Vagus Nerve Dysfunction in the Post-COVID-19 Condition

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RESEARCH IN CONTEXT

- **Evidence before this study**

The post-COVID-19 condition (PCC) or “Long-COVID" is a major global public health and medical challenge affecting at least 5-10% individuals who survive acute SARS-CoV-2 infection. The clinical management of PCC is limited by the lack of effective treatments and the absence of objective diagnostic biomarkers. Clinical trials must largely rely on clinical PCC definitions like WHO’s, which are imprecise. A better understanding of PCC pathogenesis is urgently needed to develop more accurate diagnostics and better treatments. An early, persistent alteration of the Xth cranial nerve or vagus nerve, could explain a considerable number of PCC symptoms. The vagus nerve innervates the larynx, pharynx, lungs, heart and gastrointestinal tract, sites primarily affected by PCC. However, comprehensive objective evidence of vagus nerve dysfunction in subjects with PCC is lacking.

We performed a PubMed search with no language restrictions up to March 9th, 2023, with search terms “(Long COVID OR Post Covid Condition OR Post-Acute COVID-19 Syndrome) AND (vagus nerve OR dysautonomia)”, yielding 16,716 results. After adding filters for English language and search terms “(Long COVID) OR (Post Covid Condition)) AND (vagus nerve)”, and manual literature screening, relevant studies identified were 14.

The first studies described possible pathways of SARS-CoV-2 entry into the brain including transmission through the vagus nerve (May and September 2020). Another study (June 2021) suggested that infection of the vagus nerve could be a possible cause of dysfunctional brainstem/vagus nerve signaling and chronic symptoms. In 2022 a study suggested that autonomic dysfunction may contribute to PCC symptoms and described vagus atrophy and prolonged sympathetic skin response latencies. In September 2022 a study suggested that vagal underactivation may be the root cause of dysautonomia and fatigue and suggested non-invasive vagus nerve stimulation (nVNS) as a therapy for fatigue. In March 2023 a study suggested vagus nerve neuropathy as a cause of persistent chronic cough or other COVID-19 long-term effects. In May 2023 four clinical trials of nVNS in Long-COVID were registered.

- **Added value of this study**

Using a wide range of structural and functional objective measurements, this study provides consistent evidence of structural and functional alterations in various organs and body territories innervated by the vagus nerve in subjects with PCC, including the respiratory and digestive apparatus and the autonomous

innervation of the heart. The most frequent objective observations were altered dysphonia scales, reductions in maximum inspiratory pressure and diaphragm flattening, followed by reductions in esophageal-gastric-intestinal peristalsis and altered swallowing efficiency and safety. These observations are well in line with the frequently reported dysphonia, exertional dyspnea and digestive symptoms. An important result of our study was the frequent structural and functional involvement of respiratory muscles. More than 60% of subjects with PCC had reduction in maximum inspiratory pressure, often associated with flattening of one or both hemidiaphragms and significant reductions in diaphragmatic thickness and mobility. These findings suggest respiratory muscle weakness that could explain dyspnea in spite of normal lung imaging.

- **Implications of all the available evidence.**

Our findings point to a central pathogenic role of vagus nerve dysfunction in the pathophysiology of the PCC, are highly informative to systematize clinical evaluations of this syndrome, inform larger PCC cohort studies and open a first avenue of interventions to ameliorate some of the most disabling symptoms of the PCC, such as dysphagia, dyspnea and dysautonomia.

ABSTRACT

Background: The post-COVID-19 condition (PCC) is a disabling syndrome affecting 5-15% of subjects who survive COVID-19. SARS-CoV-2 mediated vagus nerve dysfunction could explain some of the PCC symptoms, including persistent dysphonia, dysphagia, dyspnea, dizziness, tachycardia, orthostatic hypotension, gastrointestinal disturbances or neurocognitive complaints.

Methods: We performed a cross-sectional pilot study in subjects with PCC with symptoms suggesting vagus nerve dysfunction (n=30) and compared them to subjects fully recovered from acute COVID-19 (n=14) and individuals never infected with SARS-CoV-2 (n=16), matched by age and sex. We evaluated the structure and function of the vagus nerve, including dysphonia, dysphagia, and dysautonomia tests, and evaluated the structure and function of respiratory muscles with vagus nerve innervation.

