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Faculteit Revalidatiewetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

The role of fatigue and other symptoms on functioning and quality of life in post COVID-19syndrome

Lize Gieraerts
Saranke Juvyns

Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie, afstudeerrichting revalidatiewetenschappen en kinesitherapie bij musculoskeletale aandoeningen

PROMOTOR :
Prof. dr. Katleen BOGAERTS

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Contextualization

This thesis is situated within the curriculum ‘In-depth Scientific Internship and Master’s Thesis' of the Rehabilitation Sciences and Physiotherapy department for the academic year 2023-2024. The master's thesis belongs to the research domain of Somatically Unexplained Physical Complaints (SOLK) and is part of the research project named "Cognitive, psychological, and physical functioning in post COVID-19 (PCS) patients with different levels of fatigue."

The project is identified by the Clinical Trials Identifier NCT05758558 and has been approved by the Committee for Medical Ethics at Hasselt University with code CME2022/021 and by the Ethics Committee Research UZ/KULeuven with code S66200.

PCS is defined by the World Health Organization (WHO) as the persistence or development of new symptoms three months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least two months without any other explanation (Kryuchkov, 2022). Currently, there is limited evidence available regarding this condition. Therefore, it is crucial to understand the underlying causes and mechanisms of this pathology, with the eventual goal of developing effective treatments for this specific group of patients (Davis et al., 2023).

The aim of this study is to investigate potential contributions of fatigue and other symptoms on daily functioning, psychological functioning, and quality of life in individuals suffering from PCS. Identifying these potential contributions can serve as a starting point for further evidence-based rehabilitation interventions.

This research was conducted at the University of Hasselt, located at Agoralaan, Building A, B-3590 Diepenbeek, within the Faculty of Rehabilitation Sciences and Physiotherapy. This observational, cross-sectional study was carried out under close supervision and in collaboration with Prof. Dr. Katleen Bogaerts, and Dr. Stef Feijen.

Abbreviations

Table 1

List of Abbreviations

Abbreviation	Definition
AICc	Akaike Information Criterion corrected for small sample sizes
BAT	Burnout Assessment Tool
BIC	Bayesian Information Criterion
BMI	Body Mass Index
CAT	COPD Assessment Test
CFS	Chronic Fatigue Syndrome
COVID-19	Coronavirus Disease 2019
CT	Computerized Tomography
DSM	Diagnostic and Statistical Manual of Mental Disorders
EQ-5D-5L	EuroQol 5-Dimension 5-Level
FSS	Fatigue Severity Scale
GST	Grip Strength Test
HADS	Hospital Anxiety Depression Scale
IC	Informed Consent
MINI	Mini International Neuropsychiatric Interview
MoCA	Montreal Cognitive Assessment
mMRC	modified Medical Council Research Scale
MS	Multiple Sclerosis
NVL	Nijmeegse Hyperventilatieschaal
PEM	Post Exertional Malaise
PCS	Post COVID-19 Syndrome
PCFS	Post COVID-19 Functional Status Scale
PEM	Post Exertional Malaise
PSS	Perceived Stress Scale
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
VBE	Vragenlijst Belastende Ervaringen
WHO	World Health Organization
6MWT	Six Minute Walking Test

Note. Alphabetical ranking of abbreviations.

Abstract

Background: Fatigue is consistently identified as one of the most problematic symptoms of post Coronavirus disease (COVID) 2019 Syndrome (PCS). However, its impact on functioning and quality of life remains inadequately characterized.

Objectives: This study aimed to investigate the contribution of fatigue, along with other symptoms, to daily functioning, psychological functioning, and quality of life in individuals with PCS.

Method: Baseline data from a sample of participants were analysed in this clinical trial. Fatigue and other symptoms were assessed using both patient-reported outcomes and objective measures. Multivariate regression models were constructed to estimate the contribution among these variables.

