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REVIEW ARTICLE

Clinical presentation and management strategies of cardiovascular autonomic dysfunction following a COVID-19 infection – A systematic review

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Abstract

Background: Cardiovascular autonomic dysfunction may reportedly occur after a coronavirus-disease-2019 (COVID-19) infection, but the available evidence is scattered. Here we sought to understand the acute and mid-term effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on cardiovascular autonomic function.

Methods: We performed a systematic PubMed, Embase, Web of Science, medRxiv, and bioRxiv search for cases of cardiovascular autonomic dysfunction during an acute SARS-CoV-2 infection or post-COVID-19 condition. The clinical-demographic characteristics of individuals in the acute versus post-COVID-19 phase were compared.

Results: We screened 6470 titles and abstracts. Fifty-four full-length articles were included in the data synthesis. One-hundred and thirty-four cases were identified: 81 during the acute SARS-CoV-2 infection (24 thereof diagnosed by history) and 53 in the post-COVID-19 phase. Post-COVID-19 cases were younger than those with cardiovascular autonomic disturbances in the acute SARS-CoV-2 phase (42 vs. 51 years old, $p = 0.002$) and were more frequently women (68% vs. 49%, $p = 0.034$). Reflex syncope was the most common cardiovascular autonomic disorder in the acute phase ($p = 0.008$) and postural orthostatic tachycardia syndrome (POTS) the most frequent diagnosis in individuals with post-COVID-19 orthostatic complaints ($p < 0.001$). Full recovery was more frequent in individuals with acute versus post-COVID-19 onset of cardiovascular autonomic disturbances (43% vs. 15%, $p = 0.002$).

Conclusions: There is evidence from the scientific literature about different types of cardiovascular autonomic dysfunction developing during and after COVID-19. More data about the prevalence of autonomic disorders associated with a SARS-CoV-2 infection are needed to quantify its impact on human health.

KEYWORDS
autonomic nervous system, COVID-19, orthostatic hypotension, postural orthostatic tachycardia syndrome, syncope

See editorial by M. J. Hilz on page 1170.

INTRODUCTION

Almost 3 years after the beginning of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic, the scientific community has gained insights into most of its possible clinical complications both in the acute phase and in the long term of this post-viral condition which is commonly referred to as post-COVID-19 syndrome [1, 2].

Neurological complications of an acute coronavirus disease 2019 (COVID-19) infection are commonly recognized immune-mediated, peri-, para-, and post-infectious neurological syndromes affecting both the peripheral and central nervous system [3]. In addition, there is increased risk of cerebrovascular disease, including hemorrhagic stroke and subarachnoid hemorrhage [4].

The post-COVID-19 syndrome, on the other hand, refers to the residual symptoms of an ongoing SARS-CoV-2 infection that persist for more than 4 weeks, or to newly developed symptoms within 3 months after such an infection, that cannot be explained by other conditions [5]. Fatigue, orthostatic intolerance, impaired cognitive performance, shortness of breath, chest pain, and palpitations are persistent symptoms commonly experienced by individuals with a post-COVID-19 syndrome [6].

Neurological signs and symptoms triggered by SARS-CoV-2 have been postulated to depend upon the inflammatory response of the body to the SARS-CoV-2 infection [7]. A close, bidirectional relationship in fact exists between changes in the autonomic nervous system and immune system activation, based on multiple neuronal and non-neuronal pathways. Cytokines and other immunological factors modulate, for example, the activation of autonomic reflex arches, which in turn influence peripheral immune responses and various signaling mechanisms, including neurotransmitters, neuromodulators, and the behavior of specific adrenergic receptors [8]. In this context, the cardiovascular autonomic domain appears to be particularly vulnerable to the effects of a SARS-CoV-2 infection [9, 10].

Early case reports and short series addressed symptoms of cardiovascular autonomic dysfunction in both the acute and post-COVID-19 phases, but difficulties in characterizing autonomic signs and symptoms or in performing structured cardiovascular autonomic function assessments may have led to under-reporting [11, 12]. For example, large-scale studies on neurological complications following a SARS-CoV-2 infection did not include detailed cardiovascular autonomic assessments, possibly due to the uneven geographical distribution of clinical autonomic laboratories and pandemic-related restrictions in accessing non-emergency neurological care [13–15]. Reports of cardiovascular autonomic involvement following COVID-19 infection have been published not only in neurology journals, but also in internal medicine, general medicine, cardiology, and other journals, resulting in a fragmented and incomplete view of the phenomenon.

With the aim of identifying the continuum of cardiovascular autonomic involvement from the acute phase of a SARS-CoV-2 infection to the long haul of the post-COVID-19 condition, we hereby systematically reviewed all pre-print and published cases of cardiovascular autonomic disorders occurring either in individuals with acute COVID-19 infections or in the post-COVID-19 phase.

METHODS

This systematic review followed the PRISMA guidelines, which lay out a minimum set of elements for reporting on systematic reviews of health care interventions [16].

Information sources and search method

We performed a literature search of the PubMed, Embase, and Web of Science databases, and the preprint servers medRxiv and bioRxiv, from January 2020 to 24 April 2022 according to the search strategy indicated in Table S1. No language restrictions were applied. The quality of reporting and study biases were assessed using the Newcastle-Ottawa Scale, a clinical trial quality assessment tool devised for use in systematic reviews [17].

Eligibility criteria

We searched for all types of human studies that reported cardiovascular autonomic dysfunction in individuals with acute SARS-CoV-2 or post-COVID-19 syndrome. We only included reports in which an acute SARS-CoV-2 infection was confirmed by real-time polymerase chain reaction (RT-PCR), or antibody testing, or in which it was clearly stated that the patient had been investigated in the context of current or recent COVID-19 infection. We included studies in adult patients (aged over 18 years) who had signs and/or symptoms of cardiovascular autonomic involvement, with or without specific cardiovascular autonomic ancillary investigations (e.g., supine to standing blood pressure changes or other cardiovascular autonomic function tests under continuous hemodynamic monitoring). In cases for which no additional tests were available, reports were only included if alternative causes of transient loss of consciousness and orthostatic intolerance were reportedly excluded. Only studies with original data were included in the downstream analyses.