Findings: Participants were mostly (80%) women with median 44 years of age. Their most prevalent symptoms were cognitive dysfunction (83%), dyspnea (80%) and tachycardia (80%). Compared with COVID-19-recovered and uninfected controls, respectively, subjects with PCC were more likely to show thickening and hyperechogenic vagus nerve in neck ultrasounds (mean ± SD left vagus nerve cross-sectional area: 2.4 ± 0.97mm^2 vs. 2 ± 0.52mm^2 vs. 1.9 ± 0.73 mm^2, p=0.080), flattened diaphragmatic curve (47% vs 6% vs 14%, p=0.007), reduced esophageal peristalsis (34% vs 0% vs 21%, p=0.020), gastroesophageal reflux (34% vs 19% vs 7%, p=0.130), hiatal hernia (25% vs 0% vs 7%, p=0.050) and reduced maximal inspiratory pressure in functional respiratory tests (62% vs. 6% vs. 17%, p ≤0.001).

Interpretation: Vagus nerve dysfunction has a central pathogenic role in the pathophysiology of the post-COVID condition.

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Keywords: SARS-CoV-2; post-COVID-19 condition; persistent symptoms; vagus nerve, autonomic dysfunction

INTRODUCTION

The post-COVID-19 condition (PCC) or “Long-COVID" is a major global public health and medical challenge affecting 5-10% individuals who survive acute SARS-CoV-2 infection. Even previously, healthy, young individuals with mild or asymptomatic acute COVID-19 presentation may subsequently develop long-lasting, systemic organic damage, which causes significant disability and severe deterioration of quality of life and social functioning [1,2,3]. By the end of 2022, at least 65 million people worldwide had developed this syndrome. Numbers continue to rise as new SARS-CoV-2 variants become increasingly transmissible.

The clinical management of PCC is limited by the lack of effective treatments, but also by the absence of objective diagnostic biomarkers[4-7], which further complicates the advancement of clinical PCC science. Clinical trials must largely rely on clinical PCC definitions like WHO’s[8], which are useful, but imprecise. A better understanding of PCC pathogenesis is urgently needed to develop more accurate diagnostics and better treatments.

Among the different, possibly overlapping pathogenetic hypotheses, an early, persistent alteration of the Xth cranial nerve or vagus nerve, could explain a considerable number of PCC symptoms[9]. The vagus nerve innervates the larynx, pharynx, lungs, heart and gastrointestinal tract, sites primarily affected by PCC. It controls involuntary visceral functions as part of the autonomic nervous system, including the heart rate and digestive rhythm, and modulates systemic inflammation through the nicotinic cholinergic anti-inflammatory pathway[10,11]. Sympathetic / parasympathetic unbalances have been described in various pathologies such as inflammatory bowel diseases and rheumatoid arthritis[12,13,14] where they often precede chronic inflammation[15]. Non-invasive vagus nerve stimulation has been shown to reduce inflammation in severe COVID-19 [16], and is being evaluated in clinical trials[17].

To test our hypothesis of the existence of vagus nerve damage in PCC, we evaluated its structure and function using a comprehensive set of imaging and functional tests in subjects with PCC, in comparison with individuals fully recovered from acute COVID-19 and subjects without previous SARS-CoV-2 infection.

METHODS

Study population

This was a pilot cross sectional study (Vagus-COVID-19 study). Subjects with PCC according to the WHO definition, who had at least one of a prespecified list of vagus nerve-related symptoms (i.e: dysphonia, dysphagia, cough, dyspnea, tachycardia, orthostatic hypotension, gastrointestinal disturbances, dizziness or neurocognitive complaints) were prospectively identified from an observational cohort of patients exposed to SARS-CoV-2 (King Cohort, HUGTIP/PI-20-217) between September 2021 and March 2022. Subjects with dementia, diabetes mellitus or pregnant women were excluded from this study.

The first 30 consecutive PCC patients with vagus nerve-related symptoms who accepted to participate in the study were included. In addition, we identified 16 COVID-19-recovered participants without persistent symptoms, and 14 SARS-CoV-2-uninfected individuals, matched 2:1 by sex and age to the PCC subjects. Lack of previous SARS-CoV-2 infection in the third group was confirmed by an *in-house* sandwich-ELISA test measuring antibodies against the SARS-CoV-2 nucleoprotein, as previously described[18].

Participants were followed in the Germans Trias Long-COVID Unit of the Department of Infectious Diseases, Germans Trias i Pujol University Hospital, Spain, by a multidisciplinary team of specialists including rehabilitators, neurologists, cardiologists, rheumatologists, radiologists, nutritionists and psychologists.

This study was approved by the Germans Trias Hospital Ethics Committee Board (HUGTiP/PI-21-184) and was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent to participate.

