GLOBAL CARDIOLOGY SCIENCE & PRACTICE

Review article

Postural orthostatic tachycardia syndrome and post-acute COVID-19

Youssra Amekran*, Narjisse Damoun, Abdelkader Jalil El Hangouche

Department of Physiology, Faculty of Medicine and Pharmacy of Tangier, Abdelmalek Essaadi University, Tangier, Morocco
*Email: amekran.youssra@gmail.com
+ These authors contributed equally to this manuscript.

ABSTRACT

While the acute illness of COVID-19 was the initial focus of concern, there are increasing reports of patients with chronic symptoms, known as long-COVID. Dysautonomia may be a possible post-acute neurological complication explaining the persistent symptoms observed in long COVID. Postural tachycardia syndrome (POTS), a form of dysautonomia characterized by sustained tachycardia and orthostatic intolerance, has been increasingly reported in patients after SARS-CoV-2 infection. In this context, this review aimed to report and discuss the available literature pertaining to post COVID-19 POTS.

https://doi.org/10.21542/gcsp.2022.13

Received: 19 March 2022
Accepted: 11 June 2022

Cite this article as: Amekran Y, Damoun N, El Hangouche AJ. Postural orthostatic tachycardia syndrome and post-acute COVID-19, Global Cardiology Science and Practice 2022:13 https://doi.org/10.21542/gcsp.2022.13

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread worldwide since December 2019. The COVID-19 pandemic is described as a multi-organ disease, and the acute phase of infection results in a broad spectrum of manifestations ranging from asymptomatic and mild symptoms to severe outcomes and death[1–4].

While medical attention has been focused on the management of acute illness, an increasing number of patients have experienced symptoms such as fatigue, dyspnea, chest pain, palpitations, cognitive disturbance and orthostatic intolerance, long after their acute infectious period[3,5]. These persistent symptoms have been termed post-acute COVID-19 syndrome or long-COVID[6]. Among these symptoms, several are associated with neurological disorders, notably postural orthostatic tachycardia syndrome (POTS)[6].

POTS is a blood-circulation disorder that affects the autonomic nervous system[7]. Its principal feature is orthostatic intolerance and is characterized by a sustained heart rate increment of 30 beats/min or more in the absence of orthostatic hypotension (OH)[7–9].

The most commonly associated symptoms include fatigue, nausea, dizziness, light-headedness, palpitations, chest pain and exercise intolerance[8,10–14]. Data on the worldwide prevalence of POTS are missing; however, an estimation of 0.1 to 1% is the most frequently reported in the literature based on estimations in the United States[12,13].

Females are affected more often than males with F:M ratio › 4:1[12,13].

POTS has largely been involved in post-viral symptomatology[15–18], with 28–41% of POTS cases reported to be associated with viral infections[19,20], suggesting post viral autoimmune activation is a possible pathophysiological mechanism[16]. With an increasing number of patients being described with a wide variety of symptoms, particularly those implicated in autonomic dysfunction, long after their acute COVID-19 infectious period, we aimed to review the available literature on post COVID-19 POTS cases.

METHODS

A literature search was conducted to identify relevant literature pertaining to post COVID-19 POTS, using PubMed, Scopus, Web of Science and Embase databases. The keywords used were: "Postural Orthostatic Tachycardia Syndrome", "POTS", "dysautonomia", "autonomic dysfunction", "novel coronavirus", "severe acute respiratory syndrome coronavirus 2", "SARS-CoV-2", "Corona virus disease pandemic", "COVID-19", "2019-nCoV". We included articles published in English from the period between January 2020 and November 2021. A total of 9 papers were found.

RESULTS

Post COVID-19 postural orthostatic tachycardia syndrome

POTS is one of the most common autonomic disorders and is characterized by a wide range of clinical manifestations, including lightheadedness, palpitations, blurred vision, headaches, dyspnea, exercise intolerance, fatigue, gastrointestinal symptoms, pain, near-syncope, and syncope, resulting in a reduced daily functional capacity[21].

POTS is defined as an increase in HR of ≥30 bpm when moving from a recumbent to an upright posture within 10 min of standing (or ≥40 bpm in individuals of 12–19 years of age), without significant OH[22–24]. Acute stressors have been reported to trigger POTS, including immunological triggers such as viral infection, frequent upper respiratory or gastrointestinal tract infections, vaccination, pregnancy, surgery, and traumatic

events[15,19,25]. Viral infection is the most commonly reported and has been shown to trigger POTS in 28–41% of patients[19]. Various infectious pathogens have been suggested to be associated with the onset of POTS, including the Epstein Barr virus[25–27], upper respiratory infections, gastroenteritis and recently SARS-CoV2[17,28,29].

