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Composite Autonomic Symptom Score-31 for the diagnosis of cardiovascular autonomic dysfunction in long-term coronavirus disease 2019

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Abstract:

BACKGROUND: Composite Autonomic Symptom Score-31 (COMPASS-31) is an easy-to-use screening tool for the evaluation of autonomic dysfunction in various diseases affecting neural function but has rarely been used in the assessment of long coronavirus disease 2019 (COVID-19). This study aimed to evaluate the diagnostic accuracy of the COMPASS-31 score in detecting dysfunction of the autonomic nervous system in patients 3 months after COVID-19 infection.

MATERIALS AND METHODS: Fifty-nine subjects were recruited and grouped into 2: (a) controls ($n = 31$) who had never had positive polymerase chain reaction results for COVID-19 before and (b) the post-COVID-19 patients ($n = 28$) who had confirmed COVID-19 infection 3–6 months before recruitment. COMPASS-31 questionnaire was utilized to evaluate subjective symptoms or evidence of autonomic dysfunction. Autonomic dysfunction was assessed objectively by cardiovascular autonomic reflex tests (CARTs) and heart rate variability (HRV). For comparison of quantitative variables between two groups, t-test or Mann-Whitney U test, as appropriate, were used. Sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), negative likelihood ratio (LR), and positive LR were used as measures of diagnostic accuracy. Receiver operating characteristic (ROC) curve analysis determined the overall accuracy of COMPASS-31.

RESULTS: The median COMPASS score was found to be significantly higher in post-COVID-19 participants than controls (15.5 vs. 10, $P = 0.021$). The median total CART score was also significantly higher in post-COVID-19 participants (0 vs. 1, $P < 0.001$). Out of 6 domains of the COMPASS score, the median value for orthostatic dysfunction was found to be significantly higher in post-COVID-19 participants than controls (12 vs. 0, $P = 0.008$). There was significantly fair accuracy of the COMPASS score with an area under the receiver operating curve 0.68 (0.54–0.82) following the total CART score ≥ 2 as the gold standard in the diagnosis of autonomic dysfunction ($P = 0.021$). The best cutoff point of the total COMPASS score was 12.5, where the optimal values of sensitivity, specificity, and positive and negative predictive values were achieved. Nonsignificant and weak correlations between CARTs, HRV parameters, and COMPASS score were found.

CONCLUSION: COMPASS-31 could be used as a user-friendly screening tool to detect autonomic dysfunction in post-COVID-19 cases with acceptable sensitivity and specificity.

Keywords:

Autonomic dysfunction, cardiovascular autonomic reactivity test, Composite Autonomic Symptom Score-31, coronavirus disease, heart rate variability

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Introduction

Several studies have demonstrated the long-term effects of coronavirus disease 2019 (COVID-19) that could affect different body systems besides the respiratory system. Palpitation, fatigue, sleep disturbance, dizziness, and impaired concentration are some of the long-term manifestations of COVID-19, and the condition is now termed long COVID-19.[1] Symptoms of this COVID-19 infection can be present for more than 2 weeks.[2,3] Various body dysfunctions have been correlated to the impact of long-term COVID-19 including gastrointestinal (GIT) disturbances, renal impairment, respiratory distress syndrome, coagulation abnormalities, hyperglycemia, and neurological deficits.[2]

A recognized chronic consequence of COVID-19 infection is dysfunction of the autonomic nervous system (ANS).[4,5] Clinical features of dysautonomia comprise orthostatic hypotension (OH), increased heart rate (HR), upper and lower GIT problems, pupillomotor and sweating abnormalities, and urogenital dysfunction.[5] COVID-19 has been associated with reports of cardiovascular (CV) autonomic dysfunction 3–6 months after recovery manifested in a reduction in HR variability (HRV) which could increase cardiac risk in post-COVID-19 patients.[6] Several patients also complained of Postural Orthostatic Tachycardia Syndrome (POTS) and OH following the acute phase of COVID-19.[6] In addition to postural hypotension, gastrointestinal disturbances and secretomotor abnormalities have also been recorded in the period of recovery following COVID-19 disease.[7] Moreover, parasympathetic hyperactivity with increased HRV was found 90 days after acute infection of COVID-19. Furthermore, a recent publication showed a higher incidence of altered CV reactivity with OH in about 39.3% of post-COVID-19 patients.[8]