Variables and study measurements

For each group, we collected demographic data, SARS-CoV-2 infection history, and a questionnaire of 36 persistent symptoms (see Supplementary table 1). We performed the following morphological and functional evaluations of the vagus nerve:

Morphological assessments

Vagus nerve neck ultrasound: a neck soft tissue ultrasound measured the maximum diameter (mm), perimeter (mm), cross-sectional area (CSA) (mm^2), and ultrastructure of the cervical segment of left and right vagus nerves, including presence of thickening and hyperechogenicity of the epineurium.

Thoracic ultrasound of respiratory muscles: both hemidiaphragms were evaluated by thoracic ultrasound. In the brightness mode (B-mode), the thickness of the muscle belly on each side was measured both at maximum inspiration and at maximum expiration. In motion mode (M-mode), a dynamic study of the respiratory curve was performed in several cycles.

Functional assessments

Dysphonia: a screening of voice alterations was self-reported using the Spanish version of Voice Handicap Index-30 items (VHI-30)[19]. Three categories were identified: scores 0-30 were considered mild, 30-60 moderate and >60 severe.

Dysphagia: dysphagia was evaluated with the swallowing screening Eating Assessment Tool-10 (EAT-10)[20], where scores ≥3 were considered altered, and the volume-viscosity clinical examination (MECV-V) to assess alterations in deglutory efficacy and safety.

Swallowing, motility and gastric emptying: were assessed by an esophago-gastro-duodenal transit (EGDT) guided by scope.

Maximum inspiratory pressure (MIP): respiratory muscle pressures were determined by MIP using a Micro RPM (Micro Medical/CareFusion, Kent, UK) device. The highest value of 3 reproducible maneuvers (<10% variability between values) was expressed as a percentage relative to reference values determined for a Mediterranean Caucasian population and used for the analysis[21]. Values below 70% were considered as decreased.

Heart rate variability (HRV): the HRV was used as a surrogate of the autonomous system function. It was measured as the variability of the interval between the R wave of the QRS complex of a conventional electrocardiogram placing two surface electrodes on the palms of the subjects[22] .The HRV measurements were recorded for 10 seconds at rest and after the following provocative tests: 6 deep breaths (6 deep inspirations and expirations with a frequency of 6 breaths/minute), Valsalva maneuver (holding a deep inspiration for 10 seconds), clino-orthostatism maneuver (moving from clino-orthostatism to orthostatism as quickly as possible). R-R variance (%) in HRV was recorded at baseline and for each test.

Sympathetic-reflex response (SRR): was performed by electrical stimulation (0.2ms duration and 15-30mA intensity) and impedance recording between two electrodes placed on the palm and dorsum of the hand to analyze distal latency and amplitude[23].

Statistical analysis. Data were collected and stored in a specifically designed RedCap data base. Continuous variables were described using mean and standard deviation (SD) or median (25-75 interquartile range); whereas categorical factors were reported as percentages. Quantitative variables were compared using the Mann–Whitney test for comparison between two groups, and the Kruskal–Wallis test for comparisons between more than two groups. Proportions were compared using the chi-squared test. Statistical analyses were performed with Prism 9.1.2 (GraphPad Software). The statistical significance threshold was set at p-values ≤ 0.05. P-values were not corrected for multiple comparisons.

RESULTS

Participants´ characteristics. Of 341 patients identified as PCC in the prospective KING cohort, 67% had one or more vagus nerve-related symptom (Figure 1). Participants included in our study were mostly women in their 40's, with frequent pre-COVID-19 history of allergies (Table 1). In addition, 23% of individuals with PCC had history of autoimmune disease and 20% had required hospitalization during the acute COVID-19 episode. None required high flow oxygen or mechanical ventilation during acute COVID-19.

The study evaluations were performed a median of 19 (IQR: 18-20) and 23 (IQR: 15-24) months after acute COVID-19 diagnosis in the PCC and COVID-19-recovered groups, respectively. The median number of symptoms per individual in the PCC group was 17 (IQR: 11-19), whereas symptoms were rare in the other two groups (Figure 2). Vagus nerve-related symptoms were much more prevalent in subjects with PCC than in COVID-19-recovered and uninfected individuals (Figure 3).

Morphological alterations

Vagus nerve neck ultrasound. Six out of 30 subjects with PCC (20%) as well as one SARS-CoV-2 uninfected individual (who also complained of tachycardia, dyspnea, fatigue, arthralgia and myalgia; Figure 2) had vagus nerve alterations in the neck ultrasound (Table 2). No alterations were found in the COVID-19-recovered group. Among participants with PCC, the most frequent alterations involved thickening and increase in echogenicity of the perineurium (4 subjects) followed by focal thickening of the nerve (2 subjects). The left vagus nerve cross-sectional area was (mean ± SD) 2.4 ± 0.97 mm^2 vs. 2 ± 0.52 mm^2 vs. 1.9 ± 0.73 mm^2 (p=0.080) in the PCC, COVID-19-recovered and uninfected groups, respectively.

