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Association between COVID-19 exposure and autonomic nervous system dysfunction in apparently healthy adults: an observational study

A.M. OSAILAN[1], M. BATARFA[1], Z. ALDOSARI[1], A. ALGHAMDI[1], F. ALQAHTANI[1], M. ALABDULLAH[1], R.K. ELNAGGAR[1,2]

[1]Department of Health and Rehabilitation Sciences, College of Applied Medical Sciences, Prince Sattam Bin Abdulaziz University, Alkharj, Saudi Arabia
[2]Department of Physical Therapy for Pediatrics, Faculty of Physical Therapy, Cairo University, Giza, Egypt

Abstract. – OBJECTIVE: Coronavirus disease (COVID-19) is a respiratory disease caused by SARS-CoV-2, which complicates the functioning of multiple systems, including the autonomic nervous system (ANS), causing dysautonomia. Investigation of dysautonomia and its association with exposure to COVID-19 is limited in healthy people. Therefore, the study aimed to investigate the relationship between ANS dysautonomia and coronavirus exposure and compare the ANS function between exposed and non-exposed to COVID-19.

SUBJECTS AND METHODS: The study involved 141 participants, with a mean age of 18-24.5 years, 83% male (49.6% exposed to COVID-19). The ANS was measured using a composite autonomic symptom scale (COMPASS-31) questionnaire and heart rate variability (HRV) using photoplethysmography. Exposure to COVID-19 was investigated using two national health-status tracking and COVID-19 exposure applications, "Sehhaty" and "Twakkalna".

RESULTS: A significantly inverse weak correlation between COMPASS-31 scores and COVID-19 exposure (r=-0.2, *p*=0.04). No significant association was found between HRV and COVID-19 exposure. COMPASS-31 scores for the exposed group (median=15, n=70) were significantly higher than those for the non-exposed group (median=12, n=71), U=1,913.5, *p*=0.03. Height (r=-0.4, *p*=0.002) and gender (r=0.3, *p*=0.001) were moderately correlated with COMPASS-31 among the exposed group.

CONCLUSIONS: These findings indicated that exposure to COVID-19 was associated with poorer ANS scores measured via COMPASS-31. Additionally, exposure to COVID-19 resulted in higher dysautonomia symptoms than non-exposed. Height and gender differences contribute to the severity of dysautonomia among exposed people.

Key Words:
Autonomic nervous system, Heart rate variability, Photoplethysmography, Coronavirus, Composite autonomic symptom scale.

Introduction

COVID-19 has been one of the most contiguous diseases in recent history, resulting in an unprecedented health crisis with over 600 million cases accumulating over 6.5 million deaths[1]. The symptoms are highly diverse and can range from asymptomatic infection to pneumonia, which can present life-threatening consequences. Despite the common symptoms of the disease, including shortness of breath, cough, pneumonia, and anosmia[2], COVID-19 can also cause critical changes in other systems, including the cardiovascular system (e.g., hypertension, arrhythmia, and myocarditis)[3], the musculoskeletal (e.g., arthritis, muscle weakness, and tendinopathy)[4], and the autonomic nervous system (e.g., lightheadedness, orthostatic headache, and burning pain)[5].

Autonomic nervous system (ANS) imbalance is a neurological condition commonly known as dysautonomia, which affects the functioning of multiple systems, including the heart, sweat gland, bladder, pupils, intestines, and other autonomic functions[6]. The influence of dysautonomia is manifested in both arms of the autonomic nervous system, including the sympathetic (SNS) and parasympathetic nervous system (PSN), leading to abnormal autonomic responses, including resting tachycardia, postural hypotension, excessive sweating, exercise intolerance, urinary and gastrointestinal symptoms[7,8].

Corresponding Author: Ahmad Osailan, Ph.D; e-mail: ahmad.osailan@gmail.com; a.osailan@psau.edu.sa

Measurement of the ANS profile can be performed in various ways ranging from a questionnaire, such as the Composite Autonomic Symptom Score (COMPASS-31)[9], to laboratory-based non-invasive tests, such as cardiovascular autonomic reflex tests[10], heart rate recovery (HRR)[11], and heart rate variability (HRV)[12]. COMPASS-31 is a valid and simple tool for assessing dysautonomia[9]. Other tests like cardiovascular autonomic reflex and HRR require laboratory setup and advanced lab-based equipment. Recent technological advances[13,14] allowed photoplethysmography (PPG) to use smartphone cameras as a valid and reliable method of measuring HRV. Photoplethysmography (PPG) is a simple portable optical method used to detect blood volume changes in the micro-vascular bed of the index finger to track the heartbeat.

