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Original article

The Long-COVID autonomic syndrome in hospitalized patients: A one-year prospective cohort study

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ABSTRACT

Long-COVID syndrome is characterized by fatigue, orthostatic intolerance, tachycardia, pain, memory difficulties, and brain fog, which may be associated with autonomic nervous system abnormalities. We aimed to evaluate the short and long-term course of COVID-19 autonomic symptoms and quality of life (QoL) after SARS-CoV-2 infection through a one-year follow-up combined with validated questionnaires. Additionally, we aimed to identify patients with worsening autonomic symptoms at 6 and 12 months by dividing the patient cohort into two sub-groups: the Post-COVID healed Control sub-group (total score<16.4) and the Long-COVID autonomic syndrome sub-group (total score>16.4). This prospective cohort studied 112 SARS-CoV-2 positive patients discharged from Humanitas Research Hospital between January and March 2021. Autonomic symptoms and QoL were assessed using the composite autonomic symptom scale 31 (COMPASS-31) and Short Form Health Survey (SF-36) questionnaires at various time points: before SARS-CoV-2 infection (PRE), at hospital discharge (T0), and at 1 (T1), 3 (T3), 6 (T6), and 12 (T12) months of follow-up. COMPASS-31 total score, Orthostatic Intolerance and Gastrointestinal function indices, QoL, physical functioning, pain, and fatigue scores worsened at T0 compared to PRE but progressively improved at T1 and T3, reflecting the acute phase of COVID-19. Unexpectedly, these indices worsened at T6 and T12 compared to T3. Subgroup analysis revealed that 47% of patients experienced worsening autonomic symptoms at T6 and T12, indicating Long-COVID autonomic syndrome. Early rehabilitative and pharmacological therapy is recommended for patients at the T1 and T3 stages after SARS-CoV-2 infection to minimize the risk of developing long-term autonomic syndrome.

1. Introduction

A growing body of evidence [1–6] suggests that some patients who survive an acute SARS-CoV-2 viral infection (COVID-19) may experience persistent symptoms for months, resulting in a clinical syndrome known as Long-COVID or PASC (Post-Acute Sequelae of COVID). These symptoms, including fatigue, shortness of breath, diffuse pain, orthostatic intolerance with excessive tachycardia upon standing, palpitations, memory difficulties, brain fog and others, may reflect underlying abnormalities in autonomic nervous system functioning and negatively impact overall quality of life [QoL] [3–5]. Recent observations suggest that Long-COVID patients may have symptoms [7] similar to those found in Postural Tachycardia Syndrome (POTS) [8,9], a disorder characterized by dysautonomia [10,11] and consistent with cardio-vagal abnormalities and cardiovascular sympathetic over-activity [12]. Notably, a previous infective event can be identified

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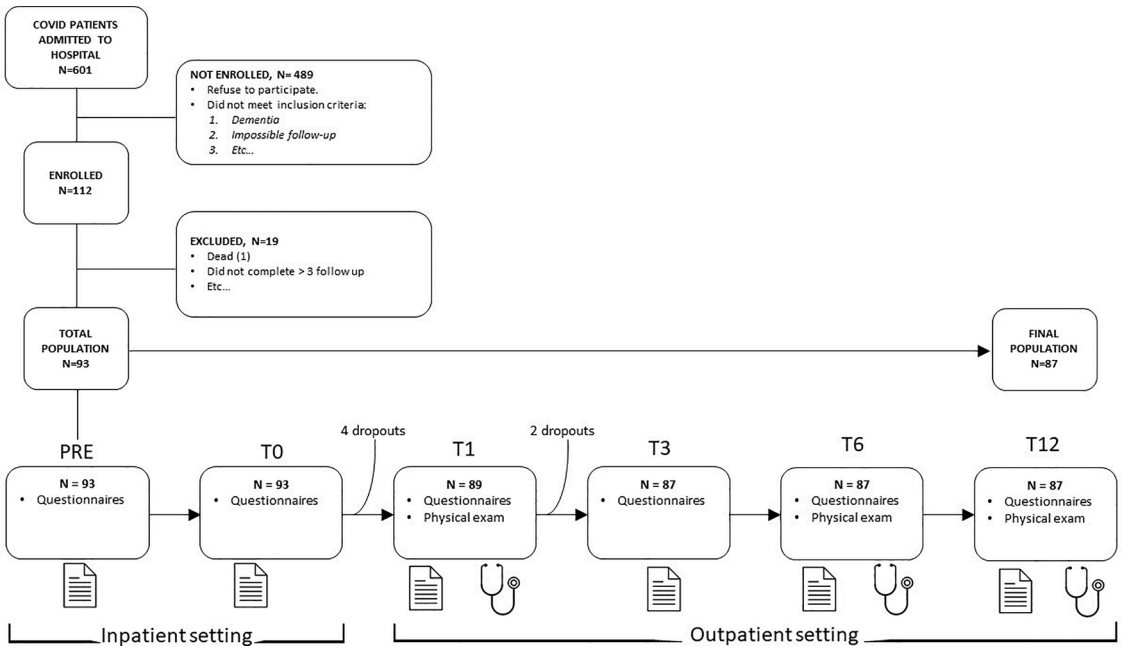

Fig. 1. Flowchart of the population enrollment procedure, follow-up timing and data collection.

in approximately 50% of POTS patients [11,13].

The Long-COVID syndrome has been originally addressed by retrospective investigations [2,14], case reports [8,9], or studies analyzing outpatient cohorts of individuals [15,16]. Recently, prospective observational investigations addressed the persistence of COVID-19 symptoms over time up to six months [17,18], one year [4,19,20], and few studies set the follow-up at two years [5,21]. However, periodical patients' assessments were mostly scheduled every six months or longer after acute disease [4,19,20,22]. These time settings may have obscured subtle changes in amelioration or worsening of symptoms over time. Indeed, only few investigations considered a more frequent follow-up after the acute disease [23–25] and only one [26] provided data related to the period before SARS-CoV-2 infection for comparison. Finally, previous prospective investigations mostly reported the number of Long-COVID symptoms [23,25], with few mentioning changes in intensity [4,24]. To our knowledge, none have addressed the potential persistence of autonomic-related symptoms after a SARS-CoV-2 infection.