Thoracic ultrasound. Fourteen out of 30 (47%) participants with PCC, but only 1/16 (6%) COVID-19-recovered (p=0.007) and 2/14 (14%) SARS-CoV-2-uninfected subjects (p=0.049) had flattened diaphragmatic curves in the thoracic ultrasound exploration (p=0.007) (Table 2).

Functional alterations

Dysphonia. The VHI-30 questionnaire was altered in 21/27 (78%) of subjects with PCC; 12 (44%) with a moderate to severe score. There were no alterations in controls.

Dysphagia. Twenty-one out of 28 (75%) of subjects with PCC had an altered EAT-10 screening. MECV-V was abnormal in 8/27 (30%) of patients, showing deglutory inefficacy in 7 individuals and unsafe deglutition in 3. No subject in either control group had alterations in these two tests.

Esophago-gastro-duodenal transit. Subjects with PCC (n=29) were more likely to show reductions in esophageal peristalsis (34%), presence of gastroesophageal reflux (34%) and hiatal hernia (25%) than COVID-19-recovered (n=16, 0%, 19% and 0%, respectively) and SARS-CoV-2-uninfected (n=14, 21%, 7% and 7%, respectively) individuals (p=0.020, p=0.130 and p=0.050, respectively).

Inspiratory and expiratory pressures. Sixteen out of 26 (62%) subjects with PCC vs 1/16 (6%) COVID-19-recovered and 2/12 (17%) non-infected individuals showed clinically significant reductions in the maximum inspiratory pressure (MIP <70%, p<0.001). Eight out of 16 subjects (50%) with altered MIP also had flattened diaphragms.

Heart rate variability. Subjects with PCC showed larger R-R duration than COVID-19-recovered and uninfected controls (1.63±0.26 sec. vs 1.50±0.12 sec. vs 1.48±0.26 sec., p=0.070), respectively) during the Valsalva maneuver. The other provocative tests (6-deep breaths and clino-orthostatism) did not modify the R-R variance.

Sympathetic-reflex response. Latencies were significantly shorter in subjects with PCC compared to the two control groups. Subjects with PCC had a faster sympathetic reflex response than controls (1.62±0.19 sec. vs 1.70±0.20 sec. vs 1.72±0.14 sec, p=0.09, respectively).

DISCUSSION

This study provides evidence of structural and functional alterations in various organs and body territories innervated by the vagus nerve in subjects with PCC, including the respiratory and digestive apparatus and the autonomous innervation of the heart. Our findings point to a central pathogenic role of vagus nerve dysfunction in the pathophysiology of the PCC. This possibly occurs in addition to other SARS-CoV-2-related pathophysiological insults not evaluated in this work and should be further characterized in larger prospective cohorts. Our findings open a possible first avenue of interventions to ameliorate some of the most disabling symptoms of the PCC, such as dysphagia, dyspnea and dysautonomia.

Using objective measurements, this study contributes to underscore the organicity of the PCC. The most frequent objective observations were altered dysphonia scales (VHI-30), reductions in Maximum Inspiratory Pressure and flattening of one or both hemidiaphragms, followed by reductions in esophageal-gastric-intestinal peristalsis and altered swallowing efficiency and safety. These observations are well in line with the frequently-reported dysphonia, exertional dyspnea and digestive symptoms, and likely occur in relation to vagus nerve inflammation.

Neural or perineural thickening was indeed observed in several subjects using lateral neck ultrasound and suggest direct (viral invasion) or indirect (neuroinflammatory response) damage of the nerve induced by SARS-CoV-2. Ultrasound studies in subjects with *Guillain-Barré* syndrome show structural changes in different peripheral nerves, including the vagus nerve and cervical spinal roots, compared to healthy controls[24]. Such changes consist of an increase in the cross-sectional area of the nerve, which may be patchy, and alterations in the ultrastructural echogenicity, similar to what we observe in our study. In the *Guillain-Barré* syndrome, neural changes can be observed early from the onset of the disease and reflect immuno-mediated histological alterations that lead to irregular thickening of the perineural fascicles due to interfascicular, perineural and epineural edema.

