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ORIGINAL ARTICLE

Postural orthostatic tachycardia syndrome and other autonomic dysfunctions following COVID-19: Incidence, characteristics, and associated factors

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Abstract

Background: Long-COVID syndrome has become a new health concern. Many major clinical centers have experienced more patients with symptoms suggestive of autonomic dysfunction, especially postural orthostatic tachycardia syndrome (POTS) following COVID-19. However, there is a lack of information regarding the incidence and associated factors in Asian population.

Methods: A retro-prospective study was conducted to evaluate patients with symptoms suggestive of POTS or other autonomic dysfunctions. These symptoms last at least 3 months after PCR-proven COVID-19. Exclusion criteria were age under 18 years old, pregnancy, and pre-COVID-19 autonomic dysfunction symptoms. Patients with a symptom severity score greater than two were assessed with blood tests, 24-h Holter, 24-h ambulatory blood pressure, echocardiogram, and head-up tilt table (HUTT).

Results: Seven hundred ninety-three patients were interviewed at 146 ± 37 days after COVID-19. The majority of patients were middle-aged females (53%). Of those, 15 patients had the symptom severity score greater than 2. Out of those 15 patients, 12 had positive HUTT (1 demonstrating POTS, 10 neurocardiogenic syncope, and 1 orthostatic hypotension). Among those with positive HUTT patients, C-reactive protein (CRP) was significantly higher (OR 1.01; *p*-value 0.041). Fatigue and dyspnea on exertion were the two most complaint symptoms.

Conclusions: This study shows the incidence of autonomic dysfunction and POTS is 1.5% (12/793) and 0.1% POTS (1/793), respectively, in a primary care setting (among general post-COVID-19 patients). The most common symptoms for these patients were fatigue and dyspnea.

KEYWORDS

COVID-19 induced autonomic dysfunction, COVID-19 induced POTS, long-COVID in Asian population, long-COVID syndrome, post-COVID-19 condition

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1 | INTRODUCTION

Coronavirus disease (COVID-19), caused by SAR-CoV-2, not only has acute effects during infection but also leads to many sequelae for survivors. Many studies have shown that patients who survive COVID-19 have prolonged symptoms even after the infection was cured, known as "long-COVID" or "long-haulers".¹ Long-COVID affects not only severely ill patients but also those with mild symptoms. The United Kingdom National Institute for Health and Care Excellence (NICE) guidelines define various symptomatic phases of COVID-19, in which "long-COVID" includes both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more). The prevalence of long-COVID varies across studies²: 1% in Denmark,³ 5%–51% in Italy,⁴ 1.6%–71% in UK,^{5,6} 16%-53% in USA,⁷ 22% in India,⁸ and 49%-76% in China.⁹ Studies assessing hospitalized patients have typically reported higher prevalence estimation. In those studies, the risk factors for long-COVID include female gender, elderly age, obesity, asthma, poor general health, and poor sociodemographic factors.^{5,10,11}

Cardiovascular (CVS) symptom is one of the pronounced sequelae experienced in post-COVID-19 syndrome. An international online survey of 3762 patients showed that cardiac symptoms, including chest pain (~53%), palpitations (~68%), and fainting (\sim 13%), were experienced at 7 months following infections.¹² One increasingly recognized sequela is postural orthostatic tachycardia syndrome (POTS). This syndrome is associated with a number of symptoms, such as orthostatic intolerance, fatigue, sleep disturbance, bloating, nausea, diarrhea, palpitations, tremor, generalized weakness, blurred vision, exercise intolerance, etc.¹³ By definition. POTS is characterized by a heart rate increment of \geq 30 beats/min when moving from a recumbent to a standing position held for more than 30s in the absence of orthostatic hypotension (OH; >20 mm Hg drop in systolic blood pressure).¹⁴ Approximately 2%-14% of PASC develop POTS, and 9%-61% demonstrate POTSlike symptoms within 6-8 months after infections.¹⁵⁻¹⁷ POTS commonly occurs after infections, especially viral infection, such as Epstein-Barr virus and influenza infections.¹⁸ There are increasing reports of post-COVID-19 POTS and other cardiac autonomic dysfunctions, but little is known about epidemiological data in an Asian primary care setting after COVID-19 infection. Thus, we aimed to study the incidence, characteristics, and associated factors of POTS and other autonomic dysfunction following COVID-19 in this population.

