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Coronavirus Pandemic

Persistent COVID-19 symptoms and associated factors in a tertiary hospital in Thailand

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Abstract

Introduction: Coronavirus disease 2019 (COVID-19) is associated with long-term symptoms, but the spectrum of these symptoms remains unclear. We aimed to identify the prevalence and factors associated with persistent symptoms in patients at the post-COVID-19 outpatient clinic.

Methodology: This cross-sectional, observational study included hospitalized severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected patients followed-up at a post-COVID-19 clinic between September 2021 and January 2022. Persistent symptoms, defined as lasting > 4 weeks after infection, were analyzed alongside symptom timing (28–90, 91–120, and > 120 days) and associated factors using multivariate analysis.

Results: Among 277 patients, mean (SD) age was 56 (16.6) years, and 58.5% were male. Of these, 80.9% reported at least one persistent symptom. Common symptoms included dyspnea (48.2%), insomnia (42.4%), and myalgia (42.1%). In multivariate analysis, being female [odds ratio (OR) 3.41; 95% confidence interval (CI) 1.5–7.76], and oxygen therapy (OR 3.39; 95% CI 1.3–8.81) were independently associated factors with persistent symptoms. High-sensitivity C-reactive protein (HsCRP) (> 75 mg/dL) was an independent risk factor for dyspnea (adjusted OR 2.29; 95% CI 1.28–4.12), and fatigue (adjusted OR 2.24; 95% CI 1.25–4). Oxygen therapy was an independent risk factor for neurologic symptoms, i.e. insomnia (adjusted OR 2.05; 95% CI 1.15–3.65), and brain fog (adjusted OR 2.02; 95% CI 1.14–3.58).

Conclusions: There was a high prevalence of persistent COVID-19 symptoms. The most common symptom was dyspnea. Female gender and oxygen supplementation were independent associated factors. Continuous follow-up of these patients is still required.

Key words: COVID-19; long-COVID; post COVID.

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Introduction

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, termed coronavirus disease 2019 (COVID-19), caused a global pandemic in early 2020. Thailand did not have many cases in 2020, but cases increased rapidly to approximately 20,000 in 2021 [1].

The spectrum of COVID-19 ranges from asymptomatic infection to severe pneumonia with respiratory failure [2], and many post SARS-CoV-2 infected patients experienced long-term effects of COVID-19 [3–6]. Many patients experienced persistent COVID-19 related symptoms, including those who had mild COVID-19 symptoms. Post-COVID-19 conditions, post-acute sequelae of COVID-19 (PASC), and long COVID are some terms used to describe the condition where those who were previously infected with SARS-CoV-2 continue to experience symptoms [7,8].

The World Health Organization (WHO) defines a clinical case of "post-COVID-19 conditions" as a condition which occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, after 3 months from the onset of acute COVID-19 symptoms, lasting for at least 2 months and unable to be explained by an alternative diagnosis [9]. Meanwhile, the guideline developed from collaboration of UK National Institute for Health and Care Excellence (NICE), the Scottish Intercollegiate Guidelines Network (SIGN), and the Royal College of General Practitioners (RCGP) describe symptoms occurring from 4 to 12 weeks after infection as 'an ongoing symptomatic COVID-19' and symptoms persisting beyond 12 weeks as 'post-acute COVID-19 syndrome' [10]. Moreover, the term 'long COVID' has been commonly used to describe

symptoms that continue or appear after acute COVID-19. It includes both ongoing symptomatic COVID-19 and post-COVID-19 syndrome.

Previous studies of post-COVID-19 infection have shown that the most prevalent symptoms were fatigue, shortness of breath, muscle pain, joint pain, headache, cough, chest pain, anosmia, diarrhea, and mood disorders [11–14]. The incidence rate of this condition has been reported to vary widely, from 4.5% to 87.4% due to the variations in definitions [15]. Previous studies identified several factors, which were commonly associated with developing long COVID, including an increase in age, female gender, presence of over 5 symptoms in acute COVID-19, and presence of comorbidities [5,13,16–18].