Data extraction and case definition

The initial screening focused on the title and summaries of the citations using the Rayyan platform [18]. The full-text reports of all potentially relevant studies were obtained and included in the review according to the eligibility criteria mentioned above. The references of the selected articles were searched for other relevant publications. For each of the included publications, we extracted data on the study design, geographical localization of the reported cases, patient demographics, signs and symptoms suggestive of cardiovascular autonomic dysfunction, results of ancillary investigations, type of

treatment, follow-up, and outcome. The severity of acute COVID-19 infection was also assessed using the World Health Organization (WHO) outcome criteria (10-point scale) [19].

The likelihood of an association between the occurrence or worsening of cardiovascular autonomic dysfunction and COVID-19 infection was defined as "probable" or "possible". As there was no previous case definition for determining the association between COVID-19 and a given cardiovascular autonomic disorder, we based our assessment on the evaluation scheme previously devised by Ellul and co-workers for other neurological conditions (Table 1) [13]. A cut-off of 6 weeks between the COVID-19 infection and a specific cardiovascular autonomic disorder was set to define the association as "probable" based on previously published time cut-offs for other immune-mediated neurological conditions, such as Guillain-Barré syndrome [13]. In terms of temporal profile, cases were divided into acute COVID-19 infection and post-COVID-19 illness, if symptoms suggestive of cardiovascular autonomic dysfunction developed within or after 28 days from the initial SARS-CoV-2 symptoms.

Statistical analysis

The clinical-demographic characteristics of the reported cases with cardiovascular autonomic dysfunction in the acute and post-COVID-19 phases were summarized with descriptive statistics (frequency and percentage for qualitative variables, mean and standard deviation for quantitative variables) and compared with Chi-squared and t-tests for independent samples. Statistical significance was assumed in the case of a two-sided $p < 0.05$. Due to the large number of comparisons, a Bonferroni correction was applied. The authors confirm that the data supporting the present findings are available in the article and its supplementary materials.

RESULTS

Systematic review and bias assessment

The search of the electronic databases retrieved 2043 studies in Medline, 2805 studies in Embase, 1881 studies in Web of Science, 2286 studies from preprint servers, and 1 study from other sources, giving a total of 9016 entries (Figure 1). After removing 2546 duplicates, 6470 titles and abstracts were screened. Three hundred and twelve full-length articles were assessed after applying the eligibility criteria. Two hundred and fifty-eight studies were excluded at the final stage of the process, allowing 54 full-length articles to be included in the data synthesis (Figure 1). Of the selected articles, 134 cases with individual clinical data available were categorized into two groups: 81 patients developing cardiovascular autonomic disturbances in the acute COVID-19 phase and 53 during the post-COVID-19 phase.

Most of the studies were of moderate quality (Table S2) and most of the publications were single case reports. In cases of low quality, this was mainly due to selection and reporting bias, lack of representativeness of the general population, and selective reporting of the information of interest. Table 2 provides an overview and comparison of all cases with cardiovascular autonomic dysfunction associated with acute versus post-COVID-19 condition. Full case descriptions are provided in Table S3 (acute COVID-19) and Table S4 (post-COVID-19).

Cardiovascular autonomic dysfunction during an acute SARS-CoV-2 infection

Demographics

Eighty-one cases from 48 articles reported cardiovascular autonomic dysfunction associated with an acute SARS-CoV-2 infection. Most of the reported cases originated from the USA, followed by Italy (Figure 2). Fifty-one per cent of cases were men. The mean age was 51 ± 19 years. Sixty patients (74%) reported previous comorbidities, including cardiovascular disorders (53%), autoimmune/allergic diseases (12%) or previously manifest features of autonomic dysfunction, including autonomic small fiber neuropathy, orthostatic hypotension associated with Parkinson's disease, baroreflex dysfunction with exaggerated blood pressure fluctuations, mild heat intolerance, early satiety, and chronic constipation (12%). Seventeen patients (28%) had no concomitant diseases (53% of whom were women, with a mean age of 40 ± 15 years).

Clinical presentation

Symptoms suggestive of cardiovascular autonomic dysfunction included orthostatic intolerance (orthostatic lightheadedness, dizziness,

TABLE 1 Provisional case definition for the causal association between COVID-19 and new onset of cardiovascular autonomic dysfunction.

Probable	1 – Disease onset within 6 weeks of acute infection AND
	2 – Either SARS-CoV-2 RNA detected in any sample OR antibody evidence of acute SARS-CoV-2 infection AND
	3 – No evidence of other commonly associated causes
Possible	1 – Either SARS-CoV-2 RNA detected in any sample, antibody evidence of acute SARS-CoV-2 infection OR clinical and epidemiological context of SARS-CoV-2 infection AND
	2 – Possibility of other commonly associated causes

