, insomnia, palpitation and poor concentration. Most of the cases had mild symptoms. Non-vaccinated patients with COVID-19 infection having initial multiple symptoms, co-morbidity with initial oxygen requirement were likely to suffer long COVID syndrome. Both the patient himself and their care givers should be warned about the possibility of long COVID syndrome to get early diagnosis and appropriate treatment. Vaccination may prevent long COVID syndrome; it should be prioritized to those with comorbidity.

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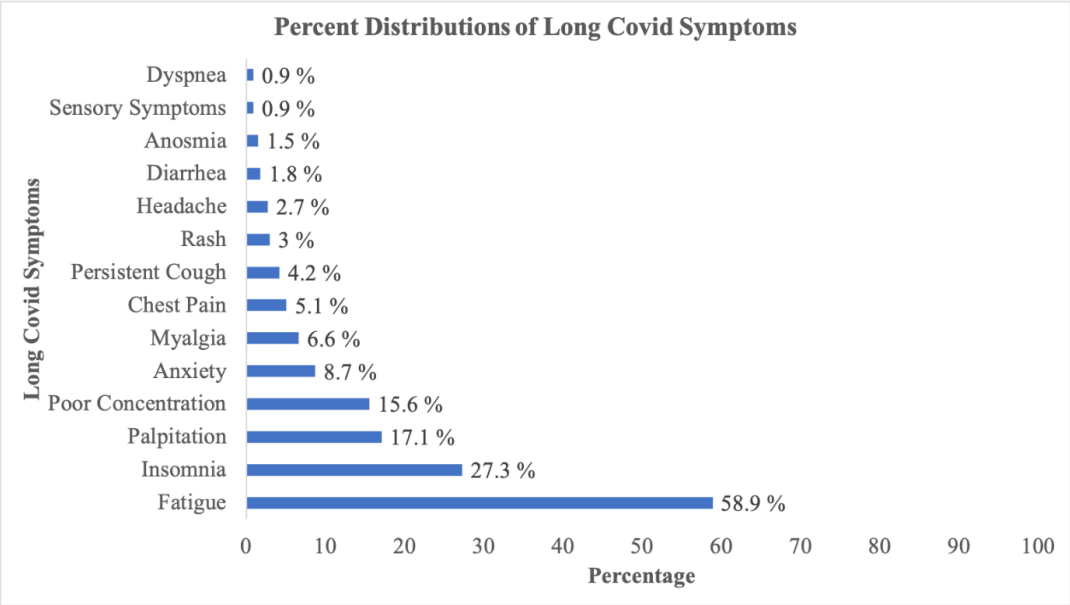

FIGURE 1. Frequency distributions of Long Covid Symptoms (n = 333)

Table 1. Association between clinical parameters and Long Covid Symptoms (n = 333)

Factors	Long Covid Symptoms			X^2 (df, N)	*p* Value
	Yes	No	Total		
Age Groups					
≤ 30 years	94 (38.4 %)	151 (61.6 %)	245 (100 %)	2.16 (2, 853)	.340
31 – 60 years	182 (37.8 %)	299 (62.2 %)	481 (100 %)		
> 60 years	57 (44.9 %)	70 (55.1 %)	127 (100 %)		
Gender					
Male	193 (35.5 %)	296 (60.5 %)	489 (100 %)	.09 (1, 853)	.766
Female	140 (38.5 %)	224 (61.5 %)	364 (100 %)		
BMI					
Under	20 (32.8 %)	41 (67.2 %)	61 (100 %)	3.40 (3, 774)	.333
Normal	152 (35.0 %)	282 (65.0 %)	434 (100 %)		
Over	96 (40.9 %)	139 (59.1 %)	235 (100 %)		
Obesity	19 (43.2 %)	25 (56.8 %)	44 (100 %)		
Vaccine					
Completed	100 (28.8 %)	247 (71.2 %)	347 (100 %)	25.67 (1, 853)	< .001
Not completed	233 (46.0 %)	273 (54.0 %)	506 (100 %)		
Comorbidity					
No Comorbid	171 (32.6 %)	353 (67.4 %)	524 (100 %)	23.64 (2, 853)	< .001
1 - 2 comorbid	144 (48.8 %)	151 (51.2 %)	295 (100 %)		
> 2 comorbid	18 (52.9 %)	16 (47.1 %)	34 (100 %)		
Covid Symptoms					
Asymptomatic	30 (16.0 %)	157 (84.0 %)	187(100 %)	140.84 (2, 853)	< .001
1 - 2 Symptoms	99 (28.5 %)	248 (71.5 %)	347 (100 %)		
> 2 Symptoms	204(63.9 %)	115 (36.1 %)	319 (100 %)		
Oxygen Requirement					
Yes	54 (64.3%)	30 (35.7%)	84 (100 %)	24.96 (1, 853)	< .001
No	279 (36.3%)	490 (36.3%)	769 (100 %)		
Hospitalized/ Quarantine Center /Home Care					
Hospital	76 (39.8 %)	115 (60.2 %)	191 (100 %)	5.46 (2, 853)	.065
Quarantine	65 (47.4 %)	72 (52.6 %)	137 (100 %)		
Home	192 (36.6 %)	333 (63.4 %)	525 (100 %)		