During the pandemic, the Phramongkutklao Hospital, Bangkok, Thailand, established a post-COVID-19 outpatient clinic for patients discharged from the hospital after recovery from acute COVID-19. Therefore, this study aimed to describe the symptoms of COVID-19 that were persistent after hospital discharge, and identify the factors associated with these symptoms at the post-COVID-19 outpatient clinic.

Methodology

Study design

We conducted a cross-sectional, single center observational study of hospitalized SARS-CoV2 infected patients, who were followed-up in our post-COVID-19 outpatient clinic between September 2021 and January 2022. This study was approved by the Ethics Committee and the Institutional Review Board of Royal Thai Army (R008h/65_Exp).

Participants

Patients aged 20 years and over, previously admitted to the Phramongkutklao Hospital with COVID-19 infection that was confirmed by reverse transcription polymerase chain reaction (RT-PCR), and followed-up in our post-COVID-19 outpatient clinic were included. The Thailand public health policy from 2020 to 2021 was to admit every confirmed SARS-CoV2 infection regardless of symptoms [19]. So, our cohort had a wide variety of SARS-CoV2 infection severity, ranging from asymptomatic to severe pneumonia requiring mechanical ventilation.

Methods

All patients had face-to-face interviews, on the day of visit, using COVID-19 symptom checklists that focused on persistent symptoms that the patients experienced. Demographic and laboratory variables at the time of hospital admission; including age, gender, pre-existing comorbidities, inflammatory markers and other laboratory data, type of oxygen supplement, and hospital length of stay; were recorded. All the data were recorded by a single, well-trained physician to minimize interobserver variability. If patients had

Table 1. Clinical characteristics of 277 patients according to the presence of persistent symptoms identified.

Characteristics	Total (n = 277)	Persistent symptoms (n = 224)	Full recovery (n = 53)	*p* value
Gender, n (%)				
Female	115 (41.5)	105 (46.9)	10 (18.9)	< 0.001*
Male	162 (58.5)	119 (53.1)	43 (81.1)	
Age, mean ± SD, years	55.55 ± 16.59	57.18 ± 15.58	48.66 ± 18.99	0.003*
< 30, n (%)	28 (10.1)	16 (7.1)	12 (22.6)	0.003*
30–59, n (%)	120 (43.3)	95 (42.4)	25 (47.2)	
> 60, n (%)	129 (46.6)	113 (50.5)	16 (30.2)	
Comorbid condition, n (%)				
Hypertension	120 (43.3)	104 (46.4)	16 (30.2)	0.03*
Diabetes mellitus	86 (31.0)	78 (34.8)	8 (15.1)	0.005*
Chronic lung disease	19 (6.9)	15 (6.7)	4 (7.5)	0.826
Cardiovascular disease	16 (5.8)	14 (6.3)	2 (3.8)	0.487
Chronic kidney disease	13 (4.7)	12 (5.4)	1 (1.9)	0.283
Oxygen supplementation, n (%)				
None	160 (57.8)	115 (51.3)	45 (84.9)	< 0.001*
Cannula or facemask	50 (18.1)	46 (20.5)	4 (7.5)	
HFNC or NIV	57 (20.6)	54 (24.1)	3 (5.7)	
Mechanical ventilator	10 (3.6)	9 (4)	1 (1.9)	
Investigation, median (IQR)				
HsCRP, mg/dL	38.91 (11.64, 104.44)	54.86 (14.55, 112.9)	18.41 (6.26, 54.88)	< 0.001*
D-dimer, mg/dL	0.72 (0.41, 2.45)	0.86 (0.45, 3.28)	0.45 (0.27, 0.84)	0.001*
LDH, U/L	390 (236, 620)	442 (273, 663)	235.5 (172, 381)	< 0.001*
Ferritin, ng/dL	733 (323, 1597)	827 (372, 1684)	402.5 (166, 681)	< 0.001*
Follow-up days**, median (IQR), days	78 (42, 105)	86 (43, 106)	45 (39, 97)	0.004*

**p* value < 0.05; ***Follow up days, total days between viral detection and symptom report; HFNC, high flow nasal cannula; HsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDH; lactate dehydrogenase NIV, non-invasive ventilation; SD, standard deviation.