We reasoned that a long-term, prospective, cohort study characterized by frequent follow-up and the use of validated questionnaires providing a semi-quantitative assessment of symptom severity over time would help us to assess the natural course of acute and post-acute COVID autonomic related symptoms and possibly identify when COVID-19 survivors will fully recover.

2. Methods

This single-center prospective observational cohort study included 150 out of 601 subjects who were discharged from Humanitas Research Hospital after acute Sars-Cov-2 virus infection (variants Alpha and Delta), during the second COVID-19 outbreak (January 1-March 31, 2021) in Italy.

None of the patients had been vaccinated against COVID-19 or experienced a known reinfection at the time of admission to the hospital. They were all diagnosed with SARS-CoV-2 using a real-time reverse transcription-polymerase chain reaction (RT PCR) test on a nasopharyngeal swab.

Inclusion Criteria: self-sufficient patients who had tested positive for SARS-CoV-2, were able to maintain a standing position independently, and agreed to participate in the 12-month follow-up.

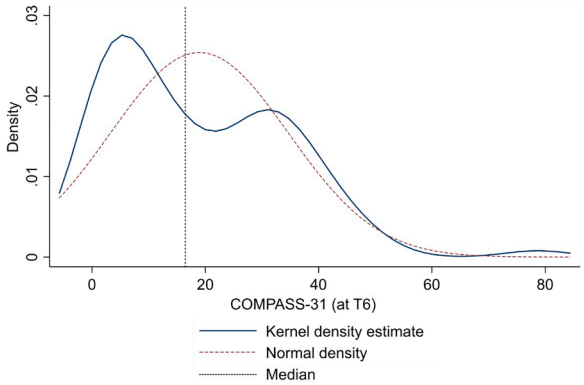

Fig. 2. Kernel density plot of the COMPASS_31 total score of the whole population at T6, showed a bimodal distribution (blue line) suggestive of the presence of two distinct sub-populations which were not evident at PRE. The vertical dotted line indicates the total score cut-point of 16.4 (i.e. the median value) identifying the Post-COVID control group (total score <16.4, first peak) and the Long-COVID autonomic syndrome (L-Cas) group (total score >16.4, second peak).

Exclusion Criteria: patients with associated diseases with a prognosis of less than 12 months, patients unwilling to provide written consent to participate, and those who would be difficult to follow-up (foreigners, homeless).

Re-infection during the follow-up period was not considered as an exclusion criterion.

The study was approved by the Ethical Committee on Human Research of Humanitas Research Hospital (#2742). All participants provided written consent.

3. Study end points

The primary aim was to assess the time course of autonomic-related symptoms and QoL for up to one year after acute SARS-CoV-2 infection. To achieve this, subjects were followed up at various time points: hospital discharge (T0), 1 month (T1), 3 months (T3), 6 months (T6), and 12 months (T12) after hospital discharge (Fig. 1). Additionally, data on

symptoms and QoL for the month prior to infection (PRE) were retrospectively obtained at T0 (Fig. 1).

The second objective of our study arose from the observation of an unexpected worsening of the synthetic index of autonomic-related symptoms [27], i.e. the COMPASS-31 total score at T6. A previous study had established that a total score value less than 16 was indicative of a population without autonomic neuropathy [28]. Based on this, a total score cut point of 16.4 was used to divide the total cohort into two subgroups at T6. The first group had a total score of less than 16.4 (Post-COVID healed Controls), indicating individuals without dysautonomia. The second group had a score greater than 16.4, indicating those who were still suffering from autonomic-related symptoms at T6 and T12, i.e., the Long-COVID autonomic syndrome (L-Cas) population. Moreover, the Kernel density estimate plot (Fig. 2) performed on the COMPASS-31 total score of the entire population at T6 supported this analysis. It revealed a bimodal distribution of COMPASS-31 total score, indicating the presence of two distinct sub-populations that were not apparent at PRE.

3.1. Composite autonomic symptom scale 31 (COMPASS-31)

The COMPASS-31 questionnaire is a 31-items tool that assess global autonomic signs and symptoms and has been validated for use in clinical settings [12,27]. The 31 items in COMPASS-31 are gathered into 6 domains: orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder, and pupillomotor symptoms [29]. The orthostatic intolerance domain includes 4 items related to the presence, severity and change in intensity over time of signs and symptoms such as lightheadedness, dizziness, vertigo and brain fog upon standing. The vasomotor domain includes 3 items related to cutaneous color changes (i.e. livedo reticularis). The secretomotor domain includes 4 items related to sweating, dry eyes and xerostomia. The gastrointestinal domain includes 12 items related to early satiety and postprandial fullness, bloating, vomiting, abdominal pain, diarrhea and constipation. The bladder domain includes 3 items related to incontinence, dysuria and urinary retention. The pupillomotor domain includes 5 items related to photophobia, light sensitivity and visual accommodation.

Detailed information about the items evaluated in the questionnaire and scoring system are provided elsewhere [27].

3.2. Short form health survey (SF-36) questionnaire

The 36-Item Short Form Survey (SF-36) is a widely used self-reported health evaluation tool to assess an individual's or a population's QoL [30]. It comprises 36 questions addressing eight different aspects of health: limitations in physical activities due to health problems, limitations in social activities due to physical or emotional problems, limitations in daily activities due to physical health problems, bodily pain, general mental health (psychological distress and well-being), limitations in habitual role activities due to emotional problems, vitality (energy and fatigue), and general health.

The scores for the various domains are transformed and aggregated using a scoring key, resulting in a total score that indicates a range of low to high QoL [30].

3.3. Data collection and management, and statistics

All Pre and T0 data was collected by two physicians who were granted access to the COVID-19 Humanitas Research Hospital medicine wards during the second SARS-CoV-2 outbreak in Italy in 2021. For the remaining follow-up data (from T1 to T12), four physicians collected the data after seeing patients in our outpatient clinic. After the data was anonymized, it was stored in a prospectively constructed database, which is currently stored in a suitable repository (Zenodo) and accessible upon request.