Our vagus nerve ultrasound findings contrast with those from Papadopoulou[25] in 11 subjects with PCC, who had a smaller cross-sectional area of both right and left vagus nerves compared to controls. Whereas those findings suggest vagus nerve atrophy, the study did not report detailed information of the internal structure of the nerve or the perineurium and did not specify when ultrasounds were performed after SARS-CoV-2 infection. Future studies should explore whether vagus nerve ultrasound may yield different findings in subjects with PCC during the course of the disease (i.e., neural edema in early stages and perhaps atrophy in advanced disease). As of today, this remains an open question which however may have a bearing on potential therapeutic interventions.

An important result of our study was the frequent structural and functional involvement of respiratory muscles. More than 60% of subjects with PCC had reduction in maximum inspiratory pressure, often associated with flattening of one or both hemidiaphragms and significant reductions in diaphragmatic thickness and mobility. These findings suggest respiratory muscle weakness that could explain dyspnea in spite of normal lung imaging. Diaphragm dysfunction with significant reduction in contractility has been described in survivors of severe COVID-19 as critical illness myopathy of the post-intensive care syndrome using neuromuscular ultrasound[26,27]. Our findings are noteworthy because none of our study participants required intensive care during acute COVID-19, so our observations are not attributable to post-intensive care syndrome.

Strengths and limitations

This study provides consistent evidence of vagus nerve-related organicity in the PCC, but has several limitations: The cross-sectional design does not allow for causal inference. The study was small, so could be affected by alpha error. Measurements of autonomic dysfunction are not well standardized and ultrasound interpretation is examiner-dependent. Subjects with PCC were selected from an ongoing hospital-based cohort, which is likely to be enriched in individuals with more severe forms of PCC. Moreover, individuals with PCC were selected according to the presence of symptoms believed to be associated with vagus nerve dysfunction. Thus, this study is not able to produce a precise estimation of the true prevalence of the observed alterations among subjects with PCC and cannot be necessarily generalized to all individuals with PCC. Differences between groups, however, were not subtle, and were consistent using different independent objective measurements.

Conclusions

In summary, this study provides evidence of organic alterations along the vagus nerve territory in subjects with PCC, including the respiratory and digestive apparatus and the autonomous innervation of the heart. Our findings point to a central pathogenic role of vagus nerve alterations in the pathophysiology of the PCC, are highly informative to systematize clinical evaluations of this syndrome, inform PCC cohort studies and support evaluating therapeutic interventions to ameliorate PCC-associated dysautonomia.

Contributors

GLL, MM, RP, LM contributed to study design. RCF and MJD conducted the study of dysphagia and inspiratory pressures. RR and EH, PC, JB and MT assessed neck and thoracic ultrasound and esophago-gastro-duodenal transit. GL and AMP assessed the heart rate variability and the sympathetic-reflex response. GLL, SEE, CL, CL, JRS and LM characterized PCC patients. MN and EG performed serologic tests. GLL, MM, RP, LM and FML performed statistical analysis and GLL, MM, RP, LM wrote the manuscript. All authors reviewed and approved the manuscript.

Declaration of interests

The authors declare no conflicts of interest. CB is a shareholder of Electrocore Inc.

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Table 1. Participant characteristics.

Characteristics	PCC (n=30)	Recovered (n=16)	Uninfected (n=14)
Female, n (%)	24 (80)	12 (75)	12 (86)
Age, years, median [IQR]	44 [35-51]	41 [33-44]	49 [40-53]
Comorbidities, n (%)			
Allergies	14 (47)	6 (38)	2 (14)
Pneumopathy	4 (13)	1 (6)	0 (0)
Obesity	4 (13)	0 (0)	2 (14)
Autoimmune disease	7 (23)	1 (6)	0 (0)
Oncologic disease	3 (10)	0 (0)	0 (0)
Immunosuppressive treatment	0 (0)	0 (0)	0 (0)
SARS-CoV-2 diagnosis, n (%)			
PCR	9 (30)	13 (81)	-
Serology	7 (23)	3 (19)	-
Clinical manifestations	14 (47)	0 (0)	-
Hospitalization, n (%)	6 (20)	0 (0)	-
Ambient air or low-flow oxygen	6 (20)	0 (0)	-
Months since symptom onset, median [IQR]	19 [18-20]	23 [15-24]	-