Dysautonomia can be diagnosed objectively by performing a set of tests of autonomic functions. Currently, cardiovascular autonomic reflex tests (CARTs) are considered the confirmatory tests in the detection of CV autonomic dysfunction.[9-11] CARTs include the measurement of the HR in relation to Valsalva maneuver (VM), head-up tilt (HUT), deep breathing (DB), and the alteration in blood pressure (BP) in response to HUT and isometric hand grip exercise (IHGE). In addition, HRV analysis is commonly involved in diagnosing CV autonomic neuropathy. HRV evaluates the sympathetic and parasympathetic nervous system effects on CV system (CVS) from electrocardiography recording[11,12] The American Diabetes Association as well as the Toronto Consensus Panel on Diabetic Neuropathy suggested the use of HRV for early detection of autonomic dysfunction[13,14] and was recommended in some clinical trials for use as an indicator of dysfunction of the ANS affecting the CVS.[15,16] It has been demonstrated that the evaluation of HRV might be more specific and sensitive than traditional CARTs for the prompt diagnosis of the dysfunction of CV autonomic supply.[17,18] However, these methods for traditional CARTs are sophisticated, are expensive, and require heavy equipment as well as much cooperation from subjects. These factors hinder the broad application of CARTs in medical settings. Therefore, suitable symptom-based questionnaires need to be evaluated for use as screening tools to detect autonomic dysfunction in various diseases.

The Composite Autonomic Symptom Scale-31 (COMPASS-31) is a self-filling questionnaire devised by Sletten *et al*.[19] It evaluates the autonomic function across six weighted domains: orthostatic intolerance, GIT, bladder, vasomotor, pupillomotor, and secretomotor domains and provides weighted total scores ranging from 0 up to 100. An increase in the score demonstrates the severity of dysautonomia.[19] COMPASS-31 questionnaire has been validated as a useful method of screening and evaluation of dysfunction of ANS in different neurodegenerative diseases such as parkinsonism, polyneuropathy, multiple sclerosis, and fibromyalgia[20-22]. However, very few studies have used the COMPASS-31 to evalua-te autonomic dysfunctions in long COVID-19.[4,7] Therefore, the aim of this study was to evaluate the diagnostic accuracy of the COMPASS-31 score in detecting dysfunction of the ANS after recovery from acute COVID-19 infection. This was achieved by analyzing the total and domain scores derived from COMPASS-31 in postacute COVID-19 cases and controls and establishing the relation between COMPASS-31 score and CARTs and HRV values. We hypothesized that COMPASS-31 score could be helpful in the initial diagnosis of dysautonomia associated with long COVID-19.

Materials and Methods

This cross-sectional study was conducted in the laboratory of the Physiology Department at the College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia, from November 07, 2021, to March 14, 2022. Fifty-nine subjects were recruited and divided into two groups: controls (n = 31) who had never had positive polymerase chain reaction (PCR) results for COVID-19 and post-COVID-19 group (n = 28) – patients who had confirmed COVID-19 infection 3–6 months before recruitment. The sample size was determined in the range of 25–152 subjects depending on prior similar studies which analyzed comparable outcomes.[23,24] Patients had been diagnosed with COVID-19 disease by real-time reverse transcription-PCR test 3–6 months before recruitment.[23] Subjects were excluded if they had comorbidities such as Parkinson's disease, polyneuropathy, Guillain–

Barré syndrome, and multiple sclerosis that could affect the autonomic functions or had established CV diseases (e.g., valvular abnormalities, cardiomyopathies, arrhythmias, and ischemic heart disease), in addition to alcoholism, hepatic disease, and kidney disease. Ethical approval was obtained from the Institutional Review Board (IRB) vide letter no. IRB-UGS-2021-01-391 dated 31/10/2021, and written informed consent was taken from all participants in the study.