Kernel density estimate plots were utilized to visually assess the shape of the distribution of continuous variables, specifically the COMPASS-31 total score. Non-parametric tests were used due to the non-normal distributions of the data. Wilcoxon's matched-pairs signed-rank test was used for analyzing the whole population, using the "Pre" condition as the reference.

The two-sample Wilcoxon rank-sum (Mann-Whitney) test was used to assess differences between subpopulations at the same time point. Stata 17.0 software was used to analyze the data (Stata Corp., College Station, TX, USA).

p values <0.05 were considered statistically significant. All tests were two-sided.

Table 1
Demographic and clinical features of the overall population at hospital discharge (T0) and of the L-Cas and Post-COVID control subgroups.

Population n, (%)	Total	L-Cas	Post-COVID	p value
Total Population	112	44	43	–
FU Patients Drop Out	25, (21.4)	–	–	–
Deaths	*1, (0.9)*	–	–	–
Female	44, (39.3)	21, (47.7)	12, (27.9)	0.08
Weight median, (IQR)	75.0, (64.0 – 86.0)	75.5 (64.0 – 85.0)	85.0 (73.0 – 96.0)	0.02*
BMI median, (IQR)	26.2, (24.1 – 29.4)	26.0 (24.0 – 29.8)	28.0 (25.0 – 31.0)	0.23
Age n, (%)				
Median (IQR)	61.0 (53 – 70)	61.0 (54 – 67.5)	60.5 (51 – 74)	0.99
1–17yrs	1, (0.9)	1, (2.3)	0	–
18–44yrs	13, (11.6)	7, (15.9)	3, (7.0)	0.31
46–66yrs	50, (44.6)	16, (36.4)	26, (60.5)	0.03*
66–100yrs	48, (42.8)	20, (45.5)	14, (32.6)	0.27
Comorbidities n, (%)				
Hypertension	13, (11.6)	7, (15.9)	6, (13.9)	0.99
Structural Heart Disease	2, (1.8)	2, (4.4)	0	–
Heart Failure	2, (1.8)	1, (2.3)	1, (2.3)	0.99
Arrhythmias	4, (3.6)	4, (9.1)	0	–
Cerebrovascular Disease	2, (1.8)	2, (4.4)	0	–
Neurological Disease	3, (2.7)	1, (2.3)	1, (2.3)	0.99
Diabetes Mellitus	10, (8.9)	2, (4.4)	7, (16.3)	0.09
COPD	2, (1.8)	0	2, (4.7)	–
Neoplasm	10, (8.9)	6, (13.6)	3, (7.0)	0.48
Others	35, (31.2)	19, (43.2)	15, (34.9)	0.51
Therapy n, (%)				
Beta Blockers	13, (11.6)	8, (18.2)	5, (11.6)	0.55
ACE-I or ARBs	11, (9.8)	5, (11.4)	6, (13.9)	0.76
Statins	11, (9.8)	7, (15.9)	4, (9.3)	0.52
Anticoagulation	10, (8.9)	7, (15.9)	3, (7.0)	0.31
Anti-Platelets	3, (2.7)	1, (2.3)	2, (4.7)	0.62
Calcium Channel Blockers	11, (9.8)	2, (4.4)	7, (16.3)	0.09
Diuretics	4, (3.6)	3, (6.8)	1 (2.3)	0.62
Metformin & DM drugs	8, (7.1)	1, (2.3)	7, (16.3)	0.03*
Proton Pump Inhibitors	18, (16.1)	9, (20.4)	9, (20.9)	0.99
NSAIDs	5, (4.5)	3, (6.8)	2, (4.7)	0.99
Corticosteroids	6, (5.4)	5, (11.4)	1, (2.3)	0.20
Anti-arrhythmic	1, (0.9)	1, (2.3)	0	0.99
Others	20, (17.9)	11, (25.0)	8, (18.6)	0.61

Categorical variables are presented as proportions of the relative group, and p values were calculated using Fisher exact test. Continuous variables are expressed as median and interquartile range, and comparison between Long-COVID autonomic syndrome (L-Cas) and Post-COVID control groups was performed using two sample Wilcoxon rank-sum.
Weight is expressed in Kg. FU indicates follow-up; BMI, body mass index; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; ACE-I, ACE inhibitors; ARBs, angiotensin receptor blockers; NSAIDs, nonsteroidal anti-inflammatory drugs.
* $p<0.05$.

Table 2
Indicators of disease severity.

Disease Severity Indicators n, (%)	Population (*N*=87)	L-Cas (*N*=44)	Post-COVID (*N*=43)	*p* value
Length of stay > 14 days	26, (29.9)	10, (22.7)	16, (37.2)	0.16
Length of stay > 20 days	12, (13.8)	4, (9.1)	8, (18.6)	0.23
Admission to the ICU	7, (8.0)	1, (2.3)	6, (13.9)	0.06
O2 supplementation				
Patients requiring oxygen supply	64, (77.0)	29, (65.9)	35, (81.4)	0.14
NC	37, (42.6)	18, (40.9)	19, (44.2)	0.83
O2HFNC	9, (10.3)	2, (4.5)	7, (16.3)	0.09
Venturi mask	10, (11.5)	4, (9.1)	6, (13.9)	0.52
O_2 Reservoir	6, (6.9)	3, (6.8)	3, (7.0)	–
CPAP	17, (19.5)	5, (11.4)	12, (27.9)	0.06
BiPAP	1, (1.15)	1, (2.3)	0	–

Data are expressed as proportions. Comparison between Long-COVID autonomic syndrome group and Post-COVID controls was performed using Fisher exact test. L-Cas indicates Long-COVID autonomic syndrome; ICU, intensive care unit; NC, nasal cannula; O_2HFNC, O_2 high flow (5 l/min) nasal cannula; Venturi, Venturi mask; O_2 reservoir, high flow (>7 l/min) O_2 by reservoir mask; CPAP, continuous positive airway pressure; BiPAP, bi-level positive airway pressure.