Note: PCC, Post-COVID-19 Condition; IQR: 25-75% interquartile range

477 **Table 2. Summary of altered vagus nerve findings**
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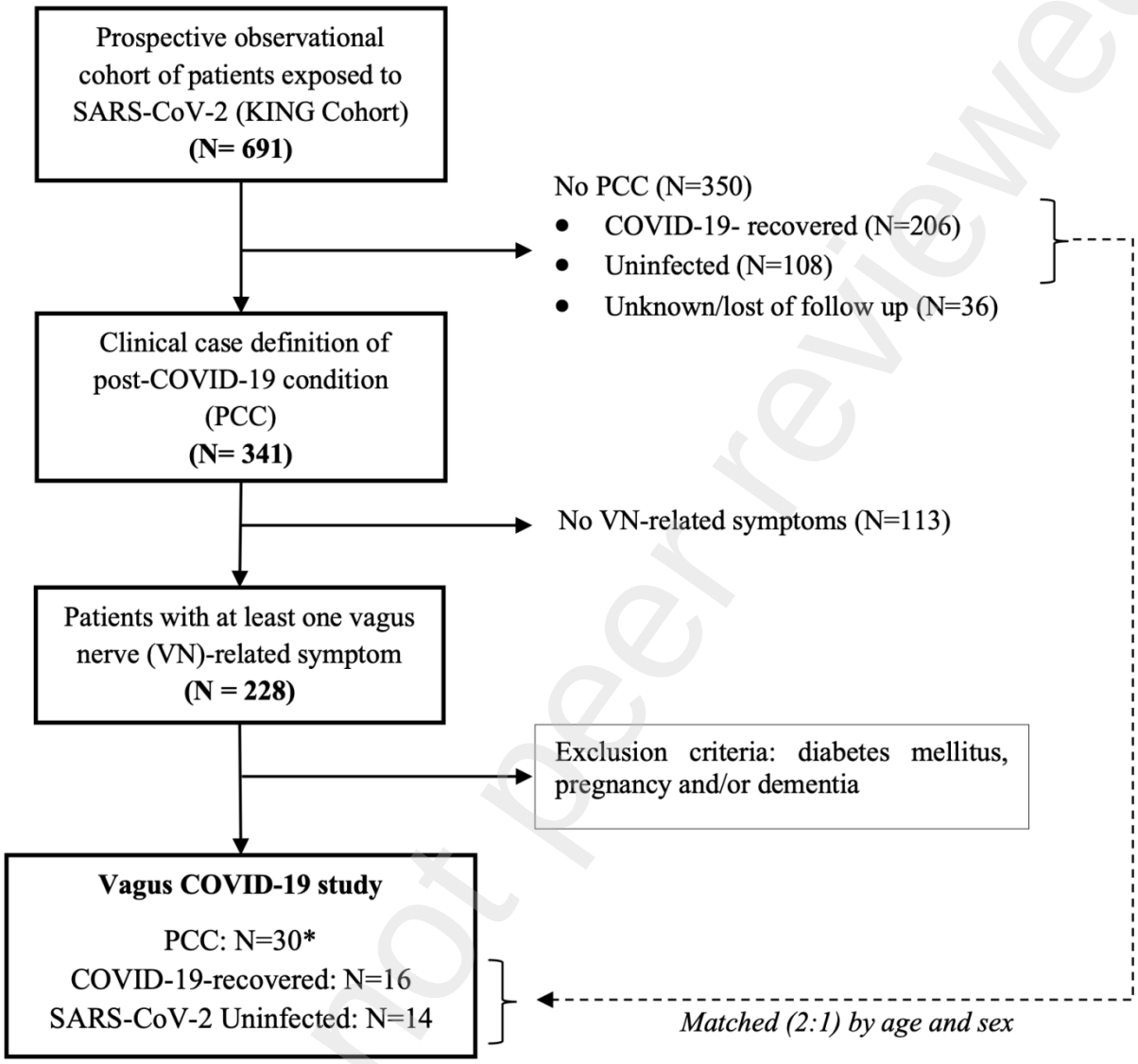
Subject ID	Group	Age	Sex	Right Vagus Nerve [a]		Left Vagus Nerve [a]		Diaphragm curve [b]		Esophageal-gastric-intestinal peristalsis [c]	Dysphonia (VHI30)	Dysphagia (EAT-10)	Maximum Inspiratory Pressure
				Perineurium	Structure	Perineurium	Structure	Right	Left				
153	PCC	41	F					Flattened	Flattened	Reduced	Altered		-
264	PCC	44	F					Flattened	Flattened	Reduced	Altered	60	60
74	PCC	45	F					Flattened	Flattened		Altered	6	49
413	PCC	41	F					Flattened	Flattened		Altered	22	-
483	PCC	48	F	Thickened & hyperechogenic					Flattened	Reduced	Altered	23	54
163	PCC	41	F		Focal thickening of the mid cervical third		Focal thickening of the mid cervical third		Flattened		Altered	8	-
404	PCC	27	F						Flattened		Altered	33	59
430	PCC	57	F						Flattened		Altered	9	42
449	PCC	48	M						Flattened		Altered	3	57
576	PCC	42	F						Flattened		Altered	4	70
9	PCC	49	M							Reduced	Altered	13	48
246	PCC	54	F							Reduced	Altered	6	59
590	PCC	40	M							Reduced	Altered		62
151	PCC	44	F			Thickened & hyperechogenic					Altered	23	32
180	PCC	29	M								Altered	21	-
194	PCC	35	F								Altered		-
410	PCC	44	F								Altered	11	54
424	PCC	52	F	Thickened & hyperechogenic							Altered	19	58
647	PCC	29	F								Altered	33	Not applicable
117	PCC	47	M					Flattened		Not done	Altered	7	52
551	PCC	56	F					Flattened		Reduced	Altered		60
537	PCC	36	F						Flattened	Reduced	-	14	-