2 | MATERIALS AND METHODS

This ambidirectional cohort study evaluated patients who came to the COVID-19 outpatient clinic at Chulabhorn Hospital during Thailand's third wave of COVID-19. During the pandemic, Chulabhorn Hospital acted as a primary care center, treating walkin patients. A retrospective chart review was performed in patients

diagnosed with COVID-19 (using the RT-PCR technique) from April to July 2021 (peak wave in Thailand). All included patients were interviewed by phone, starting at least 3months after the diagnosis. Questions comprised of demographic data, baseline health status, and COVID-19 symptoms (initial and remaining symptoms). Symptoms of cardiac autonomic dysfunction were assessed using a set of questions with the 13 most reported symptoms in postacute sequelae of COVID-19 (PASC) and POTS, including fatigue, lightheadedness/dizziness, presyncope/syncope, chest pain, dyspnea on exertion, orthostatic intolerance, dizziness after standing, increased pulse rate with mild physical activity, brain fog, difficulty concentrating, sleep disturbance, headaches, and anxiety/depression.^{19,20} Patients were asked to grade their symptoms by an adjectival scale severity score ranging from 0 to 5 (based on the performance status scale because this can evaluate how much the symptoms affect the patients' ability to care for themselves, daily activities, and physical abilities). 0=no symptom; 1=mild symptom with no limitation; 2=some bothersome symptom (<50% of the day) with limitation <50%; 3=symptom >50% of the day with limitation <50%; 4=marked symptom with limitation>50%; 5=persisting symptom with severe limitation.

Patients with the score of 3 or higher in any symptoms were recruited for further thorough investigations. They were assessed clinically with a detailed medical history. Blood tests were taken for thyroid function, complete blood count, liver function test, troponin T, and C-reactive protein (CRP). Also, 12-leads electrocardiogram, transthoracic echocardiogram, 24-h home blood pressure monitoring (HMBP), and 24-h Holter monitoring were done. The head-up tilt table (HUTT) was performed if none of the above tests could explain their symptoms by using 12-lead electrocardiogram monitoring, continuous beat-to-beat HR, and every 2 min BP measuring after 6 h of fasting. Before the test, every patient was asked to lay on a flat table in a quiet room for 10 min to stabilize their HR and BP. After that, the table was tilted head-up to 70° for 20 min with ongoing HR, BP, and symptoms monitoring. In the case of a normal response in the passive phase, 5 mg of sublingual nitrate were given for provocation with a continuation of 20min observation. β-Blockers, if any, were held before HUTT. A dedicated follow-up of symptoms was performed a week after HUTT.

2.1 | Statistical analysis

The Shapiro–Wilk normality test was used to assess the normality of continuous variables. In normal distribution data, the variables were reported as mean \pm SD. In nonnormal distribution data, the variables were presented as the median and interquartile range. Categorical variables were recorded as number and percentage. Logistic regression was applied to assess the association between various factors and cardiac autonomic dysfunction, with a p < 0.05considered statistically significant. Statistical software for data WILEY-Journal of Archythmia

analysis was STATA/SE 16.1 software (StataCorp LP, College Station, TX, USA).

3 | RESULTS

A total of 793 PCR-proven COVID-19 patients were interviewed by phone. The mean age was 42 years, and 53% were female (Table 1). The median interval between the COVID-19 diagnosis and the interview date is 146 ± 37 days. At the COVID-19 diagnosis, the majority had mild symptoms and were treated as outpatients (mostly in field hospitals because of the government's regulation). The most common symptoms were fever, upper respiratory tract symptom, and diarrhea. The majority had no underlying disease (83%). Diabetes and hypertension were the two most common diseases among subjects with comorbidity. Approximately 53% of the patients had positive CRP (normal <5 mg/L), with the mean Creactive protein (CRP) of 18.95 ± 35.41 mg/L. None of our patients was admitted to the intensive care unit. Fifteen patients had at least one out of 13 persisting symptoms with a score of 3 or higher

TABLE 1 Patient characteristics (N = 793).