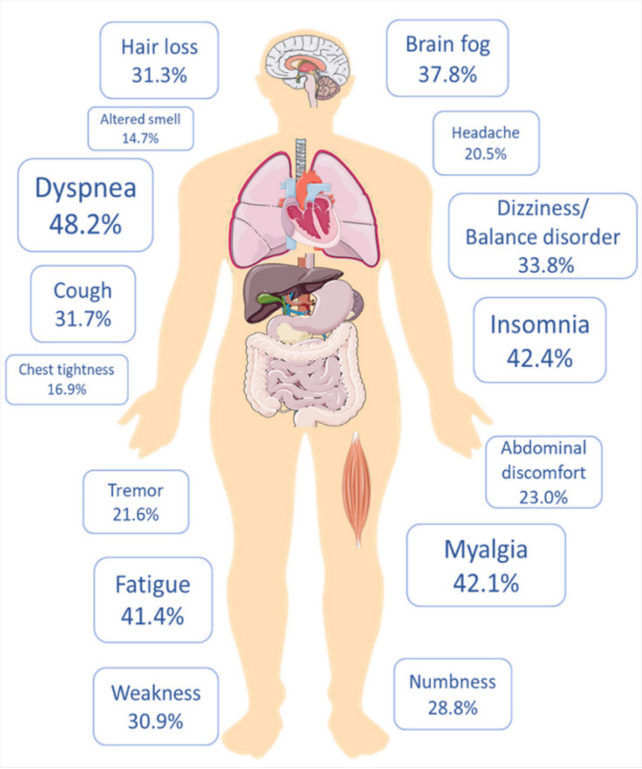
multiple visits, the data from the first visit were used in this cohort.

We measured the prevalence of persistent symptoms (defined as reporting of at least 1 symptom at the post COVID-19 outpatient clinic for over 4 weeks after SARS-CoV2 was detected), time from SARS-CoV2 detection until symptoms were reported (which was classified as 28–90 days, 91–120 days, and > 120 days), and factors associated with persistent symptoms.

Statistical analysis

The SARS-CoV2 infected patients were divided into two groups: patients who had persistent symptoms, and patients who recovered fully. The data were presented as mean (standard deviation, SD) for continuous variables with normal distribution, median (interquartile range, IQR) for continuous variables with non-normal distribution, and frequencies and percentage for categorical data. Inferential statistics were used by assuming a statistical significance at alpha of 0.05, including Pearson's Chi-square test and independent-student *t*-test or Mann-Whitney test.

Figure 1. Persistent symptoms of coronavirus disease 2019 (COVID-19). The figure shows the percentage of patients experiencing individual symptoms at the post COVID-19 outpatient clinic (n = 277).



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Analysis of risk factors used multivariate regression analysis and exhibited statistical significance at alpha of 0.05. All analyses were conducted using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, NY, USA).

Results

Demographics and characteristics

A total of 277 patients were included. Of these, 224 (80.9%) patients reported at least one symptom. The mean ± standard deviation (SD) age was 56 ± 17 years, and 162 (58.5%) patients were male. The most common comorbidities were hypertension (120 patients, 43.3%), and diabetes mellitus (86 patients, 31.0%). At the time of admission, 117 patients (42.2%) received oxygen supplementation, 50 patients (18.1%) used cannula or face mask, 57 patients (20.6%) needed high flow nasal cannula or non-invasive ventilation, and 10 patients (3.6%) required an invasive mechanical ventilator. The laboratory parameters with the highest value were high-sensitivity C-reactive protein (HsCRP), D-dimer, lactate dehydrogenase (LDH), and ferritin and their median (interquartile range, IQR) were 38.9 (11.6–104.4) mg/dL, 0.7 (0.4–2.5) mg/L, 390 (236–620) U/L, and 733 (323–1,597) ng/dL, respectively. The median (IQR) of the duration between positive RT-PCR and clinic visit was 78 (42–105) days. Other baseline characteristics are shown in Table 1.