4. Results

4.1. Demographic and clinical features of the enrolled population

As in Fig. 1, 601 SARS-CoV-2 infected patients were discharged from Humanitas Research Hospital between January 1st and March 31st, 2021. Based on a 1:4 at random enrollment,150 out of 601 discharged patients were initially considered. Out of these, 38 either refused to participate, did not meet the inclusion and exclusion criteria, or did not provide written consent, resulting in a final enrollment of 112 patients (Fig. 1). One patient died during the study, and 18 attended fewer than three scheduled follow-ups, which resulted in their exclusion from the data analysis. Final analysis was carried out on 93 patients (Fig. 1).

Table 1 (left column) provides a summary of the demographic and clinical features of the studied population at hospital discharge (T0). The population had a slight male prevalence, and the majority of admitted patients were aged 46 years or older. The most common co-pathologies were hypertension, diabetes mellitus, and neoplasms. During the 12-month follow-up study, none of these participants received a formal diagnosis of POTS, Orthostatic Intolerance disease, or reported occurrence of syncope.

Table 2 (left column) summarizes the indicators of disease severity. Almost 40% of patients had a length of stay longer than 14 days, and up to 7% were admitted to the ICU. More than 84% of hospitalized patients required oxygen supplied by various modalities, and approximately 1 in 4 individuals required some form of ventilation support.

4.2. Long term patterns of neural autonomic symptoms, quality of life, fatigue, pain and functional impairment

Table 3 summarizes the COMPASS-31 total scores and the results of the six domains in the overall population. The graphs in the upper portion of Fig. 3 illustrate the trends of the COMPASS-31 total score, orthostatic intolerance, and gastrointestinal symptoms domain scores during the follow-up period, deemed as the most informative topics. It should be noted that the three scores were significantly higher at the time of hospital admission (T0), slightly decreased at T1, and clearly declined at T3 compared to the PRE SARS-CoV-2 infection. However, an unexpected increase was observed at 6 and 12 months after hospital discharge.

Table 4 and the upper graphs in Fig. 4 summarize the time courses of the SF-36 questionnaire total score, physical function, fatigue, and pain,

Table 3
COMPASS-31 total scores and the other domains in the overall population and in the L-Cas and Post-COVID groups.

	PRE (*n*=93) Median (IQR)	T0 (*n*=93) Median (IQR)	*P*	T1 (*n*=89) Median (IQR)	*p*	T3 (*n*=87) Median (IQR)	*p*	T6 (*n*=87) Median (IQR)	*p*	T12 (*n*=87) Median (IQR)	*p*
Total score	6.7 (4.3–16.2)	17.9 (8.0–27.3)	<0.001	15.7 (6.0–31.0)	<0.001	11.1 (4.7–25.5)	0.052	16.4 (5.3–31.6)	<0.001	18.0 (9.1–31.2)	<0.001
OI	0.0 (0.0–8.0)	4.0 (0.0–16.0)	<0.001	0.0 (0.0–20.0)	<0.001	0.0 (0.0–16.0)	0.071	8.0 (0.0–16.0)	0.002	8.0 (0.0–16.0)	0.005
GI	3.6 (0.0–5.4)	3.6 (1.8–6.3)	<0.001	2.7 (0.0–5.4)	0.310	1.8 (0.0–3.6)	0.140	3.6 (0.9–6.3)	0.190	4.5 (1.8–6.3)	<0.001
Vasomotor	0.0 (0.0–0.0)	0.0 (0.0–1.7)	<0.001	0.0 (0.0–0.0)	0.270	0.0 (0.0–0.0)	0.660	0.0 (0.0–0.0)	0.390	0.0 (0.0–0.0)	0.370
Secreto	2.1 (0.0–4.3)	4.3 (2.1–6.4)	0.001	2.1 (0.0–6.4)	0.002	2.1 (0.0–6.4)	0.180	2.1 (0.0–6.4)	0.400	2.1 (0.0–6.4)	0.060
Bladder	0.0 (0.0–1.1)	0.0 (0.0–1.1)	0.200	0.0 (0.0–1.1)	0.05	0.0 (0.0–2.2)	<0.001	1.1 (0.0–3.3)	<0.001	1.1 (0.0–3.3)	<0.001
Pupillo	0.3 (0.0–1.0)	0.3 (0.0–1.3)	0.848	0.7 (0.0–1.7)	0.004	0.0 (0.0–1.3)	0.292	1.0 (0.0–2.0)	<0.001	1.0 (0.0–2.0)	<0.001
L-Cas	*N*=44	*N*=44	P	*N*=44	p	*N*=44	p	*N*=44	p	*N*=44	p
Total score	7.3 (4.3–25.6)	25.2 (16.7–35.6)	<0.001	27.3 (13.5–37.7)	<0.001	23.0 (7.5–33.5)	0.005	31.5 (25.5–36.4)	<0.001	26.8 (18.0–36.1)	<0.001
OI	0.0 (0.0–16)	12.0 (0.0–20.0)	0.007	16.0 (0.0–24.0)	0.001	12.0 (0.0–20.0)	0.010	16.0 (12.0–24.0)	<0.001	16.0 (0.0–24.0)	<0.001
GI	3.6 (0.0–5.4)	5.4 (2.7–8.0)	<0.001	3.6 (0.0–7.1)	0.170	1.8 (0.0–5.8)	0.980	6.3 (2.7–8.0)	0.002	5.4 (2.7–7.1)	0.001
Vasomotor	0.0 (0.0–0.0)	0.0 (0.0–1.6)	0.016	0.0 (0.0–1.2)	0.019	0.0 (0.0–0.0)	0.656	0.0 (0.0–0.0)	0.169	0.0 (0.0–0.8)	0.140
Secreto	2.1 (0.0–6.4)	4.3 (2.1–8.6)	0.013	4.3 (2.1–6.4)	0.013	4.3 (0.0–6.4)	0.351	4.3 (0.0–6.4)	0.065	4.3 (0.0–6.4)	0.009
Bladder	0.0 (0.0–1.1)	0.0 (0.0–2.2)	0.045	0.0 (0.0–1.7)	0.192	0.0 (0.0–2.2)	0.020	1.1 (0.0–4.2)	<0.001	1.1 (0.0–2.2)	0.001
Pupillo	0.3 (0.0–1.0)	0.7 (0.0–1.7)	0.064	1.0 (0.0–1.7)	<0.001	0.5 (0.0–2.0)	0.070	1.7 (0.3–2.7)	<0.001	1.3 (0.3–2.3)	<0.001
Post-COVID *N*=43	*N*=43	P	*N*=43	p	*N*=43	p	*N*=43	p	*N*=43	p	
Total score	6.2 (3.6–13.5)	12.3 (5.6–22.0)	0.008	8.9 (3.3–21.6)	0.020	5.8 (2.7–14.2)	0.620	5.3 (1.8–8.8)	0.031	9.2 (4.8–16.6)	0.580
OI	0.0 (0.0–0.0)	0.0 (0.0–12.0)	0.027	0.0 (0.0–16.0)	0.101	0.0 (0.0–8.0)	0.550	0.0 (0.0–0.0)	0.037	0.0 (0.0–12.0)	0.951
GI	1.8 (0.0–4.5)	2.7 (0.9–5.4)	0.440	0.9 (0.0–4.5)	0.770	0.9 (0.0–2.7)	0.016	0.9 (0.0–3.6)	0.059	2.7 (0.9–4.5)	0.360
Vasomotor	0.0 (0.0–0.0)	0.0 (0.0–0.4)	0.015	0.0 (0.0–0.0)	0.375	0.0 (0.0–0.0)	0.999	0.0 (0.0–0.0)	0.999	0.0 (0.0–0.0)	0.999
Secreto	2.1 (0.0–2.1)	2.1 (0.0–4.3)	0.057	2.1 (0.0–4.8)	0.092	0.0 (0.0–4.3)	0.453	0.0 (0.0–2.1)	0.433	0.0 (0.0–4.3)	0.710
Bladder	0.0 (0.0–1.1)	0.0 (0.0–1.1)	0.629	0.0 (0.0–1.1)	0.185	0.0 (0.0–2.2)	0.008	0.0 (0.0–1.1)	0.020	0.0 (0.0–1.1)	0.079
Pupillo	0.3 (0.0–1.0)	0.0 (0.0–0.7)	0.148	0.7 (0.0–1.3)	0.474	0.0 (0.0–1.1)	0.942	0.7 (0.0–1.3)	0.421	1.0 (0.0–1.7)	0.216