Data	N (%)/mean <u>+</u> SD
Age (years)	42.6 ± 15.5^{a}
Gender	
Male	372 (46.9)
Female	421 (53.1)
BMI (kg/m ²)	22.9 ± 4.3^{a}
Comorbidity	134 (16.9)
Diabetes	99 (15.4)
Hypertension	116 (14.6)
Dyslipidemia	68 (8.6)
Interval between COVID-19 diagnosis and interview date (days)	146 ± 37^{a}
Fasting plasma glucose (mg/dL)	108 ± 46^{a}
HbA1C (%)	6.1 ± 4.2^{a}
Creatinine (mg/L)	0.99 ± 0.9^a
C-reactive Protein (mg/L)	18.9 ± 35.4
Patient with positive result (>5 mg/L)	333 (52.8)
Chest CT severity score ^b	
Total patient	4.7±4.5ª
Patient with dyspnea on exertion ($N=40$)	6.5±4.9 ^a
Patient with fatigue ($N = 41$)	5.9 ± 3.5^{a}
Medication for COVID-19	
None	169 (21.6)
Favipiravir	577 (73.9)
Andrographis	35 (4.5)

 $^{a}Mean \pm SD.$

^bChest CT severity score meanings: mild <8, moderate 9–15, severe >15.

and sent for further investigation; 12 of them had autonomic dysfunctions as revealed by HUTT (abstract figure; symptoms persist from during infection until the interview date). Fatigue and dyspnea on exertion are the two most common symptoms (5.17%, 5.04% consecutively), as shown in Figure 1.

There was an association between patients' symptoms and the chest imaging severity score on computerized tomography of the chest (chest CT score). Those with fatigue and dyspnea on exertion had a more severe chest CT score than average patients. Patients with dyspnea on exertion and fatigue had a mean CT severity score of 6.53 ± 4.99 and 5.91 ± 3.48 , respectively. The figure for overall patients was 4.75 ± 4.53 .

Among 12 patients who had positive HUTT, 10 (83%) were female, with a mean age of 45 years. Four out of 12 patients had hypertension, and only one patient had dyslipidemia. None of the patients has diabetes mellitus. All 12 patients had experienced their symptoms since the COVID-19 diagnosis until the interview and HUTT date. For blood tests, including troponin T, showed normal results. Electrocardiograms and 24-h Holter monitoring were normal in all 12 patients. Echocardiography results yielded a normal left ventricular ejection fraction (mean $66.1\% \pm 6.1\%$) and global longitudinal strain (mean-19.7% ± 2.6%). The 24-h ambulatory blood pressure monitoring was done in 10 out of 12 patients. The reports revealed the median of mean SBP of 117 mmHg (113-129 mmHg) and the median of mean DBP of 74mmHg (73-91mmHg). All patients had a nondipping pattern during sleep, with a mean SBP drop of 6.30±3.02mmHg. Details on the HUTT response of all 12 patients were shown in Table 2. Sublingual nitroglycerin was used in 11 out of 12 patients. The definition of the HUTT test response was described in Table S1. In our study, the incidence of autonomic dysfunction is 1.5% (12 out of 793) and the incidence of POTS is 0.13% (1 out of 793).

When comparing patients with and without cardiac autonomic dysfunction (Table 3), the mean CRP was significantly higher in patients with autonomic dysfunction (OR 1.01; p=.041). Female had a higher risk of autonomic dysfunction (OR 4.50; p-value=.053), and the mean CT severity score was slightly higher (OR 1.08; p=.143) in patients with autonomic dysfunction. Regarding medication, favipiravir was the most prescribed drug in both groups, and approximately a quarter of patients in both groups were not given any medications.