In addition to the traditional symptoms of COVID-19, extra-pulmonary manifestations such as heightened SNS activity may result from post-exposure to COVID-19 through changes in blood gases, increased inflammatory markers, angiotensin-converting enzyme 1&2 imbalance[8,15,16]. Early assessment of dysautonomia and exploring the relationship with exposure to COVID-19 may provide early insight into the spectrum of the condition[8]. The rationale for linking dysautonomia following COVID-19 was suggested due to the role of immune response on ANS due to the viral infection resulting from COVID-19, which can be manifested by orthostatic intolerance and postural tachycardia[17]. It must be noted that other types of viral infection may cause acute dysautonomia, like retroviruses HIV, herpes viruses, flaviviruses, enteroviruses, and lyssaviruses, which share similar dysautonomia manifestations[18]. It is important to note that these viral infections impact the ANS in different ways, and the severity of the dysautonomia can vary widely among individuals. Thus, recognizing the association between certain viral infections and dysautonomia is crucial to identifying appropriate management.

Investigation of dysautonomia and its association with exposure to COVID-19 is limited in literature. In a longitudinal study[19] among 34 consecutive patients admitted to the hospital due to COVID-19, it was found that 24-hour HRV was associated with the severity of the disease. Another prospective observational study[20] using the COMPASS-31 questionnaire among 180 participants with confirmed COVID-19 with and without neurological symptoms showed a higher COMPASS-31 score, indicating dysautonomia, in those with neurological symptoms such as orthostatic hypotension. Furthermore, a prospective study[21] investigated the long-term impact of COVID-19 on autonomic function *via* measurement of HRR and metabolism, involving 65 patients exposed to COVID-19 and 57 controls. The results showed higher instances of blunted HRR in the COVID-19 group, suggesting dysautonomia and elevated levels of serological cardiovascular risk factors, indicating an increased risk of future cardiovascular diseases post-COVID-19. Information about the relationship between dysautonomia and exposure to COVID-19 was not investigated. Identifying the association between dysautonomia and exposure to COVID-19 may increase awareness about the complications that may arise post-COVID-19. Therefore, the study aimed to explore the relationship between ANS, using COMPASS-31 and PPG HRV, and exposure to COVID-19. The secondary aim was to compare the ANS between people exposed and non-exposed to COVID-19.

Subjects and Methods

One hundred and sixty-two participants from the Riyadh region, Saudi Arabia, volunteered to participate in the study. The data was collected between 2022 and mid-2023. Participants were approached in multiple locations (i.e., University campus, lounging area) for only one set of measurements. Inclusion criteria include adults above 18 years old. Participants must have had either "Sehhaty", a unified platform provided by the Ministry of Health in Saudi Arabia to track health status and exposure to COVID-19, or "Tawakkalna", an official Saudi Contact tracing application provided by the Ministry of Health in Saudi Arabia to track health status and exposure to COVID-19. Exclusion criteria included individuals with diseases that could affect ANS profile readings, such as cardiovascular diseases (hypertension, ischemic heart disease), chronic respiratory diseases (chronic obstructive pulmonary disease), and neurological diseases (mild cognitive disease, Alzheimer's). Additionally, participants with skin-poor signal quality on PPG were also excluded. The study was conducted according to the guidelines of the Declaration of Helsinki and its latest amendments and approved by the Ethical Committee at Prince Sattam bin Abdulaziz University (RHPT/023/010).

Procedure

Participants were invited verbally to volunteer to study on multiple locations at the University campus or outside the campus (lounging areas) and were given written information about the study. Upon acceptance to participate, informed consent was provided and then the investigator filled out the assessment sheet – a portable Stadiometer measured height to the nearest 0.5 cm (Holtain Ltd, Crosswell, UK). A portable electronic zeroed scale measured weight while standing (Wedderburn, Southampton, UK). During the assessment, participants were seated with their backs supported and arms rested comfortably. After filling out the assessment form, the COMPASS-31 questionnaire was filled out, and information about COVID-19 status was obtained from the "Sehhaty/Tawakkalna" smartphone application. Then, HRV was measured *via* the investigator's smartphone using the application "HRV4training" for 5 minutes. The PPG data was saved immediately on a Microsoft Excel spreadsheet.