After reviewing the literature on patients with persistent symptoms following SARS-COV-2 infection and diagnosed with POTS, a summary of patient characteristics is shown in Table 1. A total number of 26 patients were included. The age of the patients ranged from 22 to 59 years, and the majority of cases were females (69%), with prominent symptoms that emerged several weeks after acute infection and lasted beyond months. The most common symptoms included fatigue, palpitations, chest pain, orthostatic intolerance, exercise intolerance and cognitive impairment (brain fog). Gastrointestinal complications and mast cell activation symptoms were observed at a lower frequency. Autonomic function was evaluated using the active stand test and head-up tilt table (HUT). Valsalva test (with HUT) and quantitative sudomotor axon reflex tests (QSART) were also performed.

POTS management

The management of POTS is challenging as there are no uniformly recommended therapies, and randomized clinical trials for targeted treatments are scarce[21,24]. The currently available management of POTS (besides accurate diagnosis) includes non-pharmacologic and pharmacologic approaches, in combination with patient education about alleviating the symptoms, long-term prognosis, and available therapeutic options[21,30].

Regular, structured, progressive, and supervised exercises have been described as effective non-pharmacological treatments to improve POTS-related symptoms[9,21,30,31]. However, given the possible activity-induced symptoms, exercise should be restricted to no upright exercises such as swimming, rowing machines, and recumbent cycles[9,21,24,30,31]. A previous progressive 3-month exercise regimen was effective in reducing the standing heart rate and alleviating symptoms[32].

Other non-pharmacological interventions include increased fluid and salt intake, physical counter maneuvers (muscle contraction, leg crossing)[33], compression devices, avoidance of medication worsening POTS, and avoidance of POTS symptom exacerbation such as caffeine and alcohol intake and heat exposure[21,24,34].

Pharmacological treatments for POTS are considered first-line POTS management[35]. In addition, they are not proven to be more effective than non-pharmacological treatments and should be used with caution, given their probable side effects[30]. The most widely used medications include fludrocortisone, which is a synthetic mineralocorticoid aldosterone analog utilized to increase salt retention and plasma volume,[9,30], alpha-1-adrenergic agonist midodrine resulting in systemic vasoconstriction and increasing venous return and effective in hypotensive phenotypes, clonidine and alpha-methyldopa, beta-blockers (propranolol, metoprolol), and pyridostigmine[24,30].

Some drugs may worsen some specific symptoms such as tachycardia, including selective serotonin and/or norepinephrine reuptake inhibitors, amphetamines and droxidopa or exacerbate orthostatic intolerance including calcium channel blockers, diuretics, nitrates, and opiates. However, they may be effective in some patients in accordance with their history and clinical presentation[30,36].

Based on the studies included in this review, the treatment of POTS in long COVID-19 patients was based on both non-pharmacologic and pharmacologic treatments as summarized in Figure 1. Non-pharmacological approaches included exercise,

Table 1 Summary of published cases of post COVID-19 POTS.

Reference	Patients	Symptoms	POTS diagnosis time following the acute COVID-19	Tests and diagnosis
Johansson M. et al. [66]	Patient 1: 42-year-old woman	Unable to stand more than5 min, palpitations, dizziness, heat, and exercise intolerance.	5–6 months	HUT showed a HRincrement of 50 bpm with initial OH, and Valsalva maneuver showed a hyperadrenergic response.
	Patient 2: 28-year-old woman	Chest pain, fatigue, nausea, headache. gastrointestinal symptoms, and orbital edema.	3 months	Active standing testshowed a HR increase of 53 bpm without BP fall, and HUT revealed symptomatic sinus tachycardia superior to 130 bpm without BP fall.
	Patient 3: 37-year-old woman	Fatigue, muscle weakness, insomnia, palpitations, brain fog with trouble concentrating.	Not specified	Active standing testshowed a HR increment of 44 bpm without BP fall.
Kanjwal M et al. [28]	Patient: 36-year-old woman	Fatigue, headache, dizziness, chest pain, and palpitations, particularly while getting up from sitting position.	3-4 weeks	HUT showed a HRincrement of 41 bpm without any fall.

(*continued on next page*)

Table 1 (*continued*)

Reference	Patients	Symptoms	POTS diagnosis time following the acute COVID-19	Tests and diagnosis
Miglis MG et al. [29]	Patient: 26-year-old woman	Tachycardia, chest pain, shortness of breath, fatigue, exercise intolerance, diarrhea, tremors, and worsening restlessness.	3 months	HUT demonstrated aHR increase of 65 bpm with episodic hypertensive systolic BP surges to 170 mmHg in an oscillatory pattern, and robust BP responses to Valsalvamaneuver pattern in the absence of hyperventilation, indicating the presence of a n hyperadrenergic state.
Blitshteyn S al. [67]	Patients: 15 patients, mean age: 42.4 years old (min: 25; max: 59) with predominance of females 6M/9F.	Tachycardia, fatigue, hypersomnolence, anosmia, ageusia, exercise intolerance, chest pain, headache, fever, dizziness, weight loss, diarrhea and presyncope.	6–8 months after COVID-19	10-min stand test or TTTs.
Umapathi T et al. [68]	Patient: 39-year-old man	Tachycardia, dry mouth, pain and vibration sense.	18 days	Active standing testdemonstrated a HR increase of 35 bpm and an increase of 31 bpm after passive60-degree tilt (5min) without decrease in blood pressure.