Results: This observational, cross-sectional study included 47 participants, predominantly female (72%), with an average age of 47 years. Results indicated that higher levels of fatigue were associated with reduced daily functioning and lower quality of life. In addition to fatigue, body mass index (BMI), overall health perception, the number of walks post-COVID, and hyperventilation symptoms were significant factors influencing quality of life ($R^2 = 0.77$). Psychological functioning was negatively impacted by fatigue, BMI, burnout, and anxiety levels ($R^2 = 0.45$). Daily functioning was also significantly influenced by sex, anxiety, overall health, and the number of walks post-COVID ($R^2 = 0.42$).

Conclusion: This study emphasizes the need for comprehensive, multidisciplinary approaches to PCS-treatment that address both physical and psychological aspects of recovery.

Keywords: Post-COVID-19 Syndrome (PCS), fatigue, quality of life, daily functioning, psychological functioning.

Introduction

With the outbreak of the COVID-19 virus, also known as the coronavirus, the world faced an unprecedented health crisis (Mallah et al., 2021). The virus, caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), spread worldwide, and led to countless infections and deaths (Sharma et al., 2020). As the scientific community rushed to produce vaccines, long-lasting effects of the disease were also discovered in some individuals, resulting in a phenomenon known as the post COVID-19 syndrome, PCS (Kryuchkov, 2022).

PCS is defined by the World Health Organization (WHO) as the persistence or development of new symptoms three months after initial SARS-CoV-2 infection, with symptoms persisting for at least two months without any other explanation. PCS can affect people of all ages, including those who experienced only mild or no symptoms during the initial SARS-CoV-2 infection (Kryuchkov, 2022).

There are several studies worldwide investigating persistent symptoms after initial SARS-CoV-2 infection, in which fatigue appears to be the most frequently reported (Aiyegbusi et al., 2021; Carfì et al., 2020; Romero-Rodríguez et al., 2023; Townsend et al., 2021). PCS shares a remarkable similarity in their symptoms with the chronic fatigue syndrome (CFS). Both conditions are often preceded by viral infections and cause severe fatigue that does not disappear after rest (Davis et al., 2023). Although this long-lasting fatigue is ranked as the most frequent and limiting symptom of PCS, its impact on the patient's quality of life, social participation and functioning is not well characterized (Evans et al., 2022; Muñoz-Corona et al., 2022).

Given the high impact of fatigue, it is crucial to better understand the experienced fatigue and how it, along with related symptoms, may contribute to the PCS-patient's daily functioning, psychological functioning, and quality of life (Delbressine et al., 2021; Todt et al., 2021). Consequently, the purpose of this study is to examine the impact of fatigue and other symptoms on functioning and quality of life. We hypothesized that, when applying multivariable models, fatigue would be a strong contributor to quality of life and functioning in patients with PCS.

Methods

Study Design

This cross-sectional analysis was based on the larger study investigating "Cognitive, Psychological and Physical Functioning in PCS-patients with different levels of fatigue". Approval for this study was obtained from the Ethics Committee Research UZ/KU Leuven and the Committee for Medical Ethics of Hasselt University (B3222022000817).

Inclusion Criteria

Participants who met the criteria outlined in the recently published definition of PCS were considered eligible to participate in the study. PCS has been defined as a condition that occurs in individuals with a history of confirmed SARS-CoV-2 infection, and that occurs usually within three months from the onset of COVID-19 with symptoms that last for at least two months and cannot be explained by an alternative diagnosis (Soriano et al., 2022). Potential participants should have received a positive diagnosis for COVID-19 in the past, which can be confirmed through various methods, including Reverse Transcription Polymerase Chain Reaction (RT-PCR), Computed Tomography (CT) scan of the lungs, or a symptom-based diagnosis by a general practitioner. Participants that either had or had not been hospitalized were both allowed to participate in this study. COVID-infection status will be self-reported by participants, with the option to present a test certificate, though not mandatory.