Outcome Measures

Compass-31

COMPASS-31[22] is a valid quantitative measure of the ANS, with 31 questions evaluating six domains of autonomic system functions. These domain functions include orthostatic intolerance (total score of 40), vasomotor (total score of 5), secretomotor (total score of 15), gastrointestinal (total score of 25), bladder (total score of 10), and pupillomotor functions (total score of 5). The total score ranges from 0-100, with higher scores indicating worse ANS function.

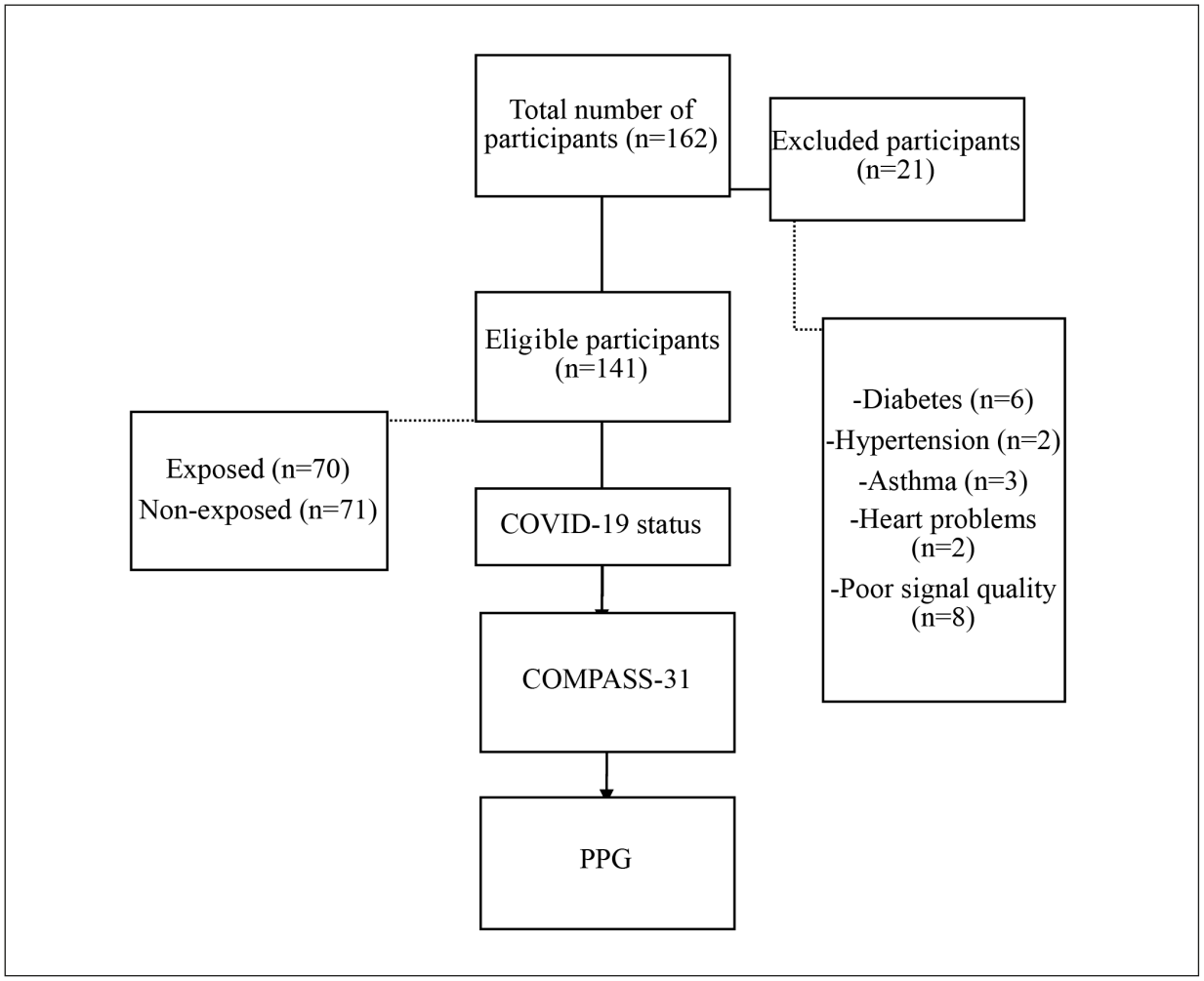

Figure 1. Flow diagram of the procedure of the study.