(*continued on next page*)

Table 1 (*continued*)

Reference	Patients	Symptoms	POTS diagnosis time following the acute COVID-19	Tests and diagnosis
Shouman K et al. [69]	Patient 1: A 35-year-old woman	Constant tingling in the feet, orthostatic lightheadedness, brain fog, orthostatic intolerance and presyncope	2 months	Tilt test showed a HR increase of 31 bpm.
	Patient 2: A 35-year-old woman	Orthostatic lightheadedness, tachycardia, and hyperhidrosis	4 months	Autonomic reflex screen revealed excessive heart rateacceleration during tilt meeting POTS criteria, with hyperadrenergiccharacteristics including an increase in bloodpressure on tilt and resting sweat activity on QSART.
Ishibashi Y et al. [70]	Patient: A 25-year-old woman	Fatigue, palpitations,dyspnea and chest pain, especially while getting up from sitting position.	3 weeks	Tilt test showed an increase in heart rate from 80 bpm in the supine position to 110 bpm in the absence of hypotension during a 10-min head-up tilt at an angle of 90°, which returned to the baseline level immediately after lowering to the supine position.

(*continued on next page*)

Table 1 (*continued*)

Reference	Patients	Symptoms	POTS diagnosis time following the acute COVID-19	Tests and diagnosis
Schofield JR et al. [71]	Patient: A 50-year-old woman	Nausea, presyncope, dyspnea, chest tightness, myalgia, constant thirst, pruritus, and temperature dysregulation.	Approximately 2 months	Active standing test showed an increase in HR from supine to standing of 55 bpm.
O'Sullivan JS et al. [10]	Patient: A 22-year-old woman	Dyspnea and chest tightness.	3 weeks	Active standing test revealed a HR increase of 30 bpm.

BP: blood pressure; HR: Heart rate; HUT: head-up tilt; OH: Orthostatic hypotension; QSART:quantitative sudomotor axon reflex test; TTT: Tilt test table

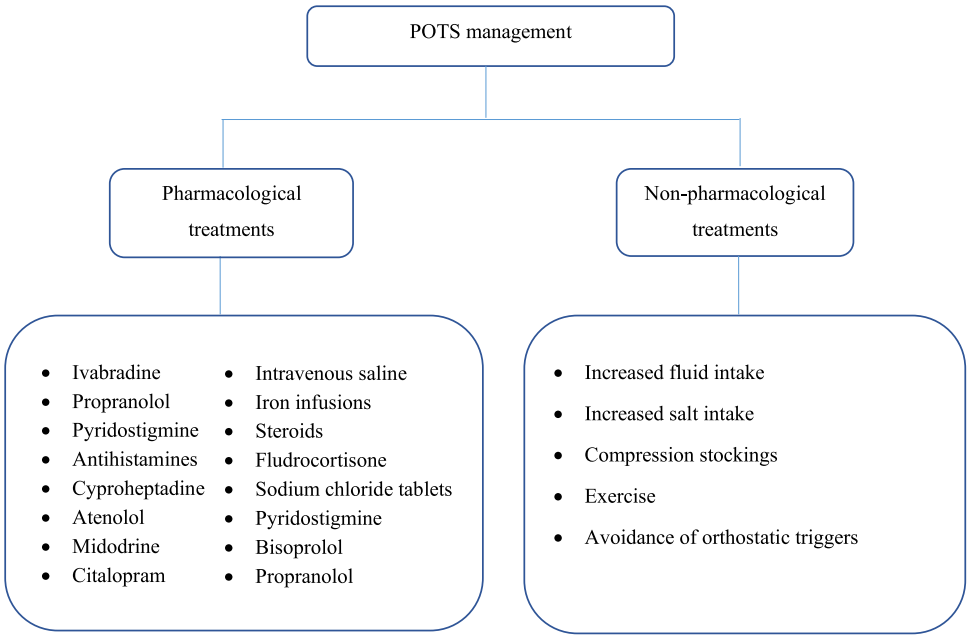

Figure 1. A summary of POTS treatments used in COVID-19 Pharmacological treatments.

fluid and salt intake, compression stockings, and avoidance of orthostatic triggers. Pharmacological treatment included ivabradine, fludrocortisone, midodrine, and antihistamines.