Characteristics of symptoms

Dyspnea was the most frequent symptom in 134 patients (48.2%), followed by insomnia in 118 patients (42.4%), myalgia in 117 patients (42.1%), fatigue in 115 patients (41.4%), and brain fog in 105 patients (37.8%) (Figure 1). These symptoms tended to be reported in high proportion after 120 days of acute COVID-19 infection. In contrast, altered smell and cough were experienced in less proportion after 120 days (Figure 2).

Factors associated with persistent symptoms

There was a higher percentage of female patients with persistent symptoms than with full recovery (46.9% vs 18.9%, $p < 0.001$). Post COVID-19 infection patients who had persistent symptoms were older (57.2 vs 48.7 years, $p = 0.003$), had more comorbidities of hypertension (46.4% vs 30.2%, $p = 0.03$) or diabetic mellitus (34.8% vs 15.1%, $p = 0.005$), required more oxygen therapy ($p < 0.001$), and had higher inflammatory markers ($p < 0.001$) (Table1). We used the variables that we identified to be significantly associated to persistent symptoms in the univariate

Table 2. Univariate and multivariate logistic regression analysis of the factors associated with persistent symptoms.

Characteristics	Univariate		Multivariate	
	OR (95%CI)	*p* value	Adjusted OR (95% CI)	*p* value
Gender				
Male	Reference	1	Reference	1
Female	3.79 (1.82, 7.92)	< 0.001*	3.41 (1.5, 7.76)	0.003*
Age, years				
< 60	Reference	1	Reference	1
≥ 60	2.35 (1.24, 4.48)	< 0.001*	1.03 (0.47, 2.28)	0.936
Diabetes mellitus				
No	Reference	1	Reference	1
Yes	3.01 (1.35, 6.69)	0.007*	1.62 (0.66, 3.99)	0.297
Oxygen supplementation				
Not used	Reference	1	Reference	1
Used	5.33 (2.4, 11.82)	< 0.001*	3.39 (1.3, 8.81)	0.012*
HsCRP, mg/dL				
≤ 75	Reference	1	Reference	1
> 75	2.53 (1.24, 5.19)	0.011*	1.1 (0.43, 2.79)	0.838
LDH, U/L				
≤ 250	Reference	1	Reference	1
> 250	4.06 (2.16, 7.66)	< 0.001*	1.54 (0.69, 3.44)	0.288

**p* value <0.05; CI, confidence interval; HsCRP, high-sensitivity C-reactive protein; LDH, lactate dehydrogenase; OR, odds ratio.

analysis, to further investigate using multivariate analysis. We used the value 250 U/L as a cut off of LDH as its normal limit, and we used Hs-CRP > 75 mg/L because the concentration of Hs-CRP around 75 mg/L distinguished fatal from non-fatal cases in early clinical studies of COVID-19 [20,21]. Being female [odds ratio (OR) 3.41; 95% confidence interval (CI), 1.5–7.76] and requiring oxygen therapy during admission (OR 3.39; 95% CI, 1.3–8.81) were independently associated factors of having persistent symptoms (Table 2).

In the case of the five major symptoms (dyspnea, insomnia, myalgia, fatigue, and brain fog), univariate and multivariate logistic regression analyses were conducted to identify the factors associated with each symptom. Being female was an independent association factor for all symptoms, except for myalgia. High HsCRP (> 75 mg/dL) was an independent association factor for dyspnea [adjusted OR 2.29 (1.28–4.12), p = 0.006], and fatigue [adjusted OR 2.24 (1.25–4), p = 0.007]. However, requiring oxygen therapy was an independent association factor for neurologic symptoms, i.e. insomnia [adjusted OR 2.05 (1.15–3.65), p = 0.015], and brain fog [adjusted OR 2.02 (1.14–3.58), p = 0.017] (Table 3).