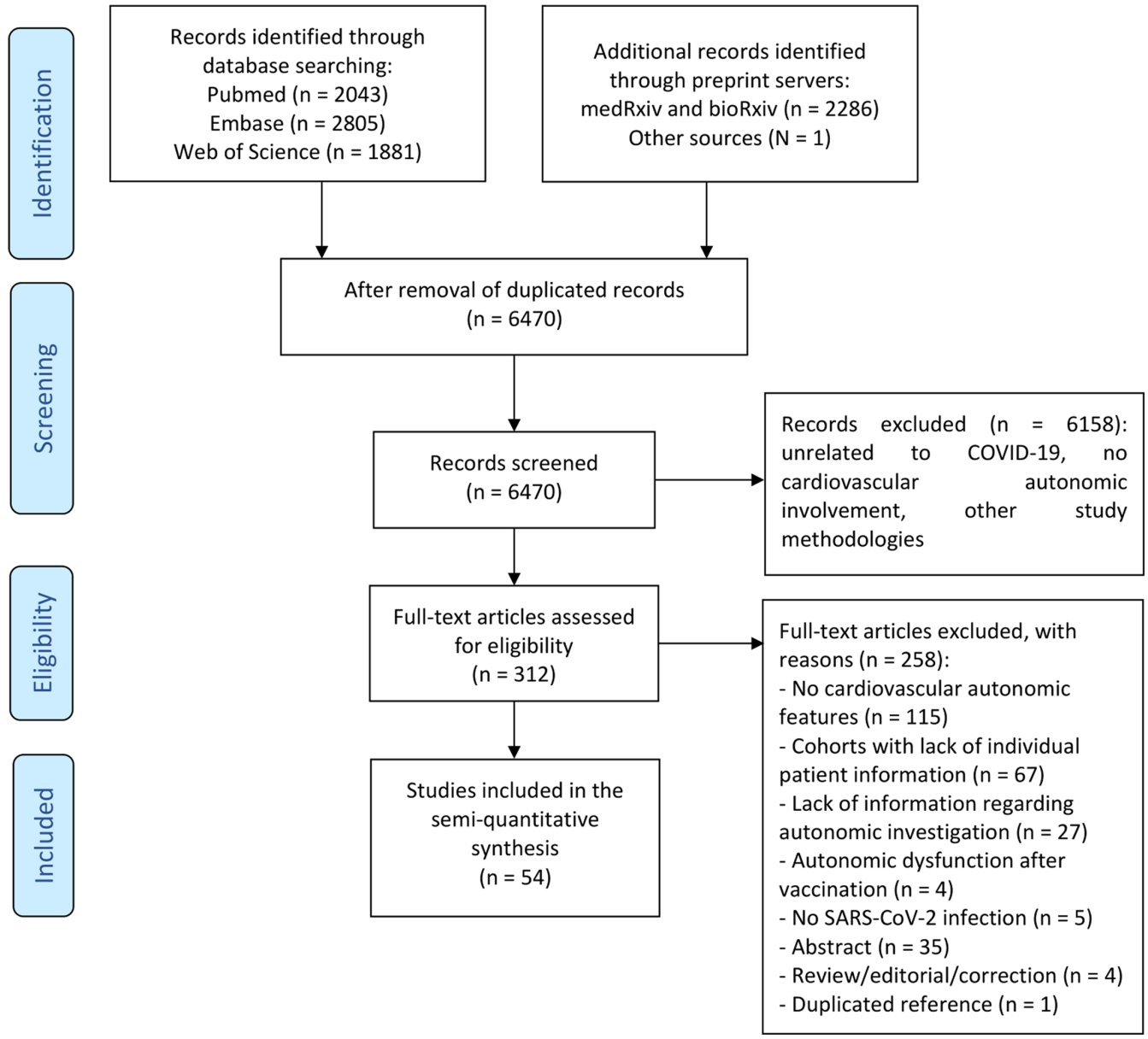

FIGURE 1 Systematic review flowchart.

tachycardia, sweating, headache, "brain fog") in 59% and syncope (including reflex and orthostatic hypotension-related syncope) in 31%. Both orthostatic intolerance and syncope were documented in 6% of cases (Figure 3). Symptoms suggestive of cardiovascular autonomic dysfunction were among the COVID-19 presenting symptoms in 43% of cases ($n = 35$) and were the only initial COVID-19 symptom in 10% (isolated syncope in eight cases). The mean latency to onset of symptoms suggestive of cardiovascular autonomic dysfunction from the beginning of SARS-CoV-2 infection was 8 ± 8 days. In 22 cases, symptoms suggestive of cardiovascular autonomic dysfunction manifested between Days 14 and 27 from COVID-19 onset. The most commonly reported COVID-19 symptoms were fever ($n = 36$, 45%), dyspnea ($n = 36$, 45%), and cough ($n = 27$, 34%). COVID-19 severity was mild (WHO 1–3) in 26% of cases, moderate (WHO 4–5) in 49%, and severe (WHO 6–10) in 24% (Table 2).

Autonomic function testing and cardiovascular autonomic diagnosis

Cardiovascular autonomic function tests, including supine to standing blood pressure measurements (the so-called Schellong test) [19], Valsalva maneuver, deep breathing, head-up tilt, cold pressor, and isometric exercise, were performed in 49 patients (61% of the analyzed cases) [20, 21]. The most frequently performed test was the head-up tilt test, followed by the Valsalva maneuver and supine to standing blood pressure measurements (Table 2). In addition, telemetry was performed in 14 patients and was the only evaluation performed in 8 patients (10%). In 24 patients (30%), autonomic testing was not performed or was not available to consult. This mostly occurred in reports of reflex syncope, for which the diagnosis was based on medical history and clinical examination [22]. Other

TABLE 2 Clinical-demographic characteristics, type of investigations, and treatment of individuals with cardiovascular autonomic dysfunction during an acute COVID-19 infection versus post-COVID-19 condition.