DISCUSSION

COVID-19 is a multi-organ disease with a broad spectrum of manifestations, including neurological manifestations, indicating the potential of COVID-19 to invade the nervous system[37,38]. In addition to the acute phase of SARS-COV-2 infection, reports have emerged on COVID-19 long term effects and complications[4]. More than 50% of survivors have ongoing symptoms several months after the acute infectious period[5], and many of these symptoms are autonomic in nature[3]. The post-acute COVID-19 condition is termed post-acute COVID-19 syndrome or long COVID-19. This phenomenon is characterized by the persistence of symptoms and/or delayed complications beyond 3 or 4 weeks from the onset of the acute phase of COVID-19[39,40]. Based on recent literature, the presence of symptoms from 4-12 weeks beyond the acute infectious period of COVID-19 is termed subacute or ongoing symptoms, and post-acute COVID-19 syndrome includes symptoms persisting for › 12 weeks.

Long COVID-19 includes both ongoing symptoms and post-acute COVID-19 syndrome[3,37,41]. The most-commonly reported symptoms are fatigue, headache, cognitive impairment, dyspnea, palpitations, and orthostatic intolerance[3]. According to a systematic review and meta-analysis reporting the long-term effects of COVID-19, five symptoms were noted as the most common among COVID-19 survivors; fatigue (58%), headache (44%), attention disorder (27%), hair loss (25%), and dyspnea (24%)[42]. Long COVID symptoms have been reported in COVID-19 survivors admitted to hospital with severe outcomes, as well as in patients with mild disease[4,5,43,44].

In a study of 143 severe COVID-19 survivors in Italy, 53% were female and 87% reported symptoms at 60 days. Fatigue was present in 53% of patients, breathing difficulty in 43%, and chest pain in 22%[45]. A survey of 274 non-hospitalized COVID-19

survivors in the US reported that 1/3 (52% female) had not returned to their usual state of health 2–3 weeks after the stage of acute infection. The most frequently reported symptoms include fatigue, present in 71%, cough in 61%, and headache in 61% of survivors[43]. Similarly, another study of 150 survivors of non-critical COVID-19 in France showed persistent symptoms in two-thirds of patients at 60 days of follow-up[46]. Other studies have reported the persistence of autonomic symptoms for over 100 days after the onset of acute infection. Autonomic symptoms include tachycardia upon mild exercise or standing, and temperature dysregulation[3].

Risk factors for long COVID-19 complications are not fully understood. However, recent studies suggested that female sex and increasing age are risk factors for long COVID-19[47]. The presence of more than five symptoms in the acute phase of infection and the presence of comorbidities are also suggested to increase the risk of developing long COVID-19[48].

The aetiology of long COVID remains unknown. However, some factors are suspected to contribute to the persistence of symptoms, including immune response or autoantibody generation, varying extent of injury, and varying time required in each organ system recovery[48,49]. Deconditioning and psychological issues may also result in the underlying symptoms[49,50].

Autonomic dysfunction was suggested to be a possible post-acute neurological complication, explaining some of the persistent symptoms observed in long COVID[6,51,52]. This review focuses on POTS as the most frequent dysautonomia that has been reported in post COVID-19 patients.

After reviewing the literature, we found that the age of post COVID-19 POTS ranged from 22 to 59 years, and female patients outnumbered male patients. Prior studies have noted that the onset of POTS typically occurs in 12- to 50-year-old females with a ratio ranging from 4:1 to 5:1[53,54]. A lower ratio was reported in pediatric population (3.45:1)[54].

The most common symptoms of POTS include fatigue, lightheadedness, palpitations, chest pain, orthostatic intolerance, exercise intolerance, and cognitive impairment (brain fog). These symptoms have been reported in previous studies as the most common symptoms in the initial presentation of POTS[16,55,56].

The pathophysiology of POTS remains unknown, however there is a number of physiological mechanisms that have been supposed to be involved. These may include sympathetic dysregulation, hypovolemia, hyperadrenergic stimulation, deconditioning[12,57], autoantibody mediated response[57], and mast cell activation[58,59]. Moreover, COVID-19 associated manifestations may be a factor contributing to deconditioning and hypovolemia[5,60].

The heterogeneity of POTS symptoms may complicate the diagnosis and divert it towards other disorders with similar manifestations, such as orthostatic hypotension, hyperthyroidism and anxiety[61]. In this review, the autonomic function of patients was mostly evaluated using the head up tilt test (HUT) and the active stand test. Valsalva test (with HUT) and quantitative sudomotor axon reflex tests (QSART) were also performed. HUT is considered as a golden standard for POTS diagnosis[61]. Additional tests may also be performed. These tests include the active standing test, used for initial screening and when there is a lacking access to autonomic laboratory equipment[61]. Other tests used as a confirmatory tests include 24 h ECG monitoring, used to discriminate POTS diagnosis from inappropriate sinus tachycardia[62], and Valsalva manoeuvre, suggested to discriminate hyperadrenergic type from other forms of POTS[61,63,64].