HRV

PPG was used to obtain HRV measurements using the smartphone application "HRV4training" (available at: http://www.hrv4training.com/). The application is a validated method[14] that measures HRV by placing the base of the index finger on the camera lens for five minutes. Alcohol swabs were applied to sanitize the camera lens and the participant's finger. The application saved the data and then exported to a Microsoft Excel spreadsheet. The measurement was done while the participant was comfortably seated upright. Frequency domain results of 5-min HRV parameters were used, including low frequency (LF), high frequency (HF), and LF/HF ratio to measure cardiac autonomic control.

COVID-19 status

COVID-19 status was acquired by using the Ministry of Health's phone applications "Sehhaty" or "Tawakkalna", which track every citizen's COVID-19 status based on a positive polymerase chain reaction (PCR) test, or serologic test performed at one of the hospitals or polyclinics governed by the Ministry of Health. The data collected from the application include number of vaccine doses, type of doses, frequency of COVID-19 exposure, and date of last exposure.

Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences (version 27, IBM Corp., Armonk, NY, USA). The normal distribution of the data was examined using Kolmogorov-Smirnov's test. To investigate the relationship between COVID-19 exposure and ANS imbalance using Spearman's correlation for skewed variables. The Mann-Whitney test was used to compare differences in the study's main outcome measures, including COMPASS-31 and HRV variables, between two independent samples (exposed *vs.* non-exposed group to COVID-19). The level of significance was set at $p \leq 0.05$.

Results

Figure 1 shows the flow chart of the study procedure. Table I presents the demographic characteristics of the participants (n=141). 49.6% of the sample was exposed to COVID-19.

Table I. Demographic characteristics.

Variable	Value
Age (years)	20 (18-24.5)
Gender	117 (83%) males, 24 (17%) females
Height (m)	1.71 (1.65-1.76)
Weight (kg)	69 (56-85)
BMI	23.4 (20.3-27.8)
Level of PA: Do you exercise?	
Yes	51 (36.2%)
No	90 (63.8%)
Type of exercise	
Walking	29 (20.6%)
Cycling	1 (0.7%)
Gym	12 (8.5%)
Other	9 (6.4%)
Duration of physical activity	
Less than 30 minutes	5 (3.5%)
30 minutes	19 (13.5%)
More than 30 minutes	27 (19.1%)
Covid-19 status	
Exposed	70 (49.6%)
Non-exposed	71 (50.4%)
Vaccination status	
Vaccinated	139
Non-vaccinated	2
Type of vaccine	
Pfizer	96 (68.1%)
AstraZeneca	7 (5%)
Moderna	1 (0.7%)
Pfizer and AstraZeneca	17 (12.1%)
Pfizer and Moderna	11 (7.8%)
Pfizer, AstraZeneca, and Moderna	7 (5%)
The autonomic nervous system measures	
COMPASS-31	13 (8-21.5)
Orthostatic	2 (0-4)
Vasomotor	0 (0-0)
Secretomotor	1 (0-2)
Gastrointestinal	5 (2-9)
Bladder	0 (0-0)
Pupilmotor	5 (3-8)
HR	86 (78-95)
LF	0.2±0.08
HF	0.19±0.08
LF/HF	1.11 (0.9-1.3)

Values are presented as mean and standard deviation or median (25^{th}-75^{th} percentile) as appropriate. BMI: body mass index, HR: heart rate, LF: low frequency, HF: high frequency, LF/HF: low frequency to high-frequency ratio.

Correlations between COMPASS-31, HRV, and exposure to COVID-19

Table II shows the relationship between COMPASS-31, HRV, and status of COVID-19. The only variable significantly and inversely correlated with exposure to COVID-19 was the COMPASS-31 score (r=-0.2, p=0.04). The direction of association between COMPASS-31 and exposure

Table II. Spearman's correlation between ANS measures and the status of COVID-19.

Variable	*r* value	*p*-value
Compass Score	-0.2	0.04
HR (bpm)	-0.1	0.5
HF (Hz)	0.03	0.7
LF (Hz)	0.1	0.4
LF/HF ratio	0.05	0.5

HR: heart rate, LF: low frequency, HF: high frequency, LF/HF: low frequency to high-frequency ratio.

to COVID-19 is shown in Figure 2, which indicates that those exposed have higher scores in COMPASS-31.

Mann-Whitney test indicated that Compass scores for the exposed group (Median=15, n=70) were significantly higher than scores for the non-exposed group (Median=12, n=71), U=1,913.5, p=0.03. No significant difference was found between the two groups in HRV parameters (Table III).