Characteristic	Acute COVID-19 (<28 days) N = 81	Post-COVID-19 (> = 28 days) N = 53	P value
Age (years)	51 (±19)	42 (±13)	**0.002**
Sex (F)	40 (49%)	36 (68%)	**0.034**
Comorbidities	Out of 60	Out of 24	
• None	17 (28%)	4 (17%)	0.311
• Cardiovascular (HT, diabetes, CAD, high cholesterol, cardiac arrhythmia, HF, obesity)	32 (53%)	5 (22%)	**0.009**
• Autoimmune/ allergic (asthma, rhinitis, urticaria, eczema, status post-Lyme, mast cell activation syndrome, arthritis, celiac disease, Hashimoto's disease)	7 (12%)	6 (26%)	0.108
• Previous autonomic dysfunction	7 (12%)	3 (13%)	0.865
Cardiovascular ANS diagnosis			
• POTS	20 (25%)	33 (62%)	**<0.001**
• Reflex syncope	23 (28%)	5 (9%)	0.008
• Orthostatic intolerance (non-specified)	14 (17%)	6 (11%)	0.347
• OH	12 (15%)	8 (15%)	0.965
• Acute baroreflex dysfunction	5 (6%)	0	0.066
• Syncope of uncertain origin	4 (5%)	1 (2%)	0.366
• AAG	3 (3%)	0	0.252
• Autonomic small fiber neuropathy	1 (1%)	0	0.421
Days between infection and symptom onset	8 (±8)	50 (±28)	**0.001**
WHO COVID-19 severity (0–10)	Out of 55	Out of 18	
• 1–3 (mild)	14 (25.5%)	12 (67%)	**0.001**
• 4–5 (moderate)	27 (49%)	2 (11%)	**0.004**
• 6–10 (severe)	14 (25.5%)	4 (22%)	0.786
Cardiovascular ANS tests	49 (61%)	48 (91%)	**<0.001**
• Supine to standing BP changes	18 (22%)	23 (43%)	0.009
• HUTT	34 (42%)	29 (55%)	0.151
• Valsalva	25 (31%)	17 (32%)	0.884
• Isometric exercise	2 (3%)	0	0.252
• Serum catecholamine measurement	2 (3%)	0	0.252
• Cold pressor test	1 (1%)	0	0.421
• 24 hour-ABPM	1 (1%)	4 (8%)	0.060
Other ANS tests			
• QSART	22 (27%)	16 (30%)	0.706
• TST	4 (5%)	3 (6%)	0.856
• SSR	2 (3%)	0	0.252
• Skin biopsy	1 (1%)	0	0.421
• Cardiac ^{123}I-MIBG Scintigraphy	1 (1%)	0	0.421
Telemetry	14 (17%)	2 (4%)	0.018
No autonomic function test available	24 (30%)	4 (8%)	0.002
Management strategy	Out of 37	Out of 30	
• Lifestyle measures	9 (24%)	29 (97%)	**0.001**
• Oral fluids and salt	8 (22%)	8 (27%)	0.632
• IV fluids	7 (19%)	1 (3%)	0.051
• IVIg	8 (22%)	1 (3%)	0.003
• Calcium channel blockers	1 (3%)	0	0.372
• β-Blockers	(14%)	9 (30%)	0.102
• Norepinephrine	1 (3%)	0	0.372
• Mechanical ventilation	1 (3%)	0	0.372
• Pacemaker	2 (5%)	0	0.202
• Corticoids	2 (5%)	3 (10%)	0.484
• Fludrocortisone	3 (8%)	3 (10%)	0.791
• Midodrine	3 (8%)	4 (13%)	0.494
• Rehabilitation	3 (8%)	2 (7%)	0.823
• Anxiolytics	2 (5%)	0	0.202
• Ivabradine	7 (19%)	2 (7%)	0.148
• Clonidine	1 (3%)	0	0.372

TABLE 2 (Continued)

Characteristic	Acute COVID-19 (<28 days) N = 81	Post-COVID-19 (> = 28 days) N = 53	P value
• Pyridostigmine	2 (5%)	1 (3%)	0.689
• Multi-vitamin complex	1 (3%)	1 (3%)	0.0882
Follow-up (weeks)	8 (±9)	19 (±16)	**0.002**

Note: Frequencies are reported as number (percentage) and continuous variables as mean ± standard deviation.

Bold type indicates *p* values remaining significant after applying Bonferroni's correction.

Abbreviations: ^{123}I-MIBG, iodine-123-metaiodobenzylguanidine; AAG, autoimmune autonomic ganglionopathy; ABPM, ambulatory blood pressure monitoring; ANS, autonomic nervous system; BP, blood pressure; CAD, coronary artery disease; CASS, composite autonomic scoring scale; F, female; HF, heart failure; HT, hypertension; HUTT, head-up tilt test; IVIg, intravenous immunoglobulin; OI, orthostatic intolerance; OH, orthostatic hypotension; POTS, postural orthostatic tachycardia syndrome; QSART, quantitative sudomotor axon reflex test; SSR, sympathetic skin response; TST, thermoregulatory sweat testing; WHO, World Health Organization.

autonomic tests included quantitative sudomotor axon reflex test (QSART), thermoregulatory sweat test, sympathetic skin response, skin biopsy, and cardiac ^{123}I-MIBG scintigraphy.

The most frequent cardiovascular autonomic diagnosis was reflex syncope, followed by postural orthostatic tachycardia syndrome (POTS), orthostatic intolerance, orthostatic hypotension, acute baroreflex dysfunction, syncope of uncertain origin, autoimmune autonomic ganglionopathy, and autonomic small fiber neuropathy (Table 2).

Treatment and clinical outcome

Information about the chosen treatment strategy was available in 50 cases (62%, see Table 2). Twenty-six percent of patients did not require specific treatment (n = 13). When needed, reflex syncope was treated with intravenous fluids (n = 4), behavioral and other non-pharmacological interventions (n = 1), a dual-chamber pacemaker (n = 1), or methylprednisolone (n = 1). One patient who presented with recurrent reflex syncope required mechanical ventilation following global clinical worsening due to the underlying acute SARS-CoV-2 infection. Non-pharmacological measures for POTS consisted of behavioral changes and oral fluid and salt supplementation. Pharmacological treatment of POTS included ivabradine, β-blockers, intravenous immunoglobulins, and pyridostigmine. Midodrine, fludrocortisone, clonidine, anxiolytics, vitamins, and rehabilitation were used in individual cases. Orthostatic intolerance was treated with anxiolytics, rehabilitation, or intravenous immunoglobulins. The last option was specifically used in a case of post-Lyme orthostatic intolerance flare after SARS-CoV-2 infection. Treatment of orthostatic hypotension included intravenous fluids, intravenous immunoglobulins, midodrine, fludrocortisone, and non-pharmacological interventions. Cases of acute baroreflex dysfunction reportedly occurred in individuals with post-COVID-19 Guillain-Barré syndrome. These were treated etiologically with intravenous immunoglobulins and symptomatically with short-acting calcium channel blockers, β-blockers, or intravenous norepinephrine and/or vasopressin. In one of the cases of syncope of uncertain origin, a dual-chamber pacemaker was implanted. Autoimmune autonomic ganglionopathy was treated with intravenous immunoglobulins, methylprednisolone, and rehabilitation. Gabapentin was prescribed in one case of autonomic and sensory small fiber neuropathy to treat the neuropathic pain.