The demographic, clinical, and anthropometric data of participants were recorded. COMPASS-31 questionnaire was used to evaluate subjective symptoms or evidence of autonomic dysfunction. Autonomic dysfunction was objectively assessed by CARTs and HRV.

COMPASS-31 is a questionnaire comprising 31 questions, which assesses six domains of autonomic dysfunction, including orthostatic intolerance, vasomotor dysfunction, secretomotor dysfunction, GIT dysfunction, urinary dysfunction, and pupillomotor dysfunction. Each domain is then scored by adding the scores of the constituent questions to make up the raw score. The raw scores are then multiplied by a weighting factor specific to each domain to result in the weighted score. The individual weighted scores are then added together and reported as the total score of 0–100; the higher the score the more severe the symptoms.[19] All study subjects were asked to fill COMPASS-31 questionnaire separately before the other assessments were made.

CARTs were performed as reference standard on the same day that COMPASS-31 was completed. Autonomic function was evaluated using Ewing's standard battery of tests.[9,10] Parasympathetic function was assessed by measuring HR changes in response to (a) DB, (b) VM, and (c) HUT. Sympathetic function was evaluated by recording the alteration of BP in response to (a) IHGE and (b) HUT.

HR was obtained through a single-lead electrocardiogram (ECG) recorded through 8/32 Power Lab (ADInstruments, Australia) connected through a bioamplifier and an ECG box (ADInstruments, Australia). Finger arterial BP recording was obtained by Finometer Pro (FMS, The Netherlands). Participants rested for 20 min before the commencement of tests and were asked to abstain from food, smoking, caffeine, and alcohol for a minimum 2 h before the test. The scoring of each test was done as "0" for normal, and 1 for abnormal, for a final score of 5. Abnormality was defined by age-related normal reference values. A total CART score of 2 and above was considered a criterion for the identification of autonomic dysfunction.[17,24]

HRV analysis was performed using the LabChart Pro software version 8.1.13 (ADInstruments, Australia) and HRV module (ADInstruments, Australia). Time domain analysis was done to obtain standard deviation (SD) of normal RR intervals representing overall HRV, root mean square of difference of successive RR intervals (RMSSD), and percentage of successive RR intervals that are different by at least 50 m s (pRR50). Data on the parasympathetic function were given by both pRR50 and RMSSD. The frequency domain analysis involved assessing high-frequency band (HF) as a representation of parasympathetic activity, as well as the low frequency (LF), which represents sympathetic activity. The LF/HF ratio indicates the balance between sympathetic and parasympathetic activities, whereas total power denotes overall HRV.

In statistical analysis, the Shapiro–Wilk test was used to assess the normality of data. Normally distributed data were presented as mean ± SD, whereas median and interquartile range were used for data that is not normally distributed. The Student's *t*-test was used to evaluate normally distributed data, whereas the Mann–Whitney *U*-test was used to evaluate nonnormally distributed data. Sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), negative likelihood ratio (LR), and positive LR were used as measures of diagnostic accuracy.

Receiver operating characteristic (ROC) curve analysis was employed to determine the overall accuracy of COMPASS-31. In the analysis of ROC, the dependent variables were domain scores and COMPASS-31 total score, and the independent variable was the status of the research participants (with autonomic dysfunction/without autonomic dysfunction) (patients with total CART score of 2 and above were defined as having autonomic dysfunction). For each domain of COMPASS-31, a separate ROC analysis was done. Data were evaluated with the support of SPSS version 28 software (IBM Corp., Armonk, N.Y., USA). The level of significance was set at P value of < 0.05.