Figure 2. Prevalence of persistent symptoms based on the duration after the diagnosis of coronavirus disease 2019 (COVID-19). There were 152, 83 and 42 patients followed-up at the clinic at 28–90 days, 91–120 days, and > 120 days after infection, respectively. Each bar represents percentage of patients who experienced each symptom.

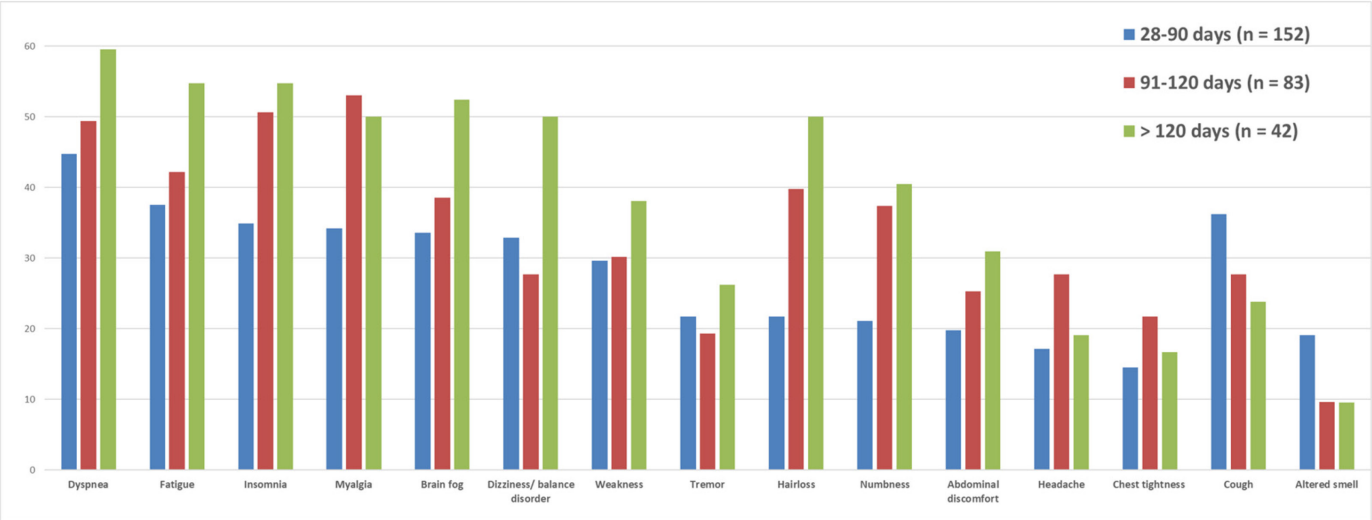

Table 3. Univariate and multivariate logistic regression analysis of the factors associated with the five common persistent symptoms.