In 43 cases, the authors reported a mean follow-up of 8 ± 9 weeks, while information on global clinical outcome was available in 64% of cases (n = 52, Figure 4). Complete recovery occurred in 24 cases, and partial recovery in 17. Four patients had a fatal outcome: one with Parkinson's disease and syncope of undetermined origin, two with reflex syncope and severe SARS-CoV-2 infection, and one with critical illness dysautonomia.

Cardiovascular autonomic dysfunction post-COVID-19 and comparison with the acute SARS-CoV-2 profile

Demographics

The search for cardiovascular autonomic dysfunction developing in the post-COVID-19 phase yielded 53 cases. Most of these reports were from the USA (Figure 2). In contrast to the reported cases during the acute SARS-CoV-2 phase, the majority of cases with cardiovascular autonomic disturbances after COVID-19 were women (68% vs. 49% in the acute SARS-CoV-2 phase, p = 0.034, Table 2). The mean age of individuals was significantly younger than in the acute SARS-CoV-2 group (42 vs. 51 years old, p = 0.002). Comorbidities were reported in 45% of cases and mostly included autoimmune or allergy disorders (26% vs. 12% in the acute COVID-19 group, p = 0.108), cardiovascular disorders (22% vs. 53% in the acute COVID-19 group, p = 0.009), and a previous history of autonomic symptoms, such as presyncope, reflex syncope, and mild orthostatic dizziness (13% vs. 12% from the acute COVID-19 group, p = 0.865). Four patients (17% vs. 28% in the acute COVID-19 group, p = 0.311) had no previous comorbidities.

Clinical presentation

Patients with post-COVID-19 cardiovascular autonomic involvement were more likely to have orthostatic intolerance (79% vs. 59% in the acute SARS-CoV-2 phase, p = 0.016) and less likely to have isolated syncope (31% vs. 13%, p = 0.019, Figure 3) compared with patients with cardiovascular autonomic involvement during acute SARS-CoV-2 infection, even though such differences did not remain

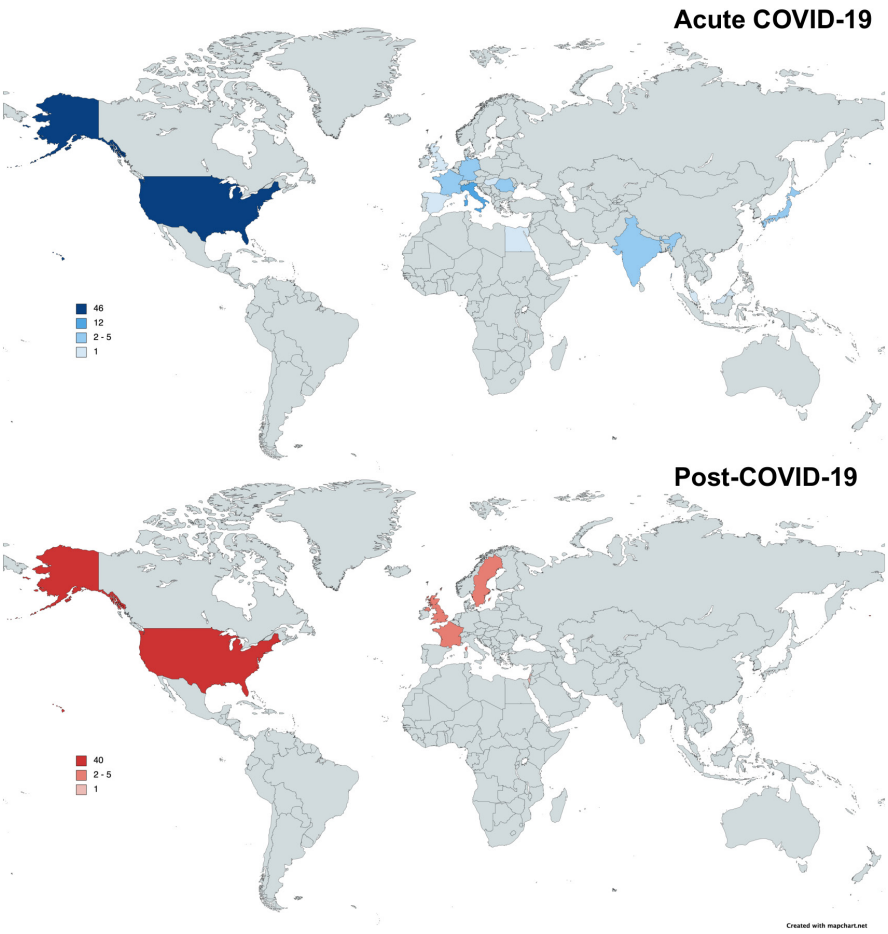

FIGURE 2 Map chart with the geographical origin of case reports with cardiovascular autonomic nervous system involvement during the acute COVID-19 phase (blue chart) and post-COVID-19 (red chart).