Results

Of the 59 subjects recruited, 57 participants (37 males and 20 females) completed the study procedures and were evaluated for the predictive yield of the total COMPASS-31 and subdomains of the COMPASS score in the diagnosis of autonomic dysfunction [Figure 1]. The participants in both the post-COVID-19 group (n = 28; 10 females) and the control group (n = 29, 10 females) were further evaluated for the predictive accuracy of the total COMPASS score and subdomains of the COMPASS score associated with post-COVID-19 effect. Both groups were comparable in terms of age (control: 23.79 ± 4.83 years, post-COVID-19: 25.46 ± 8.72 years, P

= 0.372) and body mass index (control: 25.97±5.73kg/m^2 post-COVID-19: 25.67 ± 4.78 kg/m^2, P = 0.834).

Of the 57 participants in the study, 13 (22.8%) were observed to have a total CART score of 2 or above, which revealed a prevalence of autonomic dysfunction of 22.8%. All of the 13 participants belonged to the post-COVID-19 group, forming a percentage of 46.4% as confirmed cases with autonomic dysfunction based on a total CART score of 2 or above. Fifteen participants in the post-COVID-19 group (53.6%) had a total CART score of <2 and were considered negative for autonomic dysfunction.

The median COMPASS score was found to be significantly higher in post-COVID-19 participants than controls (15.5 vs. 10, P = 0.021). The median total CART score was also significantly higher in post-COVID-19 participants (0 vs. 1, P < 0.001). Out of 6 domains of the COMPASS score, only the orthostatic dysfunction median value was found significant in post-COVID-19 participants (12 vs. 0, P = 0.008), as detailed in Table 1.

Most of the HRV parameters did not show any significant differences between post-COVID-19 cases with and without autonomic dysfunction, whereas CART scores showed significant differences in the median values in terms of sympathetic score (2 vs. 1, P < 0.001), parasympathetic score (1 vs. 0, P = 0.003), and total CART score (2 vs. 1, P < 0.001), as detailed in Table 2.

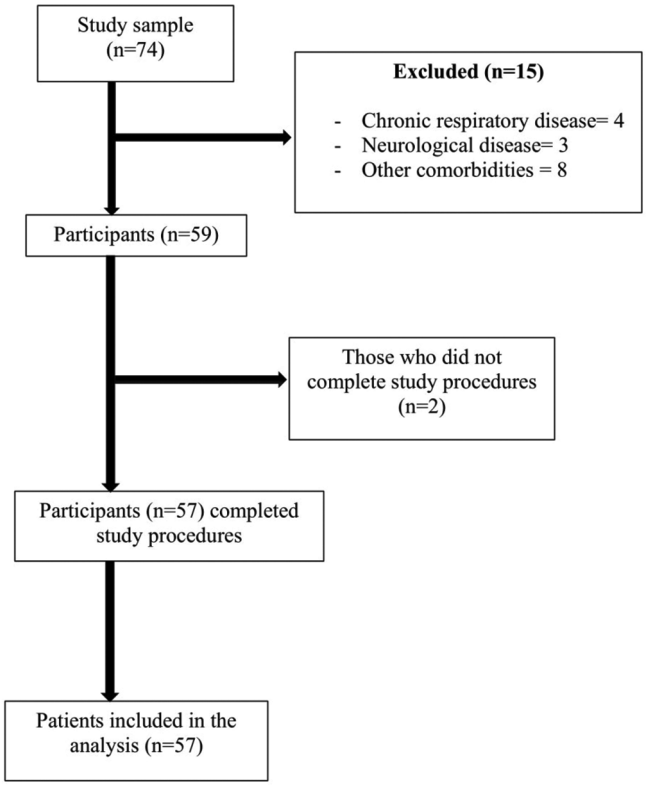

Figure 1: Participants' flowchart

There was significantly fair accuracy of the COMPASS score with an area under the ROC = 0.68 (0.54–0.82) following the total CART score as the gold standard in the diagnosis of autonomic dysfunction (P = 0.021), as illustrated in Figure 2.