In addition to meeting the criteria for the PCS-condition, participants were required to report current persistent symptoms, such as brain fog, anxiety, shortness of breath, headaches, and others. Participants should indicate the impact of these symptoms on everyday functioning on the Post COVID-19 Functional Status Scale (PCFS-scale). These symptoms may either be new onset following the initial recovery from the acute episode of COVID-19 or persist from the initial illness but must endure for longer than two months. Furthermore, patients must report current significant levels of fatigue, measured by the Fatigue Severity Scale (FSS).

Finally, to be included in the trial, participants needed to be 18 years or older, be able to communicate in Dutch or English, and be willing to complete the study procedures. All participants furthermore provided informed consent (IC).

Procedure

All eligible participants were scheduled for two separate measurement sessions, planned at least seven days apart. The participants signed the IC prior to all measurements. During the first measurement session, the participants physical functioning was assessed. Testing included the Six Minute Walk test (6MWT) (Puhan et al., 2008) and bilateral Grip Strength Test (GST) (Dodds et al., 2014). The second measurement session focused on psychological and cognitive functioning. Testing included the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983), Vragenlijst Belastende Ervaringen (VBE) (Nijenhuis et al., 2002) and the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) for psychological assessment, and the Montreal Cognitive Assessment (MoCA) for cognitive evaluation of the participant (Vandermeulen & Derix, 2015). All participants were asked to complete two questionnaires. The baseline questionnaire obtained demographics (age, gender, marital status, work, education, pre-COVID general health and medical conditions, physical activity), fatigue level and post-COVID Functional status (PCFS) (Klok et al., 2020). The follow-up questionnaire included the Fatigue Severity Scale (FSS) (Krupp et al., 1989), the modified Medical Council Research scale (mMRC) (Bestall et al., 1999), the COPD Assessment Test (CAT) (Jones et al., 2009), Nijmeegse Hyperventilatieschaal (NVL) (Van Doorn et al., 1983), the EuroQol-5 Dimension-5 Level (EQ-5D-5L) ("EuroQol--a new facility for the measurement of health-related quality of life," 1990), the Perceived Stress Scale (PSS) (Cohen et al., 1983), and the Burnout Assessment Tool (BAT) (Schaufeli et al., 2020). All questionnaires were completed either digitally or paper based.

Measures

Fatigue

Level of fatigue was measured by the FSS. The scale is designed to assist healthcare professionals in recognizing and diagnosing fatigue in daily life situations across various conditions, including CFS, which shares many similarities with PCS in terms of fatigue and other symptoms (Davis et al., 2023). The questionnaire comprises nine questions that assess the perceived severity of fatigue symptoms in various daily situations over the past week. Patients indicate the extent to which fatigue determines their functioning. For each item, responses were scored on a seven-point scale ranging from one (completely disagree) to seven (completely agree), with an ordinal measurement level. The total score, which ranges from nine to 63 (summing up scores per item), is then calculated by dividing it by nine, maintaining an ordinal measurement level. A higher score indicates greater fatigue or a more significant impact of fatigue on daily life (Krupp et al., 1989). Previous literature has suggested a cut-off score of ≥ four on this scale to indicate moderate to severe levels of fatigue (Mathiowetz et al., 2001).

Outcomes

Daily Functioning

Daily Functioning was assessed using the PCFS-scale. The scale is proposed as an ordinal instrument to assess the diverse range of functional limitations in individuals recovering from COVID-19. Modelled after the post-VTE functional status scale, the PCFS-scale divides patients into five categories, based on the presence and intensity of symptoms, pain, or anxiety, as well as the impact on daily activities. Score zero indicates no functional limitation, while score four represents severe functional limitation. The scale was considered adaptable for COVID-19, given the incidence of pulmonary embolism, myocardial damage, and neurological complications in critically ill patients. The PCFS-scale was intended for assessment at discharge, four- and eight-weeks post-discharge, and six months to monitor recovery and long-term sequelae (Klok et al., 2020). A recent study confirmed the construct validity of the PCFS-scale in highly symptomatic adult subjects with confirmed and presumed COVID-19, three months after the onset of symptoms (Machado et al., 2021).