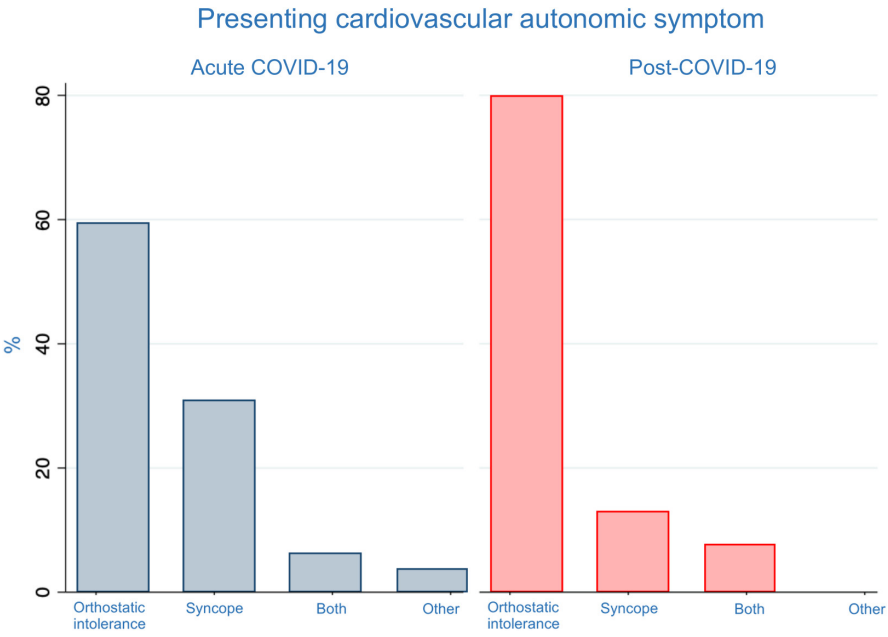

FIGURE 3 Presenting symptoms of cardiovascular autonomic dysfunction during an acute COVID-19 infection (blue bars) versus post-COVID-19 condition (red bars). The presenting symptoms suggestive of cardiovascular autonomic dysfunction did not differ between the acute and post-COVID-19 conditions after applying Bonferroni's correction for multiple comparisons. The label "Other" comprises cases that presented with severe blood pressure fluctuations.

statistically significance after Bonferroni's correction. Other presentations included the combination of orthostatic intolerance and syncope, with a similar frequency to the acute COVID-19 phase (6% vs. 8%, $p = 0.760$). The mean latency between the acute SARS-CoV-2 infection and the onset of symptoms suggestive of cardiovascular autonomic dysfunction was 50 ±28 days (data from 21 cases). In patients with post-COVID-19 cardiovascular autonomic involvement, the severity of the acute infection had been mild in 67% of the cases (vs. 25% in those with cardiovascular autonomic dysfunction during the acute COVID-19 phase, $p = 0.001$), moderate in 11%

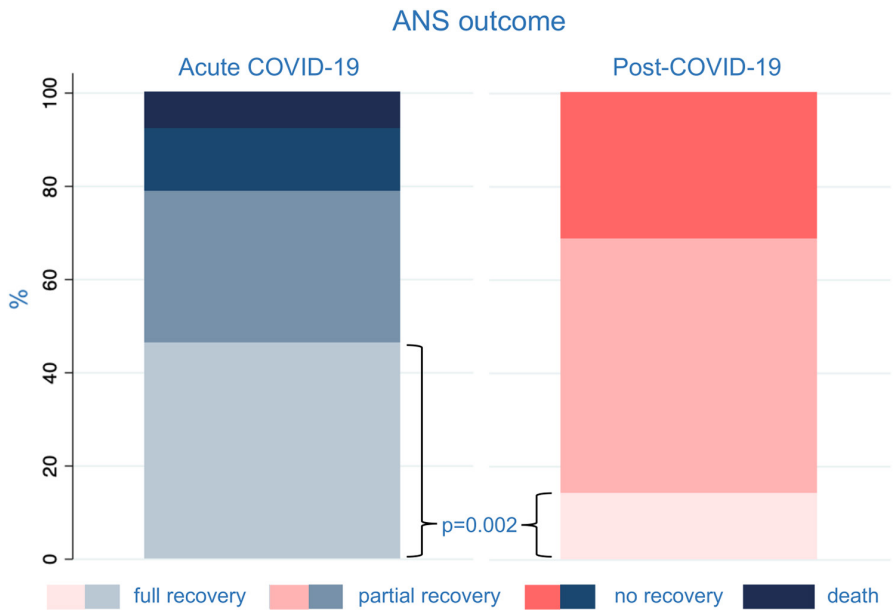

FIGURE 4 Clinical outcome of individuals with cardiovascular autonomic dysfunction during an acute COVID-19 infection (blue column) versus post-COVID-19 condition (red columns). ANS, autonomic nervous system.

(compared with 49% in the acute COVID-19 group, $p = 0.004$), and severe in 22% (compared with 25.5% in the acute COVID-19 phase, $p = 0.786$). Concomitant post-COVID-19 symptoms included fatigue ($n = 19$, 36%), dyspnea ($n = 12$, 23%), chest pain ($n = 9$, 17%), headache ($n = 5$, 9%), myalgia/body ache ($n = 5$, 9%), and anxiety/panic ($n = 3$, 6%). In addition to symptoms suggestive of cardiovascular autonomic dysfunction, two patients (4%) experienced brain fog/slowed cognition, bowel symptoms, numbness/neuropathic pain, and sweat disturbances. One patient (2%) developed pruritus and insomnia. Exercise intolerance occurred in five patients, all of whom were diagnosed with POTS (9%).

Autonomic function testing and cardiovascular autonomic diagnosis

Cardiovascular autonomic function tests were performed in 48 cases, significantly more frequently than in patients with autonomic disturbances during the acute COVID-19 phase (91% vs. 61%, $p < 0.001$). The remaining cases, for which no formal autonomic evaluation was performed, or this was not clearly stated in the report, included four cases with orthostatic hypotension due to critical illness dysautonomia and one case where only telemetry was performed. As in the acute phase, the head-up tilt test was the most frequently performed cardiovascular autonomic test (in 55% of cases, $p = 0.151$), followed by supine to standing blood pressure measurement (43% vs. 22% in the acute phase, $p = 0.009$), the Valsalva maneuver (32%, $p = 0.884$) and 24-hour ambulatory blood pressure monitoring (8%, $p = 0.060$). Non-cardiovascular autonomic tests included the QSART (30%, $p = 0.706$), thermoregulatory sweat test (6%, $p = 0.856$), and skin biopsy (6%, $p = 0.143$).

The most commonly reported cardiovascular autonomic disorder was POTS (in 62% of cases, $p < 0.001$, compared with the group of patients with autonomic disturbances in the acute COVID-19 phase), followed by orthostatic hypotension ($n = 8$, 15%, $p = 0.965$), orthostatic intolerance without a specific autonomic diagnosis ($n = 6$, 11%, $p = 0.347$), reflex syncope ($n = 5$, 9%, $p = 0.008$), and syncope of uncertain origin ($n = 1$, 2%, $p = 0.366$).