Wilcoxon matched-pairs signed-rank tests have been performed by comparing the available population at each time point against the baseline value (PRE) in the corresponding matched population (i.e. each patient's PRE value is the baseline reference). L-Cas indicates Long-COVID autonomic syndrome; IQR interquartile range; OI, orthostatic intolerance; GI, gastrointestinal; Secreto, secretomotor; Pupillo, pupillomotor.

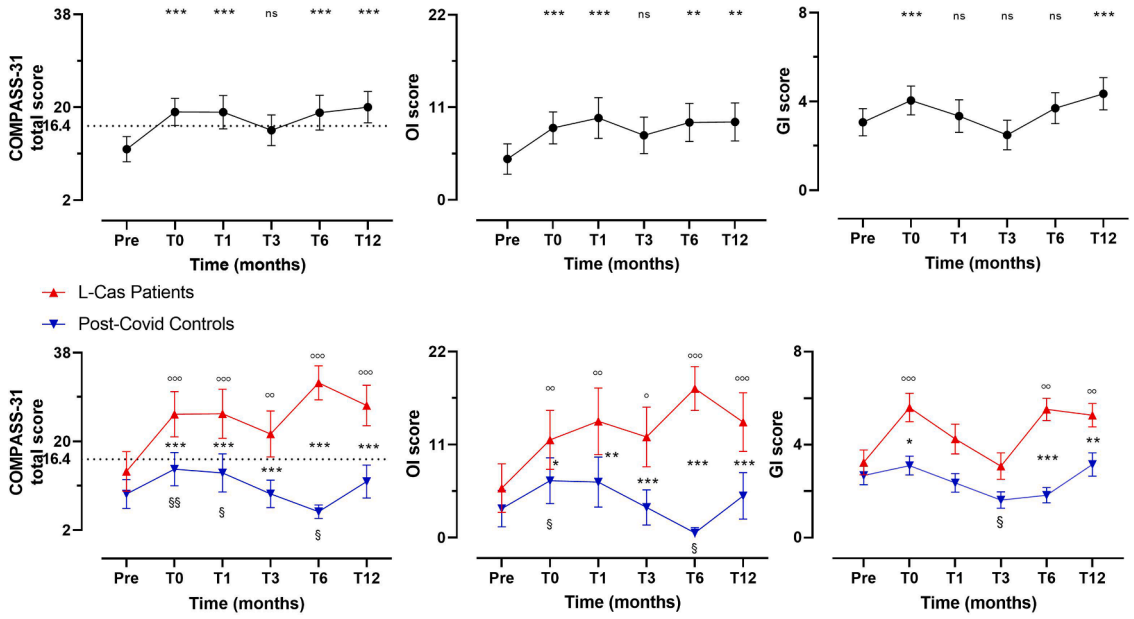

Fig. 3. Time course of COMPASS-31 total score, orthostatic intolerance and gastrointestinal tract symptom scores, as observed in the overall population (upper graphs) and in the Long-COVID autonomic syndrome (L-Cas) patients and Post-COVID controls (lower graphs) groups. Please note the bi-phasic pattern characterized by an increase in the scores suggestive of autonomic symptoms worsening during the acute phase of the disease (T0), followed by an overall symptoms improvement at T1 and T3 and then by an unexpected second worsening at T6 and T12 compared to T3 and the pre-infection periods (PRE). The use of a COMPASS-31 total score threshold value of 16.4 at T6, enabled us to distinguish two different sub-populations. The Post-COVID controls who healed (lower blue graphs) characterized by scores values at T6 and T12 similar to T3 and PRE and the L-Cas patients (lower red graphs) who conversely increased the autonomic scores at T6 and T12 suggesting an aggravation of autonomic symptoms compared with T3 and PRE.
Data are mean±95% CI.
Upper graphs, intragroup differences: * $p<0.05$; ** $p<0.01$; *** $p<0.001$
Lower graphs, intragroup differences: Long-COVID § $p<0.05$; §§ $p<0.01$; §§§ $p<0.001$
: Post-COVID $p<0.05$; $p<0.01$; $p<0.001$
Lower graphs intergroup difference: * $p<0.05$; ** $p<0.01$; *** $p<0.001$.

which mirrored those observed in the indices of autonomic symptoms intensity (Table 3).