504	PCC	65	F							Reduced	-	3	-
400	PCC	51	M								-		49
500	PCC	33	F		Focal thickening of the mid cervical third						-		-
542	PCC	34	F								-	8	54
416	PCC	57	F	Thickened & hyperechogenic					Flattened		Not done	28	Not done
243	PCC	31	F							Reduced	Not done		Not done
187	PCC	52	F								Not done		Not done
30	Recovered	33	F	-	-	-	-		Flattened	-	-	-	-
17	Recovered	33	M	-	-	-	-			-	-	-	69
22	Uninfected	53	F	Thickened & hyperechogenic	Altered	Thickened & hyperechogenic	Altered	Flattened		Reduced	-	-	Not applicable
9	Uninfected	48	M	-				Flattened		-	-	-	-
2	Uninfected	56	F	-				-		Reduced	-	-	-
6	Uninfected	35	F	-				-		Reduced	-	-	-
3	Uninfected	52	F	-				-		-	-	-	59
7	Uninfected	28	F	-				-		-	-	-	65

Only subjects with at least one altered test are shown in the table. Individuals who did not show alterations in any test were: 1/30 PCC, 14/16 Recovered, 8/14 Not SARS-CoV-2 infected. '-' : Absence of alterations; PCC: Post-COVID-19 Condition; F: female

[a] Measured by neck ultrasound
[b] Measured by thoracic ultrasound
[v] Measured by esofageal-gastric-duodenal transit

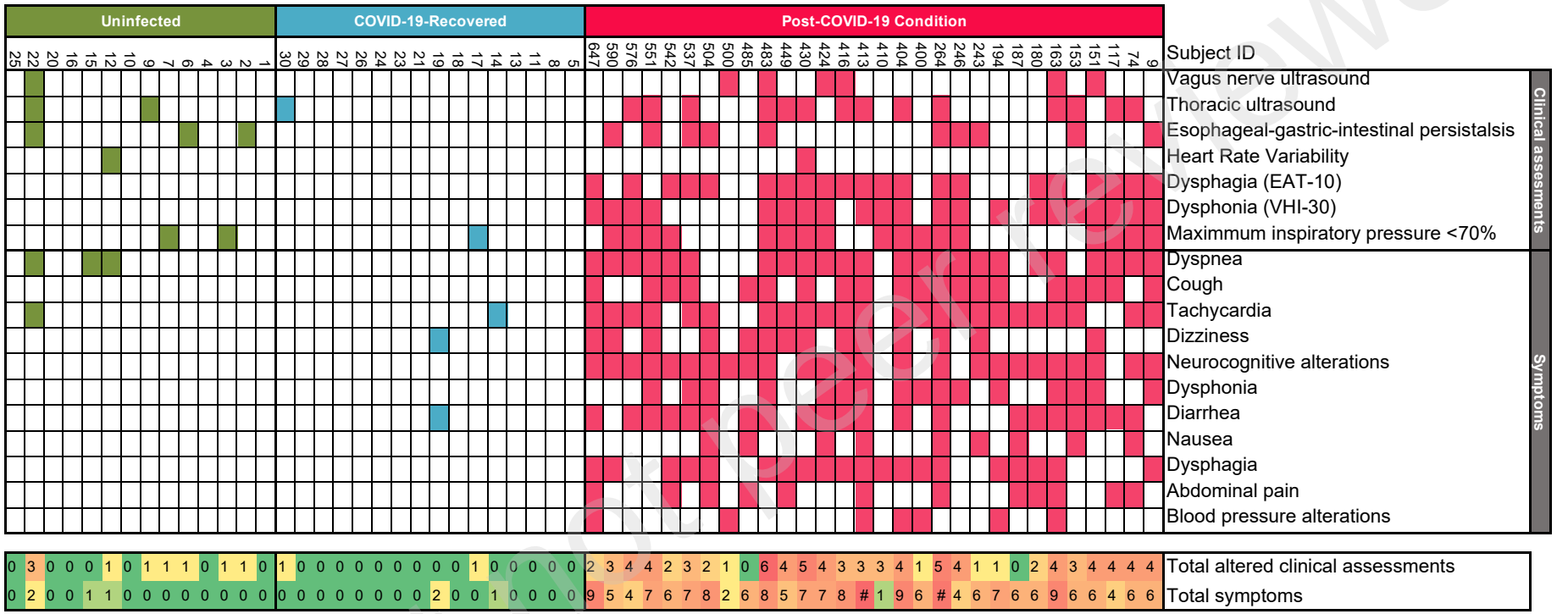
Figure 1. Study flowchart.