Predictive validity of the COMPASS score based on the gold standard (CART score ≥2) of various cutoff points is presented in Table 3. The best cutoff point of the total COMPASS score was 12.5, where the optimal values of sensitivity, specificity, PPV, and NPV were achieved. The highest sensitivity (92.3%) and NPV (93.7%) were seen on the cutoff point of the total COMPASS score >6.5 and the specificity of 33.6% and PPV of 29%. Similar

Table 1: Comparison of Composite Autonomic Symptom Score-31 and cardiac autonomic reflex test scores between groups

COMPASS domains	Median (IQR)		*P*-value
	Control (*n*=29)	Post-COVID-19 (*n*=28)	
Total COMPASS score	10 (15.75–4.5)	15.5 (27–7.5)*	0.021
Orthostatic dysfunction	0 (9–0)	12 (16–0)*	0.008
Vasomotor score	0 (0–0)	0 (0–0)	0.161
Secretomotor score	0 (4–0)	0 (4–0)	0.961
GIT symptom score	3.5 (6–1.25)	4 (7–2)	0.558
Bladder score	0 (0–0)	0 (0–0)	0.295
Pupillomotor score	0 (1.15–0)	0.33 (1.33–0)	0.375
Total CART score	0 (0–0)	1 (2–1)*	<0.001

*Highly significant post-COVID-19 effect at 5% level of significance. IQR: Q3–Q1. COMPASS=Composite Autonomic Symptom Score, CART=Cardiac autonomic reflex test, IQR=Interquartile range, GIT=Gastrointestinal, COVID-19=Coronavirus disease 2019

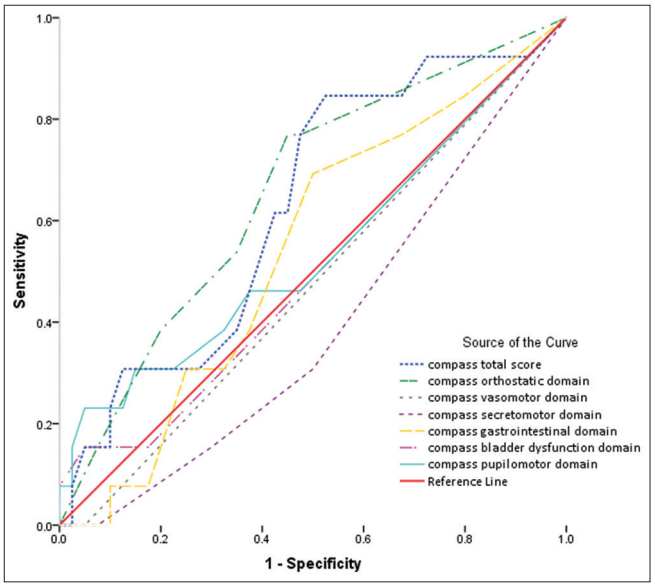

Figure 2: Receiver operating characteristic curves for COMPASS-31 total score and its subdomains in post-COVID-19 cases. COMPASS-31 diagnostic accuracy with an area under the receiver operating characteristic curve = 0.68 (0.54–0.82) showing significantly fair accuracy of COMPASS (P = 0.021). ROC = Receiver operating characteristic, COMPASS 31= Composite Autonomic Symptom Score 31

Table 2: Distribution of median scores for heart rate variability and cardiovascular autonomic reflex tests among postcoronavirus disease 2019 subjects with and without cardiovascular autonomic dysfunction