4.3. Demographic and clinical features of L-Cas patients and post-covid controls

Kernel density plot (Fig. 2), carried out on data at T6, showed a bimodal distribution of COMPASS-31 indices suggesting the presence of two distinct subpopulations. Overall, the Long-COVID autonomic syndrome group (L-Cas) had a higher number of patients aged less than 44 years, whereas the Post-COVID controls were mostly older than 45 (Table 1).

The central and right columns of Table 2 indicate that both groups had similar disease severity indices.

Additional information on vaccinations and possible re-infections in the total population and the two subgroups can be found in Table 5. Data shows that vaccinations and re-infections were similar in both the L-Cas and Post-COVID patients at T12.

4.4. Time course of autonomic related symptoms and quality of life indices in L-Cas and post-covid groups

Table 3 summarizes the changes over time of the COMPASS-31 total score and the 6 domains indices in the L-Cas and Post-COVID patients. The absolute number and incidence (%) of patients characterized by a COMPASS-31 total score > 16,4 at the different time points were 22 (23.7%) for PRE; 55 (59.1%) for T0; 43 (46.2%) for T1; 30 (32.2%) for T3; 44 (47.3%) for T6 and 44 (47.3%) for T12. The lower graphs in Fig. 3 emphasize the most relevant modifications over time of the autonomic symptom-related indices in the two subgroups. The indices were consistently higher in the L-Cas group than in Post-COVID controls at all follow-up times.

Furthermore, the COMPASS-31 total score, orthostatic intolerance, and gastrointestinal symptoms domain scores (Fig. 3) worsened at T0 compared to PRE and progressively improved at T1 and T3 in both the in the L-Cas and Post-COVID groups, thus featuring an indices swing characterizing the acute COVID-19 disease. However, while the above indices remained similar to PRE from T3 up to T6 and T12 in the Post-COVID patients, autonomic indices worsening was observed in 47% of L-Cas individuals at T6 and T12, featuring a second rise characterizing the Long—COVID autonomic syndrome.

L-Cas patients consistently showed lower QoL, physical functioning, and higher pain and fatigue scores compared to Post-COVID controls. These scores worsened at T6 and T12 for the L-Cas group. Conversely, in the Post-COVID group QoL and fatigue scores decreased at T3 and remained similar to the PRE at T6 and T12, indicating full recovery (Fig. 4, lower graphs).

5. Discussion

In a group of hospitalized patients with severe SARS CoV2, the overall autonomic symptoms measured by COMPASS-31 score followed a bi-phasic pattern over time. Symptoms worsened during the acute phase, improved from 1 to 3 months post-discharge, but aggravated at 6 and 12 months. Moreover, applying a 16.4 total score cut-point at the T6 follow-up enabled us to differentiate a subgroup of individuals (47%) who suffered from autonomic symptoms that persisted for one year (L-Cas patients) from a second group of Post-COVID patients who completely recovered (Post-COVID Controls).

Table 4
Time course of the SF-36 questionnaire total score, physical function, fatigue, and pain, which mirrored those observed in the indices of autonomic symptoms intensity.

	PRE (n=93) Median (IQR)	T0 (n=93) Median (IQR)	p	T1 (n=89) Median (IQR)	p	T3 (n=87) Median (IQR)	p	T6 (n=87) Median (IQR)	p	T12 (n=87) Median (IQR)	p
QoL	748 (654–780)	462 (363–600)	<0.001	539 (452–649)	<0.001	665 (525–759)	0.009	610 (471–721)	<0.001	644 (542–753)	<0.001
Physical function	95 (85–100)	75 (55–85)	<0.001	82 (70–90)	<0.001	90 (75–100)	0.104	85 (70–95)	<0.001	90 (66–95)	0.001
Fatigue (normalized)	35 (20–45)	55 (40–65)	<0.001	45 (35–55)	<0.001	40 (25–55)	0.210	40 (30–50)	0.012	40 (25–55)	0.036
Pain (normalized)	0 (0–30)	20 (0–65)	0.002	22 (0–54)	0.015	22 (0–45)	0.017	22 (0–45)	0.002	22 (0–42)	<0.001
L-Cas	N=44	N=44	p	N=44	p	N=44	p	N=44	p	N=44	p
QoL	734 (644–777)	405 (324–516)	<0.001	488 (349–572)	<0.001	605 (417–675)	0.002	551 (425–648)	<0.001	605 (451–673)	<0.001
Physical function	90 (70–100)	70 (40–80)	<0.001	75 (55–85)	<0.001	82 (65–95)	0.388	75 (59–91)	0.006	85 (55–95)	0.041
Fatigue (normalized)	35 (20–50)	60 (43–78)	<0.001	50 (45–60)	<0.001	43 (30–55)	0.160	43 (30–55)	0.019	45 (30–55)	0.029
Pain (normalized)	0 (0–32)	38 (0–77)	0.260	30 (0–55)	0.110	22 (0–46)	0.080	32 (10–52)	<0.001	31 (5–54)	0.002
Post-COVID N=43		N=43	p	N=43	p	N=43	p	N=43	p	N=43	p
QoL	751 (666–783)	507 (406–635)	<0.001	578 (502–724)	<0.001	733 (617–775)	0.470	678 (559–764)	0.033	707 (582–775)	0.110
Physical function	95 (90–100)	80 (70–90)	<0.001	85 (75–91)	<0.001	95 (85–100)	0.180	90 (75–100)	0.048	95 (75–100)	0.019
Fatigue (normalized)	35 (20–45)	50 (35–60)	<0.001	40 (35–55)	0.010	30 (25–45)	0.550	35 (30–45)	0.260	30 (25–45)	0.440
Pain (normalized)	0 (0–20)	10 (0–65)	0.001	25 (0–45)	0.047	21 (0–32)	0.055	10 (0–42)	0.400	16 (0–32)	0.039