Correlation between COMPASS-31 and demographic characteristics among those exposed to COVID-19

The correlation between COMPASS-31 scores and demographic characteristics in participants exposed to COVID-19 is shown in Table IV. Height (r=-0.37, p=0.002) (Figure 3) was moderately and inversely correlated with COMPASS-31, whereas gender (r=0.30, p=0.01) was significantly correlated with COMPASS-31 scores. The direction of association between COMPASS-31 and gender is shown in Figure 4, which indicates that female participants have higher scores in COMPASS-31.

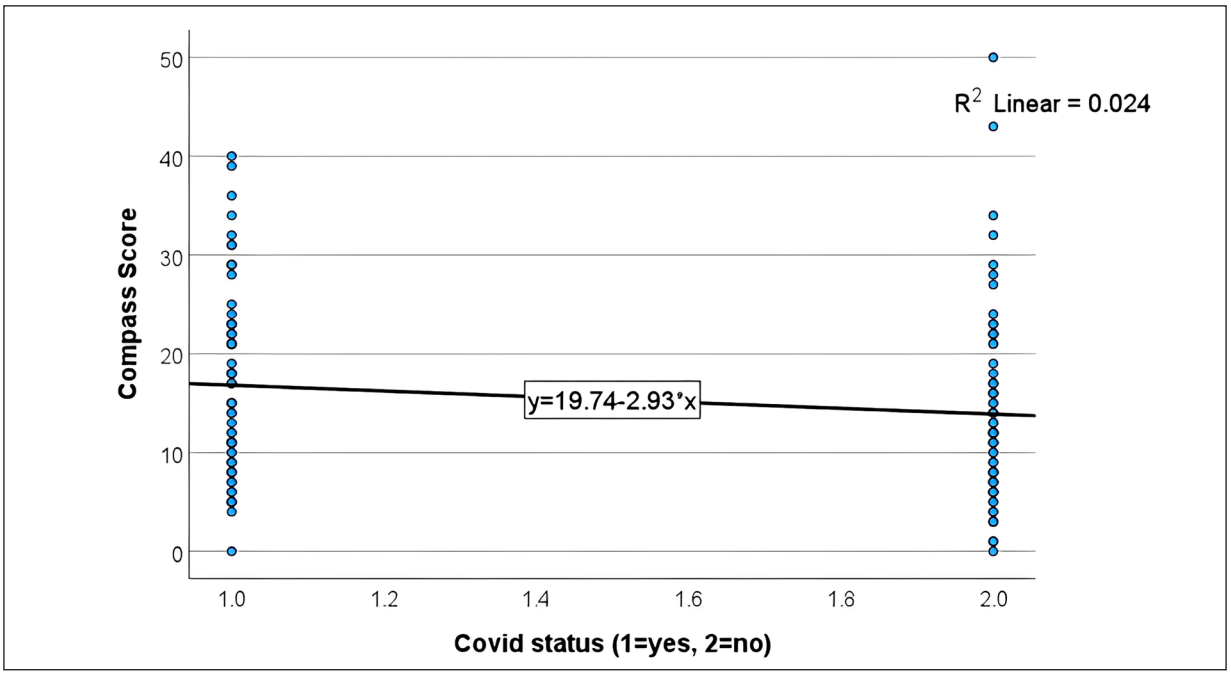

Figure 2. Scatterplot of the Relationship between COMPASS-31 (scale) COVID-19 status (nominal).

Table III. Comparison in ANS variable between people exposed *vs*. non-exposed to COVID-19.

Variable	Exposed median (n=70)	Non-exposed median (n=71)	U value	*p*-value
Compass score	15	12	1,913.5	0.03
HR (bpm)	87	84	2,209.5	0.4
LF (Hz)	0.2	0.2	2,263	0.5
HF (Hz)	0.2	0.2	2,309.5	0.7
LF/HF ratio	1.1	1.1	2,310	0.7

HR: heart rate, LF: low frequency, HF: high frequency, LF/HF: low frequency to high-frequency ratio.

Table IV. Spearman's correlation between Compass Score and demographic characteristics in people exposed to COVID-19

Variable	*r* value	*p*-value
Age	0.17	0.15
Height	-0.36	0.002
Weight	-0.19	0.12
BMI	-0.001	0.99
Gender	0.31	0.001

BMI: body mass index.