Moreover, variability in POTS-related symptoms, poorly explored aetiologies, and variable response to treatment make POTS management challenging and are responsible

for the limited data on effective therapies. Generally, the management of POTS is used to alleviate symptoms[54,64].

POTS management includes nonpharmacological and pharmacological interventions. Non-pharmacological treatments are recommended for all patients with POTS[22], and have been demonstrated to be sufficiently effective in some cases[65]. Exercise, increased fluid and salt intake, and avoidance of orthostatic triggers are the most frequently reported non-pharmacological interventions in post COVID-19 POTS cases. Single or combination pharmacologic therapies were employed in the reported post COVID-19 cases. These include fludrocortisone, midodrine, antihistamines and ivabradine. Generally, pharmacologic therapies are directed at increasing intravascular volume, increasing peripheral vasoconstriction and modulating HR[54]. However, there still no robust evidence on the effectiveness of many drugs[30].

CONCLUSION

Long term effects of COVID-19 are increasingly described in the literature and present a compromising risk for quality of life and health care systems. This review identified cases with long COVID manifestations and diagnosed to have POTS, and reported clinical characteristics, diagnosis modalities and involved therapies. Data obtained in this review can be used in optimizing and promoting surveillance of POTS disorder in populations with a history of confirmed, or of a highly suspected COVID-19.

REFERENCES

[1] Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J Autoimmun*. 2020;109:102433 doi: 10.1016/j.jaut.2020.102433.
[2] Whittaker A, Anson M, Harky A. Neurological Manifestations of COVID-19: A systematic review and current update. *Acta Neurol Scand*. 2020;142(1):14–22 doi: 10.1111/ane.13266.
[3] Larsen NW, Stiles LE, Miglis MG. Preparing for the long-haul: autonomic complications of COVID-19. *Auton Neurosci*. 2021;235:102841 doi: 10.1016/j.autneu.2021.102841.
[4] Adeloye D, Elneima O, Daines L, et al. The long-term sequelae of COVID-19: an international consensus on research priorities for patients with pre-existing and new-onset airways disease. *Lancet Respir Med*. 2021;9(12):1467–1478 doi: 10.1016/S2213-2600(21)00286-1.
[5] Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet*. 2021;397(10270):220–232 doi: 10.1016/S0140-6736(20)32656-8.
[6] Raj SR, Arnold AC, Barboi A, et al. Long-COVID postural tachycardia syndrome: an American Autonomic Society statement. *Clin Auton Res*. 2021;31(3):365–368 doi: 10.1007/s10286-021-00798-2.
[7] Reddy S, Reddy S, Arora M. A case of postural orthostatic tachycardia syndrome secondary to the messenger RNA COVID-19 vaccine. *Cureus*. 2021;13(5):e14837 doi: 10.7759/cureus.14837 Published 2021 May 4.
[8] Safavi-Naeini P, Razavi M. Postural orthostatic tachycardia syndrome. *Tex Heart Inst J*. 2020;47(1):57–59 Published 2020 Feb 1. doi: 10.14503/THIJ-19-7060.
[9] Bryarly M, Phillips LT, Fu Q, Vernino S, Levine BD. Postural orthostatic tachycardia syndrome: JACC focus seminar. *J Am Coll Cardiol*. 2019;73(10):1207–1228 doi: 10.1016/j.jacc.2018.11.059.
[10] O'Sullivan JS, Lyne A, Vaughan CJ. COVID-19-induced postural orthostatic tachycardia syndrome treated with ivabradine. *BMJ Case Rep*. 2021;14(6):e243585 Published 2021 Jun 14. doi: 10.1136/bcr-2021-243585.
[11] Vernino S, Stiles LE. Autoimmunity in postural orthostatic tachycardia syndrome: current understanding. *Auton Neurosci*. 2018;215:78–82 doi: 10.1016/j.autneu.2018.04.005.
[12] Arnold AC, Ng J, Raj SR. Postural tachycardia syndrome - diagnosis, physiology, and prognosis. *Auton Neurosci*. 2018;215:3–11 doi: 10.1016/j.autneu.2018.02.005.
[13] Bhatia R, Kizilbash SJ, Ahrens SP, et al. Outcomes of adolescent-onset postural orthostatic tachycardia syndrome. *Jornal de Pediatria*. 2016;173(2016):149–153 doi: 10.1016/j.jpeds.2016.02.035.
[14] Adamec I, Crnošija L, Ruška B, et al. The incidence of postural orthostatic tachycardia syndrome in the population of Zagreb, Croatia. *Croat Med J*. 2020;61(5):422–428 doi: 10.3325/cmj.2020.61.422.
[15] Raj SR. The Postural Tachycardia Syndrome (POTS): pathophysiology, diagnosis & management. *Indian Pacing Electrophysiol J*. 2006;6(2):84–99.
[16] Boris JR, Bernadzikowski T. Demographics of a large paediatric Postural Orthostatic Tachycardia Syndrome Program. *Cardiol Young*. 2018;28(5):668–674 doi: 10.1017/S1047951117002888.
[17] Goldstein DS. The possible association between COVID-19 and postural tachycardia syndrome. *Heart Rhythm*. 2021;18(4):508–509 doi: 10.1016/j.hrthm.2020.12.007.