Psychological functioning

For the comprehensive assessment of psychological functioning, we administered the MINI. The MINI is a structured diagnostic interview developed for assessing psychiatric diagnoses according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Due to its concise nature, the interview seems to be particularly practical for diagnosing psychiatric patients in the daily clinical setting (Van Vliet & De Beurs, 2007). Total Psychological Functioning was used as the dependent variable in a logistic regression analysis, considering it as a dichotomous variable. During the MINI assessment, various psychological events were evaluated. If a participant answers "yes" to any of these questions, they automatically receive a score of one for overall psychological functioning. Conversely, participants receive a score of zero if none of these events have taken place. The objective of this investigation is to assess the contribution between fatigue and other symptoms and psychological functioning.

Quality of Life

The experienced quality of life level is assessed using the EQ-5D-5L. The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five levels: no problems (score 1), slight problems (score 2), moderate problems (score 3), severe problems (score 4), and extreme problems (score 5). The patient is asked to indicate their health state by ticking the box next to the most appropriate statement in each of the five dimensions. This decision results in a one-digit number that expresses the level selected for that dimension. The digits for the five questions can be combined into a five-digit number that describes the patient's health state ("EuroQol--a new facility for the measurement of health-related quality of life," 1990). We have been researching the conversion of the EQ-5D-5L-scores into a metric value between zero and one. Previous research has determined the appropriate "weight" to use, as it significantly depends on the population in which this questionnaire is applied. Factors contributing to quality of life may vary greatly between different regions of the world. In Belgium, such valuation studies have already been conducted (Bouckaert et al., 2022). Generally, the index value is calculated using the following formula (EuroQol Research Fondation, 2019).

Formula 1

Conversion of EQ-5D-5L Questionnaire to Metric Index Value

Formula Index Value
1 − ((W × D1) + (W × D2) + (W × D3) + (W × D4) + (W × D5))

Note. W = weight; D = dimension; weight in the formula represents a score from 1 (no problem) to 5 (unable); the dimensions in the formula are as follows: mobility, self-care, usual activities, pain/discomfort and anxiety and depression.

Data analysis

Descriptive statistics were utilized to characterize the sample. Categorical variables were represented using proportions, while means and standard deviations were employed for continuous data. The demographic data is summarized in table 1.

Regression models were constructed for each outcome variable, namely daily functioning, quality of life and psychological functioning. In accordance with the existing literature, hypotheses have been formulated regarding the independent variables that may potentially explain these outcomes. These hypotheses were developed through collaboration with our academic advisor and were tailored for each of the three outcomes. After this, we performed a data reduction step, focusing on variables that were clinically and scientifically relevant. This was accomplished through univariate regression analyses to identify statistically significant predictors. Our initial model included a broader set of variables, which were gradually refined based on their statistical significance and clinical relevance. For the outcome of daily functioning, we utilized multinomial logistic regression, given the categorical nature of the PCFS-scale. This method allowed us to assess the likelihood of different levels of functional status based on independent predictors. In assessing the quality of life, linear regression was employed. For psychological functioning binary logistic regression was applied. The model refinement was conducted using a backward elimination process. This involved starting with all potentially relevant variables and systematically removing those with the highest p-value in iterative rounds. The adequacy and fit of each model were evaluated using several statistical measures, including R-squared, AICc, BIC, and the significance of the overall model. All analysis were conducted using JMP, version 17, SAS institute.

Results

Descriptive statistics

The characteristics of the sample have been reported in table 1.