HRV and CARTs	No autonomic dysfunction (*n*=15) Median (IQR)	Autonomic dysfunction (*n*=13) Median (IQR)	*P*-value
Age (years)	23.0 (24.0–19.0)	23 (28–21)	0.285
BMI (kg/m^2)	25.9 (29.9–23.0)	26.6 (27.0–22.1)	0.544
ARR (ms)	756 (891–707)	768 (925–717)	0.695
SDRR (ms)	45.8 (55.9–35.9)	50.5 (70.9–43.0)	0.222
AR (bpm)	79.5 (85.4–67.7)	78.7 (84.1–67.9)	0.765
RMSSD (ms)	36.2 (42.4–24.5)	40.8 (60.9–26.5)	0.394
pRRx (%)	10.2 (23.7–3.9)	12.1 (27.0–2.6)	0.982
SD1 (ms)	25.6 (30.0–17.3)	28.8 (43.1–18.7)	0.420
SD2 (ms)	62.0 (73.2–48.0)	63.7 (93.8–52.9)	0.300
TP (ms^2)	1449 (3443–1003)	2604 (5394–1285)	0.189
LF (ms^2)	647.2 (1261–287)	1054 (1649–357)	0.475
HF (ms^2)	511 (1183–227)	564 (1251–197)	0.908
LF/HF	652 (1327–359)	997 (2455–476)	0.205
CARTs			
Sympathetic score	1 (1–0)	2 (2–1)*	<0.001
Parasympathetic score	0 (0–0)	1 (1–0)*	0.003
Total CART score	1 (1–0)	2 (3–2)*	<0.001

*Highly significant at 5% level of significance. IQR=Q3–Q1. CART=Cardiac autonomic reflex test, HRV=Heart rate variability, BMI=Body mass index, ARR=Average RR interval, SDRR=Standard deviation of RR interval, AR=Average rate, RMSSD=Root mean square of successive differences, *p*RRx=Percentage of successive RR intervals that are >50 ms different from the previous RR interval, SD1=SD 1, SD2=SD 2, TP=Total power, LF=Low-frequency power, HF=High-frequency power, LF/HF=Ratio of low-frequency power to high-frequency power, IQR=Interquartile range

Table 3: Predictive validity of Composite Autonomic Symptom Score-31 based on gold standard (cardiac autonomic reflex test score ≥2)

	COMPASS-31					
Cutoff points	Sensitivity %	Specificity (%)	PPV %	NPV %	LR+	LR–
>6.5	92.3	33.6	29.0	93.7	1.39	0.23
>11.5	84.6	52.2	34.3	92.0	1.77	0.30
>12.5	76.9	55.8	33.9	89.1	1.74	0.56
>14.5	61.5	60.5	31.5	84.2	1.56	0.64
>23.5	30.8	88.4	44.0	81.2	2.66	0.78
>26.0	23.1	90.7	42.3	78.0	2.48	0.85
>31.5	15.4	95.3	49.2	79.2	3.28	0.89

Prevalence (*P*=22.8%) of positive for CARTs ≥2. COMPASS=Composite Autonomic Symptom Score, CART=Cardiac autonomic reflex test, PPV=Positive predictive value, NPV=Negative predictive value, LR−=Negative likelihood ratio, LR+=Positive likelihood ratio

values of sensitivity and specificity, 61.5% and 60.5%, respectively, were seen at cutoff point >14.5, and PPV and NPV were 31.5% and 84.2%, respectively. The highest specificity value (95.3%) was seen on cutoff point >31.5; however, the value of sensitivity was only 15.4%, whereas PPV and NPV were 49.2% and 79.2%, respectively.

For post-COVID-19 groups, the diagnostic values of subdomains of COMPASS, including orthostatic, secretomotor, vasomotor, GIT, bladder dysfunction, and pupillomotor domains, were not acceptable with the area under ROC curve, 0.530 (P = 0.790), 0.429 (P = 0.528), 0.346 (P = 0.174), 0.522 (P = 0.846), 0.453 (P = 0.680), and 0.50 (P = 0.999), respectively [Figure 2]. Nonsignificant and weak correlations between CARTs, HRV parameters, and COMPASS scores were found, as shown in Table 4.