Treatment and outcome

In 30 cases (57% of the analyzed reports), information on the individual treatment approach was available, consisting of either non-pharmacological or pharmacological interventions summarized in Table 2.

A follow-up of 19 ± 16 weeks was documented in 18 patients (34%, vs. 8 weeks in the acute COVID-19 group, $p = 0.002$), while information on clinical outcome was available in 34 cases (64%) (Figure 4). Fifteen percent of the cases achieved full recovery (vs. 46% in the acute phase, $p = 0.002$), 56% had partial recovery (compared with 33% in the acute phase, $p = 0.033$, not statistically significance after Bonferroni's correction), and no patients died.

DISCUSSION

This systematic review provides information on cardiovascular autonomic involvement throughout the continuum of SARS-CoV-2 infection, from the acute phase to long-term complications.

We identified two patterns of cardiovascular autonomic involvement associated with COVID-19. The first occurred during acute SARS-CoV-2 infections, preferentially in middle-aged individuals with cardiovascular and metabolic comorbidities. We did not find a gender prevalence in this group, which presented either with orthostatic intolerance, syncope, or sometimes a combination of both. The most common diagnosis in this phase was reflex syncope. The second pattern of cardiovascular autonomic

disturbances occurred more frequently in younger women, more than 4 weeks after the acute COVID-19 infection and consisted more homogeneously of orthostatic intolerance. Most of these cases were diagnosed with POTS. In addition to the pattern of cardiovascular autonomic dysfunction, the clinical outcome also differed significantly between the two patient groups. While reflex syncope during the acute COVID-19 infection often resulted in complete recovery, those who developed cardiovascular autonomic dysfunction in the post-COVID-19 stage most frequently experienced partial or no recovery, even after mild acute SARS-CoV-2 infections.

The analyzed evidence indicates that cardiovascular autonomic dysfunction may occur in both the acute and post-COVID-19 stages [9, 10], but the above-mentioned differences in the clinical presentation, latency to onset, and outcome at follow-up suggest that the pathophysiological basis may differ between the acute and post-COVID-19 phases. We hypothesize that cardiovascular autonomic dysfunction manifesting with reflex syncope and blood pressure instability during or immediately after an acute SARS-CoV-2 infection may be due to the pro-inflammatory state leading to fever- or cytokine-induced hypovolemia and vasodilation. Indeed, studies have shown that heart rate variability in the early stages of SARS-CoV-2 infection decreases in an inverse proportion to the increase in pro-inflammatory markers, underscoring the close relationship between the autonomic nervous system, the immune system, and the inflammasome [23, 24]. The most frequently reported cardiovascular autonomic disturbance in the acute COVID-19 phase in our cohort was reflex syncope, an early complication of COVID-19 that has been also observed in large observational studies [25]. A review of syncope of various etiologies in individuals with acute COVID-19 showed a prevalence of 4.2% in 14.437 cases studied [26]. While SARS-CoV-2-induced pneumonia and thromboembolic phenomena are life-threatening causes of syncope that need to be excluded, self-limited reflex syncope may have accounted for the majority of such cases [26].

The fact that individuals that developed cardiovascular autonomic dysfunction during acute SARS-CoV-2 infections were, on average, older adults with comorbidities such as hypertension, dyslipidemia, and diabetes suggests that pre-existing cardiovascular comorbidities might pose a higher risk of cardiovascular autonomic complications during this phase. Alternatively, pre-diagnosed arterial hypertension might have indicated subclinical cardiovascular autonomic dysfunction in the given individual, which became manifest during the acute SARS-CoV-2 infection. Several off-label strategies were used to manage cardiovascular autonomic dysfunction during the acute COVID-19 phase, in particular reflex syncope (Table 2). Sometimes the management strategies included not only classical vasoactive agents, but also drugs to treat the accompanying behavioral symptoms, such as anxiolytics, most likely in a multidisciplinary, holistic approach to the patient. These data should, however, be interpreted with caution, since solid evidence of efficacy is lacking for most of these treatments and management may be safer employing the available evidence from the literature on cardiovascular autonomic treatment [22, 27, 28].

Apart from some cases with fatal outcome possibly due to a more severe acute COVID-19 course, complete recovery was often described in individuals with cardiovascular autonomic dysfunction during the acute COVID-19 infection. This might suggest that the acute SARS-CoV-2 infection triggered functional, but not permanent, structural damage of the cardiovascular autonomic nervous system in those cases and that, altogether, the severity of the acute SARS-CoV-2 infection rather than the autonomic involvement was a major determinant of the global clinical outcome at follow-up.

At least one-third of patients worldwide remain symptomatic or newly develop multiple symptoms several weeks after an acute SARS-CoV-2 infection [29]. Many post-COVID-19 symptoms are non-specific (e.g., dizziness, brain fog, headache, palpitations) but usually occur during standing or exertion and have been therefore attributed to an underlying cardiovascular autonomic dysfunction [10].

Chronic complications of other coronavirus infections (SARS, Middle East respiratory syndrome virus) have been published and include symptoms similar to those described in the post-COVID-19 condition [1, 30, 31]. Several mechanisms are likely causative for the symptoms observed in post-COVID-19 illness: immune-mediated mechanisms and direct tissue damage may occur first, but deconditioning, concomitant fatigue, and the multiple pandemic-related restrictions may contribute to the persistence of symptoms over time [32, 33]. The high frequency of newly diagnosed POTS cases in the post-COVID-19 phase is particularly interesting and may point towards an immune-mediated mechanism of disease through an alteration of the vagal anti-inflammatory effect, hypoxia-triggered baroreflex unloading, and/or altered chemoreflex sensitivities, often found in individuals with POTS [28].

While POTS per se remains a not fully understood clinical syndrome likely encompassing multiple endophenotypes and underlying etiologies, cases of POTS due to aberrant post-viral immune activation have been previously described, especially in young women [34]. The positive medical history of some of the cases included in the present analysis for autoimmune (celiac disease, eczema, status post-Lyme, Hashimoto's disease) or allergic disorders (mast cell activation syndrome, asthma, rhinitis, conjunctivitis), especially in the group of individuals who developed cardiovascular autonomic dysfunction in the post-COVID-19 phase, might point towards an immune-mediated mechanism of action.