Table 1

Means and Standard Deviations of Demographic Data

Variable	N = 47
Age	47.13 (9.06)
Sex (M:F)	13:34
BMI	25.84 (4.67)
Fatigue (FSS)	5,72 (1.04)
Distance 6MWT	486.59 (80.20)
Fatigue post – pre 6MWT	1.07 (1.47)
Grip strength Dominant Hand	28,25 (10.79)
QOL VAS	36.36 (17.23)
Anxiety HADS	8.52 (4.01)
Depression HADS	8.29 (3.32)

Note. Standard deviations are presented in parenthesis. M = Male; F = Female; BMI = Body Mass Index; FSS = Fatigue Severity Scale; 6MWT = 6-minute walking test; QOL = Quality of Life; VAS = Visual Analogue Scale; HADS = Hospital Anxiety and Depression Scale.

Multivariate models

This analysis reveals significant relationships between various explanatory variables and outcomes related to quality of life, psychological functioning, and daily functioning in individuals experiencing PCS. The models fitted for each domain exhibit robust predictive power, highlighting the profound impact of these variables.

Quality of Life

The analysis, as summarized in Table 2, indicates that fatigue, body mass index (BMI), perceived overall health, number of walks post-COVID, and hyperventilation significantly influence the quality of life. Fatigue and BMI negatively affect quality of life, with fatigue showing a particularly strong adverse effect. Overall health and number of walks post-COVID positively contribute to quality of life, suggesting that better general health perceptions and physical activity are beneficial. Hyperventilation presents a negative association, indicating that respiratory symptoms can severely diminish quality of life. The model demonstrates a strong fit ($R^2 = 0.770$) (table 3), emphasizing the substantial variance in quality of life explained by these factors.

Table 2

Results Quality of Life

Explanatory variable	β	Sum sq	F-ratio	*P* > F
Intercept	1.774	.	.	<.0001*
Age	0.005	0.071	3.175	0.0843
Fatigue	-0.124	0.350	15.689	0.0004*
BMI	-0.023	0.317	14.258	0.0007*
Dyspnea	0.018	0.055	2.475	0.1255
Overall health	0.003	0.145	6.509	0.0157**
# walks post-covid	0.026	0.100	4.486	0.0420**
Hyperventilation	-0.014	0.625	28.081	<.001*

Note. * Significant at 0.01*;* ** Significant at 0.05; β = beta; Sum sq = sum of squares; X^2= chi-square; *P* = probability; # = number.

Table 3

Summary of Fitted Model

Model fit measures	
R^2	0.770
AICc	-23.622
BIC	-14.422
P > X^2	<0.0001*

Note. R^2 = R-squared; AICc = Corrected Akaike Information Criteria; BIC = Bayesian Information Criterion; X^2= chi-square; *P* = probability*; P* > X^2= significance of whole model.

Psychological Functioning

Table 4 provides the impacts on psychological functioning, where significant predictors include fatigue, BMI, burnout, and anxiety. Fatigue and BMI negatively correlate with psychological well-being, underscoring the psychological toll of physical health deterioration. Burnout and anxiety levels also significantly affect psychological outcomes, with higher levels exacerbating psychological distress. The fitted model (R^2 = 0.450) (table 5) indicates a moderate explanatory power, reflecting the complexity and multifactorial nature of psychological health post-COVID.

Table 4

Results Psychological Functioning

Explanatory variable	Estimate	σ_x	X^2	$P > X^2$
Intercept	3.982	4.780	0.69	0.4048
Sex	-0.990	0.619	2.56	0.1096
Fatigue	-1.619	0.768	4.44	0.0351**
BMI	-0.285	0.136	4.41	0.0356**
Burnout	0.131	0.053	6.03	0.0141**
Anxiety	0.363	0.161	5.08	0.0242**

Note. * Significant at 0.01; ** Significant at 0.05; σ_x = standard error; X^2 = chi-square; *P* = probability.

Table 5

Summary of Fitted Model

Summary of Fit	
R2	0.450
AICc	45.665
BIC	53.476
$P > X^2$	0.0001*

Note. R^2 = R-squared; AICc = Corrected Akaike Information Criteria; BIC = Bayesian Information Criterion; X^2= chi-square; *P* = probability; $P > X^2$= significance of whole model.