[18] Dixit NM, Churchill A, Nsair A, Hsu JJ. Post-Acute COVID-19 syndrome and the cardiovascular system: what is known? *Am Heart J Plus*. 2021;5:100025 doi: 10.1016/j.ahjo.2021.100025.
[19] Thieben MJ, Sandroni P, Sletten DM, et al. Postural orthostatic tachycardia syndrome: the Mayo clinic experience. *Mayo Clin Proc*. 2007;82(3):308–313 doi: 10.4065/82.3.308.
[20] Shaw BH, Stiles LE, Bourne K, et al. The face of postural tachycardia syndrome - insights from a large cross-sectional online community-based survey. *Journal of Internal Medicine*. 2019;286(4):438–448 doi: 10.1111/joim.12895.
[21] Zadourian A, Doherty TA, Swiatkiewicz I, Taub PR. Postural Orthostatic Tachycardia Syndrome: prevalence, pathophysiology, and management. *Drugs*. 2018;78(10):983–994 doi: 10.1007/s40265-018-0931-5.
[22] Sheldon RS, Grubb 2nd BP, Olshansky B, et al. 2015 heart rhythm society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. *Heart Rhythm*. 2015;12(6):e41-e63 doi: 10.1016/j.hrthm.2015.03.029.
[23] Sheldon RS, Grubb 2nd BP, Olshansky B, et al. 2015 heart rhythm society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. *Heart Rhythm*. 2015;12(6):e41-e63 doi: 10.1016/j.hrthm.2015.03.029.
[24] Hangouche AJE, Alaika O, Bakkali ME, Jniene A, Aboudrar S, Cherti M, Dakka T. Postural Orthostatic Tachycardia Syndrome (POTS): Diagnosis and Management.
[25] Fedorowski A, Li H, Yu X, et al. Antiadrenergic autoimmunity in postural tachycardia syndrome. *Europace*. 2017;19(7):1211–1219 doi: 10.1093/europace/euw154.
[26] Pohlgeers KM, Stumbo JR. Syncope in an Athlete: a case of infectious mononucleosis-induced postural tachycardia syndrome. *Curr Sports Med Rep*. 2016;15(1):41–45 doi: 10.1249/JSR.0000000000000227.
[27] Yaxley KL. Infectious mononucleosis complicated by peritonsillar abscess and postural orthostatic tachycardia syndrome: A case report. *SAGE Open Med Case Rep*. 2020;8:2050313X20915413 Published 2020 Apr 2. doi: 10.1177/2050313X20915413.
[28] Kanjwal K, Jamal S, Kichloo A, Grubb BP. New-onset postural orthostatic tachycardia syndrome following coronavirus disease 2019 infection. *J Innov Card Rhythm Manag*. 2020;11(11):4302–4304 Published 2020 Nov 15. doi: 10.19102/icrm.2020.111102.
[29] Miglis MG, Prieto T, Shaik R, Muppidi S, Sinn DI, Jaradeh S. A case report of postural tachycardia syndrome after COVID-19. *Clin Auton Res*. 2020;30(5):449–451 doi: 10.1007/s10286-020-00727-9.
[30] Baig AM. Chronic COVID syndrome: need for an appropriate medical terminology for long-COVID and COVID long-haulers. *Journal of Medical Virology*. 2021;93(5):2555–2556 doi: 10.1002/jmv.26624.
[31] Jones PK, Shaw BH, Raj SR. Clinical challenges in the diagnosis and management of postural tachycardia syndrome. *Pract Neurol*. 2016;16(6):431–438 doi: 10.1136/practneurol-2016-001405.
[32] George SA, Bivens TB, Howden EJ, et al. The international POTS registry: evaluating the efficacy of an exercise training intervention in a community setting. *Heart Rhythm*. 2016;13(4):943–950 doi: 10.1016/j.hrthm.2015.12.012.
[33] Benarroch EE. Postural tachycardia syndrome: a heterogeneous and multifactorial disorder. *Mayo Clinic Proceedings*. 2012;87(12):1214–1225.
[34] Fu Q, Levine BD. Exercise and non-pharmacological treatment of POTS. *Auton Neurosci*. 2018;215:20–27 doi: 10.1016/j.autneu.2018.07.001.
[35] Pawelczyk JA, Zuckerman JH, Blomqvist CG, Levine BD. Regulation of muscle sympathetic nerve activity after bed rest deconditioning. *American Journal of Physiology-Heart and Circulatory Physiology*. 2001;280(5):H2230–H2239 doi: 10.1152/ajpheart.2001.280.5.H2230.
[36] Grubb BP. Postural tachycardia syndrome. *Circulation*. 2008;117(21):2814–2817 doi: 10.1161/CIRCULATIONAHA.107.761643.
[37] Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19 syndrome. *Nature Medicine*. 2021;27(4):601–615 doi: 10.1038/s41591-021-01283-z.
[38] Ståhlberg M, Reistam U, Fedorowski A, et al. Post-COVID-19 Tachycardia syndrome: a distinct phenotype of post-acute COVID-19 syndrome. *American Journal of Medicine*. 2021;134(12):1451–1456 doi: 10.1016/j.amjmed.2021.07.004.
[39] Datta SD, Talwar A, Lee JT. A proposed framework and timeline of the spectrum of disease due to SARS-CoV-2 infection: illness beyond acute infection and public health implications. *Journal of the American Medical Association*. 2020;324(22):2251–2252 doi: 10.1001/jama.2020.22717.
[40] Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. Management of post-acute covid-19 in primary care. *BMJ*. 2020;370:m3026 Published 2020 Aug 11. doi: 10.1136/bmj.m3026.
[41] *COVID-19 rapid guideline: managing the long-term effects of COVID-19*. London: National Institute for Health and Care Excellence (NICE); December 18, 2020.
[42] Yan Z, Yang M, Lai CL. Long COVID-19 syndrome: a comprehensive review of its effect on various organ systems and recommendation on rehabilitation plans. *Biomedicines*. 9(8):966 Published 2021 Aug 5. doi: 10.3390/biomedicines9080966.
[43] Tenforde MW, Kim SS, Lindsell CJ, et al. Symptom duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multistate health care systems network - United States. March–June 2020. *MMWR. Morbidity and Mortality Weekly Report*. 2020;69(30):993–998 Published 2020 Jul 31. doi: 10.15585/mmwr.mm6930e1.
[44] Yong SJ. Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments. *Infect Dis (Lond)*. 2021;53(10):737–754 doi: 10.1080/23744235.2021.1924397.