Note: PCC: Post-COVID-19 Condition; COVID-19 recovered: without persistent symptoms.VN: Vagus Nerve.

* First 30 consecutive subjects seen at the Germans Trias Long COVID clinic and providing informed consent to participate in the study

Figure 2. Summary of symptoms and altered tests in subjects with Post-COVID-19 Condition and controls.



503 **Figure 3. Prevalence of symptoms in subjects with Post-COVID-19 Condition and controls**
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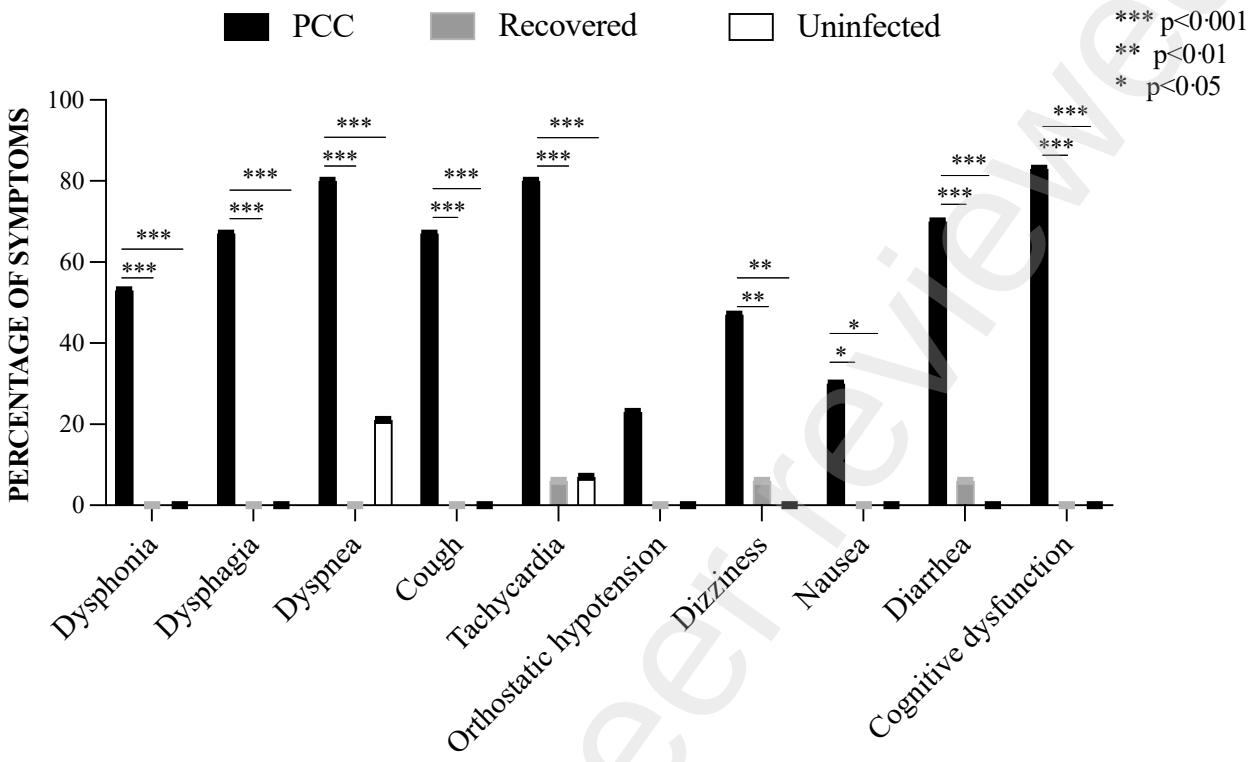

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