Daily Functioning

As per Table 6, factors significantly affecting daily functioning include sex, fatigue, anxiety, overall health, and the number of walks post-COVID. Sex shows a significant relationship, with males potentially experiencing different daily functioning outcomes than females. Fatigue, anxiety, and overall health demonstrate significant associations, with fatigue and anxiety worsening daily functioning, whereas better overall health improves it. Interestingly, the number of walks post-COVID shows a negative association. The fitted model for daily functioning also shows a moderate fit (R^2 = 0.419) (table 7), aligning with the significant but varied impact of these factors.

Table 6

Results Daily Functioning after COVID-19

Term	Estimate	σ_x	X^2	$P > X^2$
Intercept (2)	1.073	3.728	0.08	0.7736
Intercept (3)	10.772	5.058	4.54	0.0332**
Sex	2.211	0.881	6.30	0.0121**
Fatigue	-1.428	0.688	4.30	0.0380**
Anxiety	0.421	0.186	5.12	0.0237**
Overall health	0.050	0.025	3.85	0.0498**
# walks post-COVID	-0.681	0.328	4.33	0.0375**

Note. * Significant at 0.01; ** Significant at 0.05; σ_x = standard error; X^2 = chi-square; *P* = probability.

Table 7

Summary of Fitted Model

Summary of Fit	
R^2	0.419
AICc	47.641
BIC	56.242
$P > X^2$	0.0006*

Note. R^2 = R-squared; AICc = Corrected Akaike Information Criteria; BIC = Bayesian Information Criterion; X^2= chi-square; *P* = probability; $P > X^2$= significance of whole model.

Discussion

Fatigue has been reported as one of the most frequent symptoms of PCS (Aiyegbusi et al., 2021; Carfì et al., 2020; Romero-Rodríguez et al., 2023; Townsend et al., 2021). However, it is not yet clear to what extent this fatigue can impact the patient's functioning and quality of life. Therefore, our objective was to investigate the impact of fatigue and other symptoms on daily functioning, psychological functioning, and quality of life in individuals with PCS. Results of this study highlight that higher levels of fatigue significantly impair functioning and quality of life. However, fatigue is not the only contributing factor. Other significant influences on these outcomes include the number of walks post-COVID, BMI, overall health perception, and hyperventilation symptoms.

Exploration of the findings

Descriptive data

When examining the descriptive data, we observe that a significantly higher number of women were included in this study compared to men. Previous literature found that female sex is associated with more symptoms of PCS and a lower likelihood of achieving full recovery one year after COVID-19 infection (Evans et al., 2022; Tleyjeh et al., 2022). This could be a possible explanation for the higher number of women in our sample. Another explanation could be that men are less likely to seek help, which may reduce their likelihood of enrolling in this study (Sagar-Ouriaghli et al., 2019).

Daily functioning

Our analysis indicates that several variables significantly influence daily functioning among individuals with PCS. Notably, fatigue emerged as a significant contributor. The FSS-scores inversely contributed to daily functioning, demonstrating that higher levels of fatigue significantly impair individuals' ability to perform daily activities. This corresponds with previous literature stating that fatigue is a dominant symptom among PCS-patients and that it impacts their daily functioning (Walker et al., 2023). The number of post-COVID walks was another variable of interest, showing a negative association with daily functioning. Specifically, the more walks one undertakes after the diagnosis of PCS, the poorer daily functioning. This contrasts with previous research, which highlighted moderate effectivity of exercise for lowering the fatigue of the patient (Estévez-López et al., 2021). Hower, this study was