[45] Carfì A, Bernabei R, Landi F. Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent symptoms in patients after acute COVID-19. *Journal of the American Medical Association*. 324(6):603–605 doi: 10.1001/jama.2020.12603.
[46] Carvalho-Schneider C, Laurent E, Lemaignen A, et al. Follow-up of adults with noncritical COVID-19 two months after symptom onset. *Clinical Microbiology and Infection*. 27(2):258–263 doi: 10.1016/j.cmi.2020.09.052.
[47] Nabavi N. Long covid: how to define it and how to manage it. *BMJ*. 2020;370:m3489 Published 2020 Sep 7. doi: 10.1136/bmj.m3489.
[48] Raveendran AV, Jayadevan R, Sashidharan S. Long COVID: an overview [published correction appears in Diabetes Metab Syndr. 2022 May;16(5):102504]. *Diabetes Metab Syndr*. 2021;15(3):869–875 doi: 10.1016/j.dsx.2021.04.007.
[49] Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol*. 2020;20(6):363–374 doi: 10.1038/s41577-020-0311-8.
[50] Gemelli Against COVID-19 Post-Acute Care Study Group. Post-COVID-19 global health strategies: the need for an interdisciplinary approach. *Aging Clinical and Experimental Research*. 32(8):1613–1620 doi: 10.1007/s40520-020-01616-x.
[51] Dani M, Dirksen A, Taraborrelli P, et al. Autonomic dysfunction in 'long COVID': rationale, physiology and management strategies. *Clin Med (Lond)*. 2021;21(1):e63-e67 doi: 10.7861/clinmed.2020-0896.
[52] Buoite Stella A, Furlanis G, Frezza NA, Valentinotti R, Ajcevic M, Manganotti P. Autonomic dysfunction in post-COVID patients with and witfhout neurological symptoms: a prospective multidomain observational study. *J Neurol*. 2022;269(2):587–596 doi: 10.1007/s00415-021-10735-y.
[53] Wang XL, Chai Q, Charlesworth MC, et al. Autoimmunoreactive IgGs from patients with postural orthostatic tachycardia syndrome. *Proteomics Clin Appl*. 2012;6(11–12):615–625 doi: 10.1002/prca.201200049.
[54] Wells R, Spurrier AJ, Linz D, et al. Postural tachycardia syndrome: current perspectives. *Vasc Health Risk Manag*. 2017;14:1–11 Published 2017 Dec 29. doi: 10.2147/VHRM.S127393.
[55] Cheng JL, Au JS, Guzman JC, Morillo CA, MacDonald MJ. Cardiovascular profile in postural orthostatic tachycardia syndrome and Ehlers-Danlos syndrome type III. *Clin Auton Res*. 2017;27(2):113–116 doi: 10.1007/s10286-016-0392-4.
[56] Tembey RA, Bajaj AS, Wagle PK, Ansari AS. Real-time ultrasound: key factor in identifying celiac artery compression syndrome. *Indian J Radiol Imaging*. 2015;25(2):202–205 doi: 10.4103/0971-3026.155882.
[57] Fedorowski A. Postural orthostatic tachycardia syndrome: clinical presentation, aetiology and management. *J Intern Med*. 2019;285(4):352–366 doi: 10.1111/joim.12852.
[58] Doherty TA, White AA. Postural orthostatic tachycardia syndrome and the potential role of mast cell activation. *Auton Neurosci*. 2018;215:83–88 doi: 10.1016/j.autneu.2018.05.001.