Discussion

The current study explored the relationship between ANS, using COMPASS-31 and PPG HRV, and exposure to COVID-19 and compared ANS between people exposed and non-exposed to COVID-19. The results showed an association between COMPASS-31 scores and exposure to COVID-19, indicating that people exposed to COVID-19 have higher COMPASS-31 scores. Additionally, COMPASS-31 was the only ANS measure that was significantly different between people exposed and non-exposed to COVID-19. The results may indicate a potential impact of viral exposure to the ANS. Furthermore, height was inversely associated with COMPASS-31 among exposed people, and exposed females had higher COMPASS-31 scores. These results open avenues for further longitudinal studies into the interplay between COVID-19 and the ANS, shedding light on potential physiological mechanisms underlying COVID-19's impact on ANS.

A significant, albeit weak, association was found between COMPASS-31 scores and exposure to COVID-19 in the current study. This suggests that individuals exposed to the virus might experience a deterioration in ANS, as indicated by higher COMPASS-31 scores. This aligns with the findings of Furlanis et al[23], who reported alterations in the ANS measured by the COMPASS-31 score in post-COVID-19 patients (n=180, 70.6% females, age 51±13 years) among those with (n=97) and without (n=83) neurological symptoms. Additionally, a study[24] compared ANS functioning using COMPASS-31 between non-critically ill (n=38) (with acute COVID-19) and healthy people (n=38). The study reported higher COMPASS-31 scores among the non-critically ill group than the healthy group. Dani et al[17] shed light on autonomic dysfunction in the context of long COVID-19, emphasizing the enduring effects the virus might have on the ANS. Although based on apparently healthy adults, our

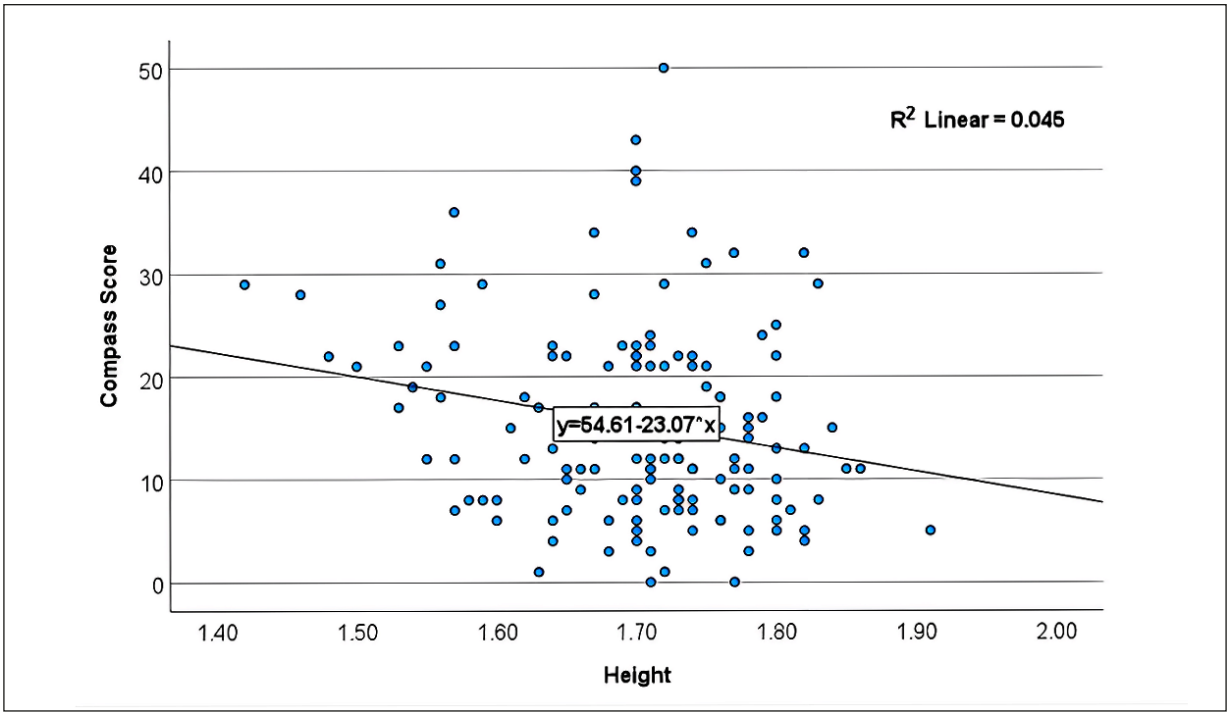

Figure 3. Correlation between COMPASS-31 and participants' height.