Discussion

Autonomic dysfunction is one of the possible disabling sequelae of acute COVID-19. Many post-COVID-19 patients experienced a group of debilitating clinical features: palpitations, dyspnea, orthostatic intolerance, and chest pain that remained for several weeks or more following acute infection.[5,25] The present study showed that 3–8 months after the acute infection, post-COVID-19 patients had significantly high median total scores on COMPASS-31 compared to the control group, with prominent OH. This indicates the significance of evaluating and monitoring autonomic functions as possible long-term complications of COVID-19.

Dysfunction of ANS during the phase of acute illness of COVID-19 infection with predominant symptoms of OH, secretomotor, and GIT symptoms has been

Table 4: Correlation between Composite Autonomic Symptom Score-31 score with cardiac autonomic reflex test and baseline heart rate variability

Variables	CART score		COMPASS total score	
	r_s	Significant (two-tailed)	r_s	Significant (two-tailed)
COMPASS total score	0.231	0.086	/	/
ARR (ms)	−0.010	0.942	0.051	0.710
SDRR (ms)	−0.178	0.184	0.004	0.976
AR (bpm)	0.012	0.931	−0.044	0.748
RMSSD (ms)	−0.135	0.316	−0.013	0.925
pRRx (%)	−0.111	0.411	−0.002	0.987
SD1 (ms)	−0.138	0.304	−0.014	0.916
SD2 (ms)	−0.175	0.193	0.008	0.953
TP (ms^2)	−0.135	0.318	0.009	0.945
LF (ms^2)	−0.194	0.148	0.025	0.857
HF (ms^2)	−0.154	0.253	−0.020	0.882
LF/HF	−0.012	0.931	−0.020	0.882

Nonsignificant correlation (r_s: Spearmen's rank correlation coefficient) at $P \leq 0.05$. COMPASS=Composite Autonomic Symptom Score, CART=Cardiac autonomic reflex test, ARR=Average RR interval, SDRR=Standard deviation of RR interval, AR=Average rate, RMSSD=Root mean square of successive differences, *p*RRx=Percentage of successive RR intervals that are >50 ms different from the previous RR interval, SD1=SD 1, SD2=SD 2, TP=Total power, LF=Low-frequency power, HF=High-frequency power, LF/HF=Ratio of low-frequency power to high-frequency power

documented.[26,27] However, only a few studies have been published using COMPASS-31 to evaluate dysautonomia at different time intervals following the acute phase of COVID-19 infection. A recent research with post-COVID-19 patients between 1 and 9 months from the onset of the disease showed a median COMPASS-31 score of 17.6 (6.9–31.4), with the prime affected subdomain being orthostatic intolerance, which is in line with our findings.[4] In another large cross-sectional online survey, about 66% of post-COVID-19 patients showed COMPASS-31 score >20, indicative of moderate-to-severe autonomic dysfunction. However, the majority of the study population (45.9%) was 46–65 years old, which could shift COMPASS toward a higher score.[28] Furthermore, a very recent study that assessed 14 long COVID-19 patients 13–28 months after the acute infection showed median COMPASS scores of 31.[29] Since a positive correlation has been identified between the duration of long-COVID-19 and COMPASS-31 score, this relatively high score reported in the above study could be explained by the longer period of time after the onset of the disease.[7]

The most affected domain of COMPASS reported in our study was orthostatic intolerance. Other domains also showed higher scores in post-COVID-19 patients but without reaching the level of significance. This agrees with many similar studies with some minor disparities. Recently, a case series reported pronounced symptoms of OH, fatigue, and reduced tolerance to physical activity in patients recovering from COVID-19, and objective autonomic testing also revealed postural hypotension and postural orthostatic tachycardia syndrome (PoTS).[25] In addition, Buoite *et al*., also found marked postural hypotension using COMPASS score with significant disturbances that affect other COMPASS domains including GIT, urinary, and pupillomotor.[4] It is noteworthy that OH as assessed by CARTs was also reported in about 39.3% of post-COVID-19 subjects 3–8 months after the onset of the acute infection.[8]