[59] Loughnan A, Gall N, James S. Observational case series describing features of cardiopulmonary exercise testing in Postural Tachycardia Syndrome (PoTS). *Auton Neurosci*. 2021;231:102762 doi: 10.1016/j.autneu.2020.102762.
[60] Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med*. 2020;382(8):727–733 doi: 10.1056/NEJMoa2001017.
[61] Shouman K, Vanichkachorn G, Cheshire WP, et al. Autonomic dysfunction following COVID-19 infection: an early experience. *Clin Auton Res*. 2021;31(3):385–394 doi: 10.1007/s10286-021-00803-8.
[62] Brignole M, Moya A, De Lange FJ, et al. 2018 ESC Guidelines for the diagnosis and management of syncope. *European Heart Journal*. 2018;39(21):1883–1948 doi: 10.1093/eurheartj/ehy037.
[63] Goodman BP. Evaluation of postural tachycardia syndrome (POTS). *Auton Neurosci*. 2018;215:12–19 doi: 10.1016/j.autneu.2018.04.004.
[64] Jones PK, Gibbons CH. The role of autonomic testing in syncope. *Auton Neurosci*. 2014;184(2014):40–45 doi: 10.1016/j.autneu.2014.05.011.
[65] Raj SR, Guzman JC, Harvey P, et al. Canadian Cardiovascular Society Position Statement on Postural Orthostatic Tachycardia Syndrome (POTS) and Related Disorders of Chronic Orthostatic Intolerance. *Canadian Journal of Cardiology*. 2020;36(3):357–372 doi: 10.1016/j.cjca.2019.12.024.
[66] Johansson M, Ståhlberg M, Runold M, et al. Long-Haul Post-COVID-19 Symptoms Presenting as a Variant of Postural Orthostatic Tachycardia Syndrome: the Swedish Experience. *JACC Case Rep*. 2021;3(4):573–580 doi: 10.1016/j.jaccas.2021.01.009.
[67] Blitshteyn S, Whitelaw S. Postural orthostatic tachycardia syndrome (POTS) and other autonomic disorders after COVID-19 infection: a case series of 20 patients [published correction appears in Immunol Res. 2021 Apr 13]. *Immunologic Research*. 2021;69(2):205–211 doi: 10.1007/s12026-021-09185-5.
[68] Umapathi T, Poh MQW, Fan BE, Li KFC, George J, Tan JYL. Acute hyperhidrosis and postural tachycardia in a COVID-19 patient. *Clin Auton Res*. 2020;30(6):571–573 doi: 10.1007/s10286-020-00733-x.
[69] Shouman K, Vanichkachorn G, Cheshire WP, et al. Autonomic dysfunction following COVID-19 infection: an early experience. *Clin Auton Res*. 2021;31(3):385–394 doi: 10.1007/s10286-021-00803-8.
[70] Ishibashi Y, Yoneyama K, Tsuchida T, Akashi YJ. Post-COVID-19 Postural Orthostatic Tachycardia Syndrome. *Internal Medicine*. 2021;60(14):2345 doi: 10.2169/internalmedicine.7626-21.
[71] Schofield JR. Persistent Antiphospholipid Antibodies, Mast Cell Activation Syndrome, Postural Orthostatic Tachycardia Syndrome and Post-COVID Syndrome: 1 Year On. *Eur J Case Rep Intern Med*. 2021;8(3):002378 Published 2021 Mar 22. doi: 10.12890/2021_002378.