The causal association between a passed SARS-CoV-2 infection and subsequent development of cardiovascular autonomic dysfunction remains overall elusive, because there is no definitive marker for such a diagnosis. We here applied provisional case definition criteria including a probable and a possible causality degree, based on a previous proposal by Ellul and colleagues for other post-COVID-19 immune-mediated neurological conditions and taking into account the limited availability of RT-PCR and antibody testing, in particular during the early stages of the COVID-19 pandemic (Table 1) [13]. We assumed that a 6-week period represented an adequate time lapse from the acute infection to classify a new onset of cardiovascular autonomic disturbances as

independent from the acute SARS-CoV-2 infection itself, yet likely related to the passed infection. These criteria, which are likely to be refined as more data emerge on the pathophysiology of post-COVID-19 cardiovascular autonomic disturbances, may guide future structured case reporting.

Symptoms of orthostatic intolerance require a high degree of alertness, as they may be due to treatable conditions and cause major morbidity if left untreated [35]. The diagnostic work-up requires both autonomic nervous system (ANS) laboratory testing and the exclusion of alternative, non-autonomic diagnoses and exacerbating factors. Tachycardia may, for instance, develop in the context of several conditions and a systematic differential diagnostic work-up should always be sought in individuals with suspected POTS [36]. We here observed a wide heterogeneity in the type of applied diagnostic work-up and significant differences between the cardiovascular autonomic test batteries used for the acute versus post-COVID-19 cases with orthostatic complaints. In the post-COVID-19 phase, supine to standing blood pressure measurements were the most frequent cardiovascular ANS test applied. Even if yielding a suboptimal diagnostic accuracy, measuring supine to standing heart rate and blood pressure changes is a helpful and easy-to-perform autonomic bedside screening test [37]. In countries without access to structured and standardized autonomic function laboratories, this may often represent the only available autonomic diagnostic option [15, 20]. During the acute COVID-19 phase, on the other hand, autonomic function testing for self-limiting reflex syncope may not have been indicated because the patient in question was deemed unfit for testing or because colleagues did not consider it appropriate to test a COVID-19-positive individual due to the risk of viral transmission [38, 39]. At the beginning of the pandemic, many laboratories were also closed or there were significant travel restrictions, which likely prevented a significant proportion of individuals from accessing specialized diagnostic testing and treatment. Difficulties in accessing autonomic healthcare services may also explain the geographical distribution of the reports included in this review. The more capillary distribution of autonomic tertiary referral centers in the USA and Europe, or eventually the overall higher incidence of COVID-19 cases in these countries (https://covid19.who.int/ accessed on 24 October 2022), rather than ethnic differences in susceptibility to cardiovascular autonomic dysfunction during or after COVID-19, may explain why the vast majority of the reviewed cases were from these areas (Figure 2).

This review has limitations. Most of the included studies were single case reports, for which a reporting bias is likely. Some of the screened reports also lacked a precise cardiovascular autonomic diagnosis. This was especially the case for reports on post-COVID-19 myelitis or Guillain-Barré syndrome, in which cardiovascular autonomic dysfunction may occur [40]. Inclusion of some of these reports in our downstream analysis was prevented by the fact that autonomic involvement was mentioned without further characterization [41]. Notwithstanding, even severe autonomic impairment may occur in such neuroinflammatory disorders, influence morbidity and mortality, and should be therefore actively investigated in cases of blood pressure instability or orthostatic complaints [42]. The retrieved reports also did not often provide clear information on whether the cases in question had any kind of orthostatic intolerance prior to SARS-CoV-2 infection, which may have caused an exacerbation of previously subtle disturbances. We also cannot exclude the possibility that individuals with pre-COVID-19 orthostatic complaints might have been seeking medical help after an acute SARS-CoV-2 infection due to the increased alertness for acute and post-COVID-19 health issues in social media [43]. One way or another, all fields of medicine have faced lower thresholds for publication since the pandemic outbreak, often resulting in lower quality scientific reports. In order to ensure high-quality data, we here counterchecked the given diagnoses of the included cases against the current diagnostic criteria for different cardiovascular autonomic disorders and included only those reports that provided consistent data on history and testing in the downstream analysis.

To distinguish between the acute SARS-CoV-2 infection and the post-COVID-19 phase we used the arbitrary cut-off of 28 days proposed by WHO. This distinction has been widely adopted because of its pragmatic definition and had proved useful in most cases. However, in the case of COVID-19-related cardiovascular autonomic dysfunction, we have observed two incidence peaks in the acute phase: the first, during the first week, characterized mainly by reflex syncope, and the second, starting in the second or third week after the infection and evolving into stable conditions such as POTS. A diagnosis of POTS, in particular, requires symptoms to evolve over at least 3 months, a follow-up time that was not always attained by the included reports [28]. A longer follow-up time than the one reported in the available literature would also be required to accurately assess the efficacy of established therapeutic regimens and the clinical outcome at follow-up.

In summary, different patterns of cardiovascular autonomic dysfunction may occur in both the acute and post-COVID-19 phases and may significantly impact on overall clinical outcome. A high degree of vigilance is recommended, and the diagnosis should ideally be laboratory-based to exclude mimicries and promptly establish appropriate therapeutic measures [21]. While we still face large gaps in knowledge, action should be undertaken to increase the alertness for cardiovascular autonomic complications following a COVID-19 infection and gain insights into their real prevalence in individuals with post-COVID-19 orthostatic complaints.

AUTHOR CONTRIBUTIONS

Study conception: DRC, MH, RH, JS, WS, GW, AF. Study design: DRC, MH, RH, JS, WS, GW, AF. Study coordination: DRC, AF. Data collection: DRC, AF. Data analysis: DRC, AF. Writing of the first draft: DRC. Writing – review and editing: DRC, IR, MH, RH, JS, WS, GW, AF.

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DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article

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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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