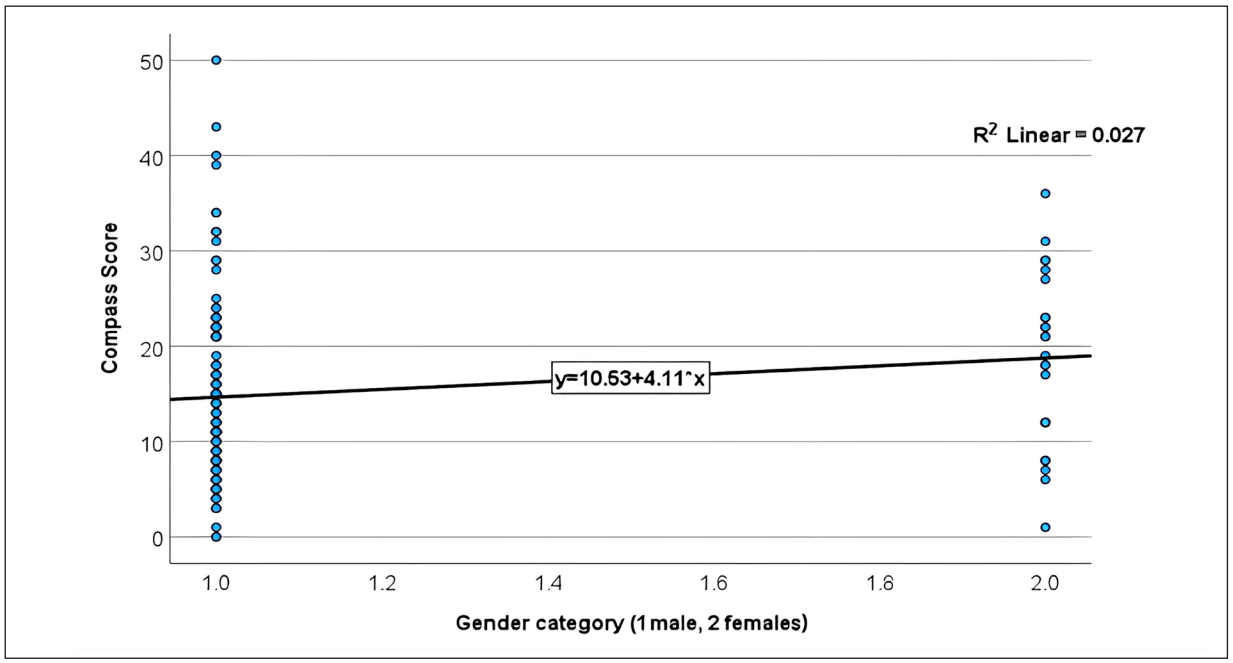

Figure 4. Correlation between COMPASS-31 scores and participants' gender.

findings underscore the importance of monitoring autonomic symptoms even in individuals who might not manifest severe clinical symptoms of the disease.

Interestingly, our study found no significant association between HRV and COVID-19 exposure. HRV is a commonly utilized metric for assessing autonomic function, with alterations in HRV often indicating disruptions in autonomic balance. There are possible reasons for the absence of a significant association in the current study. Firstly, this might be due to the complexity and multifaceted nature of COVID-19's effects on the ANS. Secondly, COVID-19's impact on the ANS might not manifest uniformly across individuals with different age groups or different stages of exposure. It is also worth noting that PPG has limitations[13,14], which might influence the accuracy and sensitivity of HRV measurements. When the association between HRV and COVID-19 was reported, the method utilized to measure HRV was the gold standard (electrocardiograph) using time domain analysis (24 consecutive hours) among older age groups compared to the current study[19]. These variations in methodology and participants may partially explain the lack of association between HRV and COVID-19 exposure.

Compared to the exposed and non-exposed groups, the exposed group to COVID-19 had elevated COMPASS-31 scores, implying potential disturbances in ANS function or heightened autonomic symptoms after COVID-19 exposure. This aligns with the findings of Furlanis et al[22], who reported ANS reduction using COMPASS-31 in post-COVID-19 patients. However, our study found no significant difference between the exposed and non-exposed groups using HRV. This discrepancy might stem from the inherent limitations of using PPG for HRV measurements. Another plausible explanation is that the age of participants, who were younger than those in prior studies, could explain the variations in results. The adaptation of the heart and its response is mainly carried out *via* multiple regulatory systems, which are strongly associated with age and pathological conditions[25,26]. The younger age bracket of our participants might have diminished HRV's sensitivity in detecting significant ANS alterations among the exposed individuals.