Wilcoxon matched-pairs signed-rank tests have been performed by comparing the available population at each time point against the baseline value (PRE) in the corresponding matched population (i.e. each patient's PRE value is the baseline reference). IQR indicates interquartile range. OI, orthostatic intolerance; GI, gastrointestinal; Secreto, secretomotor; Pupillo, pupillomotor.

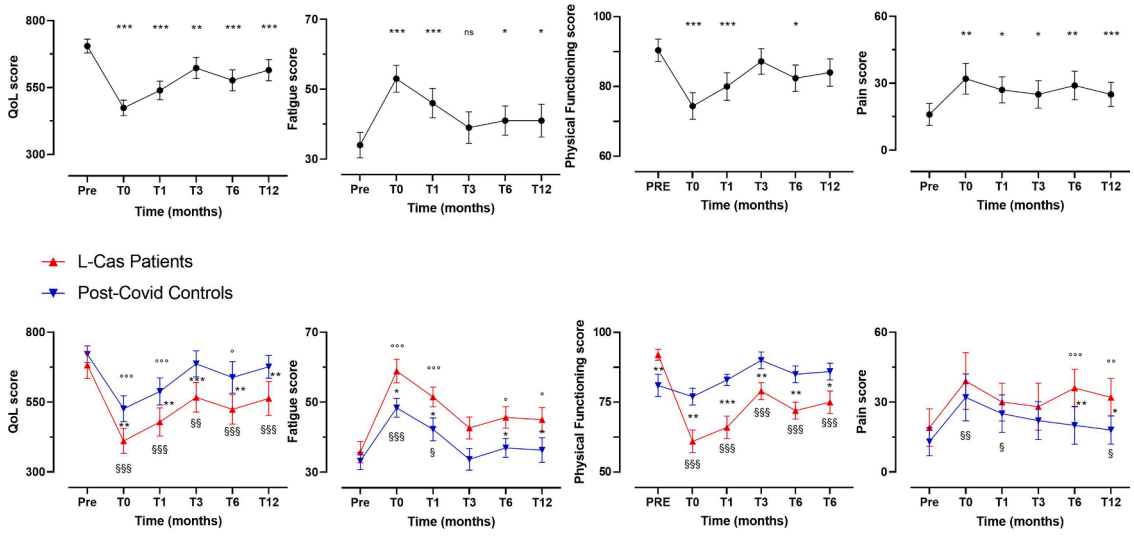

Fig. 4. Time course of SF-32 score, fatigue, physical functioning and pain scores, in the total population (upper graphs) and in the Long-COVID autonomic syndrome (L-Cas) patients and Post-COVID controls (lower graphs). The quality of life and physical functioning scores decreased during the acute phase of the disease (T0) then progressively increased up to T3 suggesting healing but subsequently decreased at T6. Notably, these indices still remained lower than PRE. Similarly, fatigue and pain scores increased at T0 pointing to a worsening of these symptoms, decreased at T1 and T3 but enhanced at T6. The subgroups pattern analyses indicate that in the Post-COVID controls (blue graphs) the quality of life indices tended to return to the PRE values starting at T3, whereas in the L-Cas patients (red graphs) quality of life indices underwent a second worsening at T6, similarly to what observed for COMPASS-31 indices (Fig. 2).
Data are mean±95% CI.
Upper graphs, intragroup differences: * p<0.05; ** p<0.01; *** p<0.001
Lower graphs, intragroup differences: Long-COVID § p<0.05; §§ p<0.01; §§§ p<0.001
: Post-COVID p<0.05; p<0.01; p<0.001
Lower graphs intergroup difference: * p<0.05; ** p<0.01; *** p<0.001.

Table 5
Vaccinations and re-infections in the total population and the in the L-Cas and Post-COVID groups.

Vaccinations (n,%)	Population (*N*=74)	L-Cas (*N*=40)	Post-COVID (*N*=34)	*p* value
Unvaccinated	6 (8.1)	4 (10.0)	2 (5.9)	0.68
Vaccinated	68 (91.9)	36 (90.0)	32 (94.1)	0.68
1 dose	11 (14.9)	4 (10.0)	7 (20.6)	0.33
2 doses	31 (41.9)	19 (47.5)	13 (38.2)	0.34
Booster	25 (33.8)	13 (32.5)	12 (35.3)	0.99
After 6 months	13 (17.6)	8 (20.0)	5 (14.7)	0.54
After 12 months	3 (4.0)	2 (5.0)	1 (2.9)	0.99
Days from discharge to vaccination, median (IQR)	151 (115 – 171)	147 (95.3 – 181)	152 (133 – 168)	0.68
Reinfections				
Non-reinfected	57 (77.0)	33 (82.5)	24 (70.6)	0.27
Reinfected	17 (23.0)	7 (17.5)	10 (29.4)	0.27
Single	13 (17.6)	5 (12.5)	8 (23.5)	0.99
Multiple	4 (5.4)	2 (5.0)	2 (5.9)	0.99
Days from discharge to reinfection, median (IQR)	309 (293–372)	325 (301–406))	313 (295–335)	0.76

For categorical variables data are presented as proportions; Fisher exact test was used to verify statistically significant differences between Long-Covid autonomic syndrome (L-Cas) and Post-COVID populations. Continuous variables are expressed as median and interquartile range and p values were obtained using two sample Wilcoxon rank-sum test. IQR indicates interquartile range.