Persistent symptoms or signs	Factors	Univariate		Multivariate	
		OR (95% CI)	*p* value	Adjusted OR (95% CI)	*p* value
Dyspnea	Age ≥ 60 years	1.04 (0.65, 1.66)	0.886	0.59 (0.34, 1.04)	0.068
	Female	1.86 (1.15, 3.02)	0.012*	2 (1.19, 3.36)	0.009*
	Oxygen supplementation	1.75 (1.08, 2.83)	0.023*	1.37 (0.78, 2.41)	0.275
	HsCRP > 75 mg/dL	2.19 (1.32, 3.61)	0.002*	2.29 (1.28, 4.12)	0.006*
Fatigue	Age ≥ 60 years	1.16 (0.72, 1.87)	0.55	0.77 (0.44, 1.35)	0.363
	Female	1.56 (0.96, 2.53)	0.073	1.68 (1, 2.82)	0.049*
	Oxygen supplementation	1.78 (1.09, 2.89)	0.02*	1.23 (0.7, 2.16)	0.472
	HsCRP > 75 mg/dL	2.25 (1.36, 3.72)	0.002*	2.24 (1.25, 4)	0.007*
Insomnia	Age ≥ 60 years	2.06 (1.27, 3.33)	0.004*	1.37 (0.78, 2.39)	0.271
	Female	3.24 (1.97, 5.34)	< 0.001*	3.01 (1.78, 5.08)	< 0.001*
	Oxygen supplementation	2.52 (1.54, 4.12)	< 0.001*	2.05 (1.15, 3.65)	0.015*
	HsCRP > 75 mg/dL	1.54 (0.94, 2.54)	0.088	1.02 (0.56, 1.85)	0.954
Myalgia	Age ≥ 60 years	0.97 (0.6, 1.57)	0.905	0.75 (0.43, 1.29)	0.299
	Female	1.57 (0.97, 2.55)	0.067	1.62 (0.97, 2.69)	0.064
	Oxygen supplementation	1.49 (0.92, 2.42)	0.106	1.58 (0.9, 2.76)	0.112
	HsCRP > 75 mg/dL	1.14 (0.7, 1.88)	0.595	1.02 (0.57, 1.81)	0.946
Brain fog	Age ≥ 60 years	1.76 (1.08, 2.87)	0.024*	1 (0.57, 1.77)	0.988
	Female	2.19 (1.33, 3.59)	0.002*	2.03 (1.19, 3.45)	0.009*
	Oxygen supplementation	2.69 (1.63, 4.44)	< 0.001*	2.02 (1.14, 3.58)	0.017*
	HsCRP > 75 mg/dL	2.37 (1.42, 3.95)	0.001*	1.78 (0.99, 3.2)	0.055

*p value < 0.05; CI, confidence interval; HsCRP, high-sensitivity C-reactive protein; OR, odds ratio.

Discussion

In this study, we assessed the persistent symptoms after acute COVID-19 infection in patients attending our post COVID-19 outpatient clinic. We found that 80.9% of the patients had at least one symptom, which was similar to previous studies [12,22–23]. The persistent symptoms were observed more frequently in patients requiring oxygen therapy, indicating more severe disease.

Dyspnea was the most frequently experienced symptom in our cohort, followed by insomnia, myalgia, fatigue and brain fog, which are similar to other reports, in terms of symptoms, but slightly different in distribution [11,12,14,24–25]. Several previous studies reported that 40–50% of hospitalized COVID-19 patients experienced dyspnea after discharge, comparable to ours [22,25–27]. The pathophysiology of dyspnea after COVID-19 is not well understood and probably multifactorial. Possible mechanisms such as long-term lung and vascular abnormalities have been published [28]. However, a Norwegian cohort [27] revealed that approximately half of the participants had dyspnea on exertion at 3 months after hospitalization. Only 25% had reduced diffusing capacity and persistent ground glass opacities on the computerized tomography scan, but most participants had normal lung volumes. Our results were similar to another study [29] where most individuals experienced symptoms of dyspnea and fatigue, but their pulmonary function were still preserved. In our patients, higher Hs-CRP was predictive of dyspnea during the follow-up period, as observed in previous studies [30]

Insomnia and myalgia were the second and third most common symptoms, up to 40% in our cohort. Although this percentage was relevant, these symptoms were slightly higher than the nearly 20–30% reported in previous studies [22,26,31]. The effects of hospitalization during acute COVID-19 illness; including living alone in a closed space, reduced mobility, concern about infection, and financial issues; could possibly lead to mood disorders and sleeping problems [14,32]. Regional practices that were prevalent in developing countries, such as the lack of financial compensation for missing work while in isolation at the hospital, may have played an important role in elevating COVID-19 patients' psychological stress [33], and may explain the higher percentage of insomnia in our cohort. Decreased neurotransmitter levels, and reduced neuronal excitability have also been hypothesized as potential factors of post-COVID-19 fatigue and myalgia [28,32].