Another intriguing finding was the moderate inverse correlation between height and COMPASS-31 scores among individuals exposed to COVID-19. While the underlying mechanisms for this association remain unclear, further investigation into potential physiological factors that might predispose shorter individuals to more significant autonomic disruptions upon exposure to COVID-19 is necessary. Differences in blood vol-

ume and circulatory dynamics are linked intrinsically with height. This hemodynamic variation might modulate how the immune response or the virus influences ANS[27]. The inverse relationship reported might suggest fewer manifestations of reduced ANS among taller people, potentially due to better adaptive mechanisms in their vascular system[28].

Although most participants were males, the findings showed that females reported higher COMPASS-31 scores. Several studies[29-31] on COVID-19 have highlighted varying male and female responses. Factors that might contribute to these differences may include hormonal influence[29], immune response variations[30], and genetic factors[31].

All the participants in the current study were healthy, and those with comorbidities that might interfere with the outcome measures utilized were excluded. This is due to the complexity and diagnostic challenges that might intersect with other diseases. For example, a case report of an 82-year-old female diagnosed with Granulomatosis with Polyangiitis (GPA), who initially tested false positive for COVID-19 based on an antibody test immunoglobulin (Igm), yet on multiple reverse transcription polymerase chain reaction (RT-PCR) tests it was negative for COVID-19[32]. This may highlight the potential for cross-reactivity in COVID-19 antibody tests, especially in patients with autoimmune diseases. This case emphasizes the importance of thorough clinical evaluation to avoid delays in proper healthcare.

Elevated COMPASS-31 scores among exposed individuals provided additional evidence supporting the notion that there might be a correlation between COVID-19 exposure and ANS dysfunction. The current study's findings support the idea that there are long-term impacts of COVID-19 on autonomous function, which is in line with the findings of previous studies[17,23], which reported similar findings in post-COVID-19 patients.

Additionally, the study's differentiation between the effects on COMPASS-31 scores and the lack of association with HRV measured *via* PPG contributes to the nuanced understanding of the virus's impact on the ANS. It may suggest that COMPASS-31, albeit a subjective measure, maybe a more sensitive measure of ANS dysfunction related to COVID-19 than PPG-derived HRV. This may be due to the parameters measured in COMPASS-31, which include multiple body systems rather than focusing only on the variation of the heartbeat. The study also highlights the need for further research into other effective methods for assessing autonomic function in longitudinal research to fully understand the progression of ANS dysfunction following COVID-19 exposure.

It is also noteworthy that the association between height and COMPASS-31 scores among COVID-19-exposed individuals, along with gender differences in COMPASS-31 scores, open new avenues for investigating the physiological and possibly genetic factors influencing the severity of ANS disruptions post-COVID-19 exposure. Therefore, future research is needed to investigate the long-term impacts of COVID-19 on ANS.

Limitations

This study is not without limitations. Firstly, the cross-sectional design restricts causality between COVID-19 exposure and autonomic symptoms. Longitudinal studies are warranted to discern the progression of ANS disruptions post-COVID exposure. Furthermore, although innovative, utilizing photoplethysmography for HRV measurements might not offer the same precision as traditional electrocardiography, potentially affecting the robustness of our HRV findings. The study's demographic was predominantly male (80.9%), which could limit the generalizability of the results to a broader population.

Conclusions

The study showed that exposure to the virus is linked to reduced ANS as manifested by elevated COMPASS-31 scores. The observation between height and COMPASS-31 scores, along with the gender differences, further highlights the influences of these factors on the severity of dysautonomia. Future longitudinal studies are needed to validate and expand the observation of the current study.

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of Interest

The authors declare they have no conflict of interest.

Authors' Contributions

A. Osailan created and designed the study. M. Batarfa, Z. Aldosari, A. Alghamdi, F. Alqahtani, and M. Abdullah contributed to the data acquisition and initial manuscript draft. A. Osailan performed the final analysis and interpretation of data and wrote and edited the manuscript. R. Elnaggar and revised the manuscript. All the authors approved the final version of the manuscript.

ORCID ID

Ahmad M. Osailan: 0000-0003-0124-4739
Ragab K. Elnaggar: 0000-0001-5080-702X

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Ethics Approval

The study was conducted according to the guidelines of the Declaration of Helsinki and its latest amendments and approved by the Ethical Committee at Prince Sattam bin Abdulaziz University (RHPT/023/010) (08/04/2022).

Informed Consent

Written informed consent was obtained from the participants included in the study.

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