4 | DISCUSSION

A retro-prospective evaluation of post-COVID-19 patients with mild symptoms was performed. All patients were proven COVID-19 cases with a positive PCR test and treated as outpatients. Most of the interviewed patients denied experiencing any symptoms and were able to perform routine activities. Only 16% experienced new symptoms of fatigue and dyspnea on exertion. Among those with high symptom severity scores, one patient was incidentally diagnosed with paroxysmal atrial fibrillation (AF) from 24-h Holter

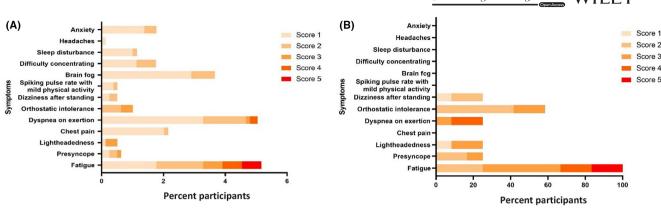


FIGURE 1 Symptoms and severity of symptoms experienced by patients. (A) Among 793 post COVID-19 patients (B) among 12 patients with postive HUTT.

monitoring, and the symptom improved after AF treatment. Previous studies showed the prevalence of POTS and sustained OH among patients with PASC is approximately 30% and 2.9%, respectively.²¹ Another study in 24 patients with PASC symptoms demonstrated that 23 of 24 patients had orthostatic intolerance, of whom four were diagnosed with POTS.²² In our study, the incidence of autonomic dysfunction and POTS (1.5% and 0.13%, respectively) seems to be lower than expected. This was probably because of (1) this study explored patients from our primary care unit during the time of COVID-19 diagnosis (not only those presented or referred to the tertiary care hospital with PASC). Our patients are likely to have experienced less symptoms and represent more of the general post-COVID-19 population. The prevalence was similar to that in the normal population (POTS: 0.1%-1%,²³ OH: 5%-30%¹⁸). (2) This study consisted predominantly of individuals with mild disease (the majority had no symptoms and a mild degree of lung involvement from chest CT score). There was an association between patients' symptoms and chest CT score during COVID-19, in which, the patients with higher chest CT scores are more likely to experienced dyspnea on exertion and fatigue.

Among our patients with positive HUTT, fatigue was the most frequent complaint, similar to previous studies.^{19,24} On the other hand, orthostatic intolerance and dizziness after standing were the two most specific symptoms in these patients.

Baseline characteristics between those with positive HUTT and the remaining patients were similar. Both groups were in their early 40s with a normal BMI. The majority of the positive HUTT group was female. One potential associated factor was the CRP level at COVID-19 diagnosis. Despite the elevated CRP in both groups, the level of elevation was significantly higher in the autonomic dysfunction group. In previous studies, some long-COVID patients had a higher level of CRP,⁷ and 9.5% demonstrated persistent CRP elevation.⁸ However, in our study, the level of CRP in autonomic dysfunction patients at the follow-up date dropped to the normal range (mean 2.6 ± 2.1). Additionally, the chest CT severity score tended to be higher in those with autonomic dysfunctions, although there was no statistical significance. From these findings, it is possible that a higher level of inflammation and worsened chest involvement during infection are possibly related to post-COVID-19 autonomic dysfunction.

4.1 | Study limitations

This was a single-center retrospective study, but a large number of patients were screened. In this retrospectively gathered database of COVID-19 patients, recall bias was unavoidable. To limit the effects of such errors, we reviewed the details of the past and present symptoms of potential subjects. In addition, patients were screened for recruitment by asking about common autonomic dysfunction symptoms. We recognized the potential of losing a small group of patients with other symptoms. In addition, patients were screened and recruited with simple autonomic dysfunction symptoms and a validated autonomic dysfunction questionnaire; it is possible that patients with very mild symptoms were not included. Given the low symptoms severity score, these patients may be only marginally symptomatic. Another limitation is that there is no nitrate spray available in Thailand, so we used 5 mg of sublingual nitrate tab for the provocation test instead. The incidence of vasovagal syncope could be falsely high; however, the incidence of vasovagal syncope is low in our study (1.5%) compared to the previously reported incidence rate of 17.2 per 1000 person-years.²⁵ Lastly, this was done in primarily an Asian population, and therefore the results cannot be generalized to the general population.