5.1. Short and long term autonomic symptoms and qol patterns in SARS-CoV-2 infected patients

Long-lasting autonomic symptoms and reduced QoL after acute viral or bacterial infections have been reported [31]. Persistent symptoms include, among others, orthostatic intolerance and tachycardia, fatigue, generalized pain, sleep disturbance and brain fog. Infectious events have also been found to precede disorders characterized by autonomic abnormalities, such as POTS [11] and chronic Lyme disease [32]. In young survivors of acute SARS-CoV-2 infection, long-lasting symptoms suggesting underlying dysautonomia [10] and resembling those observed in POTS patients [12] were recently observed [9,10].

Previous investigations [3-5,19,20,23,24] have addressed the persistence of long-term symptoms after hospital discharge from acute COVID-19 disease through prospective observational studies, or identified factors associated with a favorable disease course [33]. However, no studies have addressed the autonomic-related symptoms before, during, and after SARS-CoV-2 infection.

Based on the available PRE COVID infection data, we identified a clear two-swing curve over time in COMPASS-31 total score, orthostatic intolerance, GI tract autonomic symptoms, and QoL indices, including the acute phase and 3-, 6-, and 12-month follow-up of SARS-CoV-2 infection. There was a significant worsening of symptoms and QoL indices after 6 and 12 months from hospital discharge, following tentative healing at 1- and 3-month follow-up, the latter featuring the acute phase of COVID-19 disease.

Validated questionnaires like COMPASS-31 and SF-36 provided a semi-quantitative assessment of autonomic symptoms intensity and QoL changes over time after SARS-CoV-2 infection. Although a subjective patient evaluation and lack of objective indices are questionnaires intrinsic limitations, this approach offers an additional perspective to previous investigations only reporting symptoms rates at follow-up [1, 3-5], and may therefore provide valuable clinical insight into the natural history of Long-COVID.

Time course of the autonomic symptoms, quality of life and pain indices in L-Cas patients and Post-COVID controls.

The unexpected finding of symptoms worsening at 6-month follow-up in the overall population prompted us to conduct a post-analysis using a COMPASS-31 total score cut-point value <16.4 (Fig. 3). Furthermore, the Kernel density estimate plot (Fig. 2), generated from the COMPASS-31 total score of the entire population at T6, revealed a bimodal distribution of COMPASS-31 indices, indicating the presence of two distinct sub-populations that were not apparent at PRE. As previously reported [28], we used the <16.4 cut-point value to identify patients without a clear autonomic disorder within our overall population, who were likely to fully recover (Post-COVID recovered individuals), as evidenced by the COMPASS-31 total score at T6 and T12 remaining similar to T3 and PRE. The remaining patients were those who experienced a worsening of autonomic symptoms at T6 and continued to experience them at one year, i.e., the L-Cas patients.

Of note, the T6 follow-up time point was chosen since previous studies have shown that a six-month period is a sufficient for complete recovery from the acute phase of COVID-19 disease [17,34] and for mitigating any potential confounding effects from an extended hospital stay due to disease severity [35]. Indeed, prolonged hospital stay can result in physical signs and orthostatic and cognitive symptoms such as dizziness, shortness of breath, fatigue, orthostatic tachycardia and decreased exercise tolerance similar to Long-COVID autonomic syndrome symptoms [36].

Data concerning post-acute COVID-19 sequelae is currently lacking, and the available information is affected by variations in the clinical settings from which it is obtained. For instance, a study that followed up Swedish healthcare workers with mild COVID-19 reported a post-acute COVID-19 syndrome in 10.5% of the individuals [15]. In contrast, more than 60% of a hospitalized cohort population reported fatigue or muscle weakness at 6-month follow-up [3]. In our study, we observed an incidence for L-Cas of 47% at 6 and 12 months after hospital discharge, which was higher than the incidence previously reported in an outpatient cohort in Italy [37] at 3 months after infection (33%), but lower than the incidence extrapolated from an outpatient cohort at 4 months after hospital discharge (75%) that included patients previously hospitalized [1].

Although there were no significant differences in demographics (Table 1) or disease severity proxies (Table 2) between the L-Cas and Post-COVID control groups at hospital discharge (T0), a closer examination of the data reveals some noteworthy observations. Firstly, the L-Cas group had a higher proportion of patients under the age of 44, while the Post-COVID controls were mostly older than 45. Although not statistically significant, this observation is in line with previous studies indicating that Post-COVID-19 Tachycardia Syndrome [8–10] and POTS [11,12], an orthostatic disorder frequently triggered by a viral infection [10,38], primarily affect young adults. Secondly, several proxies of acute COVID-19 disease severity, such as length of hospital stay > 20 days, ICU admission, and the number of patients requiring high-flow oxygen therapy and CPAP support, were slightly more frequent in the Post-COVID control group than in the L-Cas one. This suggests that the development of L-Cas is independent of the severity of the acute COVID-19 disease, contrary to previous findings [3,24]. Finally, a recent investigation suggested that vaccination may reduce the risk of developing Long-COVID [39]. In our study, most patients received their first and second vaccination shots after T6, and their distribution was uniform between the L-Cas and Post-COVID control groups, making it impossible to draw conclusions about the role of vaccination based on our study design and results.

6. Conclusions

The results of our cohort study indicate that a significant proportion of patients hospitalized due to severe SARS-CoV-2 infection may experience autonomic-related symptoms for up to one year (L-Cas), which negatively impacts their QoL. The analysis of autonomic symptoms during the PRE infection, acute disease, and recovery periods in L-Cas

patients revealed a distinct pattern of two oscillations over a one-year period. The first oscillation occurred during the acute phase of the illness, followed by a tentative healing at 3 months after hospital discharge. The second fluctuation was due to an unexpected disease flare-up starting at T6.

These findings highlight the importance of early initiation of rehabilitative and pharmacological-based therapeutic strategies following SARS-CoV-2 infection.

Declaration of Competing Interest

All Authors declare no competing interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2023.08.018.

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