The heterogeneity of persistent symptoms, in terms of percentage and type of symptoms, depends on the time of assessment. In our cohort, the prevalence of headache, chest tightness, and altered smell and cough, decreased over time. In contrast, the majority of persistent symptoms were found to be at a higher percentage after 120 days of follow-up, consistent with a previous observational study [34]. An international cohort study revealed that a combination of systemic and neurologic symptoms; including fatigue, memory loss, and cognitive dysfunction; was more frequently reported after 6 months [35]. However, an increase in prevalence of individual symptoms may result from a

lower number of patients visiting the outpatient clinic over time.

We found that female gender was an independent associated factor for persistent symptoms. In a recent review [36] that included a total of 1.39 million patients, it was also concluded that being female had significantly higher sequelae of COVID-19. This could be explained by the differences in innate and adaptive immune response between genders. Females tend to show greater and more rapid innate and adaptive immune responses, which can protect them from initial infection. However, this same difference can make females more vulnerable to prolonged inflammatory symptoms. In addition, sex hormones may contribute to such a skewed gender impact [37].

In our study, the severity of acute COVID-19 was strongly correlated with persistent symptoms, similar to most of the studies with hospitalized patients [38–40]. The severity of acute COVID-19 illness could be a result of the host immune response leading to inflammation and organ damage. Higher inflammatory markers were reported to be factors associated with persistent symptoms [16,26], which correlated with our data in terms of dyspnea and fatigue symptoms. Moreover, using corticosteroid treatment in patients requiring oxygen therapy may be linked to more nosocomial infection and more long-lasting consequences.

We used multivariate logistic regression analyses to identify the independent risk factors related to each major symptom. We concluded that higher inflammation was associated with more dyspnea and fatigue, while oxygen supplementation was associated with more neurologic symptoms. Dyspnea and fatigue with higher inflammation could be explained by an intense immune and inflammatory reaction causing respiratory endothelial damage [28]. Viral neuroinvasion, endotheliopathy, hypoxic-ischemic neuronal injury, oxidative stress cascades, and cellular apoptosis have been shown to be involved in propagating persistent neurologic symptoms [41].

The key strengths of our study are as follows. First, we were able to include consecutive patients admitted during the selected period of time with minimal missing data. Second, as mentioned above, due to Thailand's public health policy, our cohort had a wide variety of COVID-19 severity. Finally, all of the data was recorded by a single, well-trained physician to minimize interobserver variability.

However, there were several limitations in our study. First, some reported symptoms were subjective and based on the patient's testimony without validated scales. Second, we did not record psychological problems, such as depression, posttraumatic stress disorder, and anxiety, which may have occurred in some patients and could have contributed to some symptoms. Third, the COVID-19 vaccine status was not recorded. Last, this study was conducted in a single center with a limited number of participants. In addition to the limitations of a cross-sectional study, only associated factors, and not risk factors, could be identified. Further extensive studies are required, and we suggest using standard measurement tools, such as the COVID-19 Yorkshire rehabilitation scale [42], in future studies.

Conclusions

We observed a high prevalence of persistent symptoms of COVID-19 in our outpatient clinic. The most common symptoms were dyspnea, insomnia, myalgia, fatigue, and brain fog. Being female and oxygen supplementation during admission were independently associated factors of overall persistent symptoms. High HsCRP during hospitalization was associated with dyspnea and fatigue; and using oxygen during admission was associated with insomnia and brain fog. These findings suggest that continuous careful observation of persistent symptoms and multidisciplinary integrated management after discharge is still required in those hospitalized COVID-19 patients.

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Authors' contributions

Conceptualization: DS, PP; formal analysis: DS; data curation: DS, PA, AL, KP, PP; writing – original draft preparation: DS; writing – review and editing: PP; approval of final manuscript: all authors.

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