5 | CONCLUSION

In our study, the incidence of autonomic dysfunction was 1.5% and the incidence of POTS was 0.1% among a panel of primary care patients with prior COVID-19 infection. The incidence of these conditions is likely higher among patients with PACS. The CRP level during infection is significantly higher in those with positive HUTT. Most complaint symptoms in the positive HUTT group are fatigue and dyspnea on exertion.

TABLE 2 Detai	Details of patients with positive head-up tilt table.	nts with	n positiv	ve head-u	p tilt table.									
Demographics					Tilt-table testing								Echocardiography	graphy
						Supine		Passive pł	Passive phase standing	After nitroglycerin	. <u> </u>			
Patient number	Gender	Age	BMI	Score	Test result	BP	HR	BP	HR	BP	HR	Loss of consciousness	LVEF (%)	GLS (%)
1	Σ	58	23	5	Neurocardiogenic syncope	105/70	55	120/75	65	67/38	46	Yes	53	-14
2	щ	52	29	5	Neurocardiogenic syncope	104/50	65	110/69	71	Unmeasurable	45	Yes	63	-18
ю	ш	57	23	9	Neurocardiogenic syncope	131/79	76	148/94	89	90/49	70	Yes	68	-20
4	ш	25	19	5	Neurocardiogenic syncope	104/72	73	109/71	92	81/26	62	Yes	65	-20
5	ш	27	17	9	Neurocardiogenic syncope	112/68	64 4	46/22	42	I	I	Yes	64	-20
6	ш	26	22	7	Orthostatic hypotension	130/88	06	110/72	100	103/71	112	No	62	-10
7	ш	57	23	9	Neurocardiogenic syncope	101/71	66	110/80	82	Unmeasurable	62	Yes	64	-17
8	ш	99	23	5	Neurocardiogenic syncope	122/70 8	80	110/70	90-105	Unmeasurable	58	Yes	67	-17
6	ш	42	26	6	Neurocardiogenic syncope	110/62	60	103/68	97-100	Unmeasurable	60	Yes	78	-22
10	Σ	36	27	9	Neurocardiogenic syncope	119/52 0	68	117/97	78	105/49	58	Yes	68	-18
11	ш	55	26	10	Neurocardiogenic syncope	119/70	60	111/82	94	81/43	52	Yes	73	-22
12	ш	36	18	10	POTS	104/69	72	122/71	120	117/64	153	Yes	68	-21
TABLE 3 Asso	ciation beth	ween vi	arious f	factors an	Association between various factors and autonomic dysfunction (severity score >2) and positive HUTT.	erity score.	>2) and	d positive	HUTT.					
					Patient without autonomic dysfunction (<i>N</i> = 778)	nomic		Patients v positive F	Patients with autonomic positive HUTT) (N = 12)	Patients with autonomic dysfunction (score >2 and positive HUTT) (N = 12)	'e >2 an	d Crude OR (95% Cl)	-	<i>p</i> -value
Age					42.55 ± 15.53			44.58 ± 14.51	4.51			1.01 (0.97, 1.04)		.652
Female					411 (52.69)			10 (83.33)	()			4.50 (0.98, 20.68)		.053
BMI					22.95 ± 4.31			22.35 ± 3.18	.18			0.97 (0.84, 1.11)		.634
Comorbid					208 (26.63)			4 (33.33)				1.38 (0.41, 4.62)		.604
CT severity score	0				4.71 ± 4.53			6.67±3.98	8			1.08 (0.97, 1.21)		.143
C-reactive protein at diagnosis (normal <5 mg/L)	in at diagnos	sis (norn	nal <5 m	ng/L)	19.24 ± 35.66			44.82 ± 67.49	7.49			1.01 (1.00, 1.02)		.041
Drug														
None					169 (21.64)			3 (25.00)				Ref.		Ι
Favipiravir					577 (73.88)			9 (75.00)				1.22 (0.33. 4.55)		.771

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169 (21.64) 577 (73.88)

35 (4.48)

Andrographis Favipiravir

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CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflicts of interest for this article.

ETHICS APPROVAL

This study was reviewed and approved by the Ethics Committee of Chulabhorn Research Institute. All patients had a written and signed consent statement.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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