Studies evaluating post-COVID-19 autonomic function using COMPASS have shown a wide range of autonomic disturbances ranging from isolated OH to the involvement of most COMPASS domains.[5,30,31] These discrepancies could be attributed to the difference in the duration of post-COVID-19 at the time of autonomic function assessment,[7] difference in the gravity of the acute illness,[2] and the part of the autonomic system mostly affected by COVID-19 infection.[32]

Most of the cardiac autonomic function is controlled by the vagus nerve. Asarcikli *et al*. found parasympathetic overtones and increased HRV in post-COVID-19 patients. This autonomic imbalance may explain the marked postural hypotension that occurs in the post-COVID-19 period.[33] Autonomic neuropathy was found to affect the vagus nerve early in comparison to other parts of the autonomic system.[34] Its involvement could, therefore, influence the cardiac autonomic activity earlier than other autonomic functions, which could explain why other domains in COMPASS did not show significant impairment at the time of assessment in some studies such as the current study.

Despite the scarcity of studies of COVID-19-related dysautonomia, many mechanisms have been postulated to explain the neurological involvement in COVID-19. Most have focused on the immune-mediated response during or following the acute phase of COVID-19 infection.[25] Immune response may influence autonomic function, autoantibodies such as anti-GD1b and anti-Caspr2, and autoantibodies against alpha- and beta-adrenoceptors, and muscarinic receptors have been associated with OH and PoTS.[35,36] In addition, a case series of 20 post-COVID-19 patients with PoTS and other manifestations of dysautonomia showed elevated autoimmune inflammatory markers.[31]

The ANS and the immune response associated with COVID-19 infection have a bidirectional relationship. It is well documented that sympathetic stimulation causes pro-inflammatory cytokine storm observed in COVID-19 illness.[37] On the other hand, the COVID-19 infection itself or its triggered immune response can induce a wide range of neurological disturbances including the effect

on the autonomic system.[35] Furthermore, an association of hand grip strength with some inflammatory mediators (interleukin-3 and C-reactive protein) has been documented in post-COVID-19 syndrome, which might signify low-level inflammation as a potential pathophysiological mechanism of autonomic dysfunction.[38]

We reported a cutoff score of > 12.5 of COMPASS-31 with maximum accuracy in detecting autonomic dysfunction in post-COVID-19 patients with sensitivity = 76.9, specificity = 55.8, and area under the curve = 0.497. To the best of our knowledge, there are no studies on the diagnostic accuracy of COMPASS-31 in post-COVID-19 patients. However, a comparable accuracy of COMPASS-31 has been reported with different neurological diseases. A cutoff score of 13.25 signifies high sensitivity (92.6%) and moderate specificity (51.2%), with an area under the curve of 0.765 in detecting dysautonomia in Parkinson's disease.[21] COMPASS-31 score also demonstrated a fair diagnostic value with a cutoff score of 19.5 (area under curve = 0.816, sensitivity = 67.4%, and specificity of 83.3%) for diagnosis of CV dysautonomia in type 2 diabetic cases.[39]

One of the limitations of the study was that we could not assess the progression of autonomic dysfunction using COMPASS-31 because of the cross-sectional design of the study.

Conclusion

As far as we know, this is a pioneering detailed investigation that explored the diagnostic accuracy of COMPASS-31 as a subjective screening tool for the evaluation of autonomic dysfunction in post-COVID-19 patients. Objective tests such as CARTs and HRV are sophisticated, time-consuming, and difficult to conduct in clinical settings. Thus, COMPASS-31 could be an easy-to-administer screening tool for autonomic dysfunction in post-COVID-19 cases with acceptable sensitivity and specificity. It is recommended that further longitudinal studies should be conducted to assess the usefulness of COMPASS-31 at different time intervals following acute COVID-19 infection.

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Conflicts of interest
There are no conflicts of interest.

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