conducted on patients with fibromyalgia and although symptoms may appear similar, it is not yet known to what extent both conditions can be compared. For instance, the phenomenon of Post Exertional Malaise (PEM) may deliver another explanation of why the number of walks could lower functioning. Physical and cognitive exertion could trigger PEM in patients with PCS (Vernon et al., 2023). PEM is a worsening of symptoms like fatigue, weakness, and orthostatic intolerance, along with signs such as heart rate variation and temperature dysregulation, after minimal physical or cognitive exertion. Symptoms can appear up to 72 hours post-exertion and last for 24 hours or more. PEM can be triggered by everyday activities, including sitting, standing, showering, driving, shopping, listening, socializing, conversing, reading, or cleaning (Hartle et al., 2021). Strategies to reduce PEM, among education, skill training on energy conservation techniques such as pacing, or alternative therapies that focus on low-intensity activity and gradual progression could be thereby targeted in rehabilitation ("WHO Guidelines Approved by the Guidelines Review Committee," 2022).

Psychological Functioning

Psychological functioning in PCS-patients is influenced by a combination of physical and mental health factors. In our analysis BMI was identified as significant factor influencing psychological functioning, with higher BMI contributing to poorer psychological outcomes. This association aligns with existing literature that higher BMI can independently affect psychological functioning, and can be linked to lower self-esteem and higher levels of depression and anxiety (Ahadzadeh et al., 2018). It is important to note that BMI data was only available for 30 participants in our sample. Within this subset, 9 individuals had a BMI of 30 kg/m^2 or higher, categorizing them as obese. This prevalence of higher BMI in our sample may have contributed to the observed negative psychological outcomes. An observational study from 2022 reported that obesity is associated with a lower likelihood of reporting full recovery one year after COVID-19 infection. This could explain the high number of obese individuals included in our study (Evans et al., 2022). Although the limited sample size restricts the generalizability of these findings, the data indicate a potential trend that warrants further investigation. Future research should aim to include a larger and more representative cohort to validate these findings and explore the underlying mechanisms linking BMI with psychological health in greater detail. Our hypothesis on this is that the relationship is due to several factors. Firstly, higher BMI is often associated with conditions such as diabetes,

hypertension, and cardiovascular diseases, which require continuous management and medical attention (Robinson et al., 2020). These compounded physical health challenges faced by individuals with higher BMI can lead to increased psychological stress (Arjmand et al., 2023).

Quality of life

In the analysis of quality of life, fatigue demonstrated a substantial negative impact. Interestingly, although fatigue is a significant predictor for quality of life, its beta-value (-0.124) is lower compared to some other factors. This indicates that, while fatigue has a broad and consistent impact, the extent of its influence might be less intense than factors like the number of walks post-covid or dyspnea symptoms. Conversely, better perceived overall health and increased physical activity (measured by the number of walks post-COVID) were associated with improved quality of life. However, the relationship between physical activity and quality of life should be interpreted with caution, as overexertion could potentially exacerbate symptoms in some patients due to post-exertional malaise (PEM), as mentioned earlier (Vernon et al., 2023; "WHO Guidelines Approved by the Guidelines Review Committee," 2022). Hyperventilation symptoms were negatively correlated with quality of life, reflecting the impact of respiratory issues on the overall well-being ("Mental wellbeing and lung health," 2020).

Limitations and Recommendations

Reflecting on the methodology of the study, several discussion points emerged that warrant further consideration. Considering the requirement for participants to travel to Diepenbeek for the study, it is probable that our sample predominantly comprised less severely affected patients. More severely affected individuals may have been unable to participate, and this selection bias has not been adequately addressed in our analysis.

Regarding the demographic characteristics of our sample, further research should aim to minimize gender selection bias and possible confounding by BMI.

Various tests and questionnaires were administered, including the MINI, a psychological questionnaire that includes some personal questions. In some cases, a partner or parent was present during the session, which could have influenced how participants responded to certain questions. This potential influence should be considered when interpreting the psychological functioning outcomes. A potential solution is to provide the MINI to participants on beforehand to notify them that it will include personal questions. On the contrary, the inclusion of a confidant during the administration of the MINI may be perceived as advantageous, as it fosters a conducive environment for candid disclosure.

Furthermore, one of our outcome measures is the daily functioning post-COVID-19, measured by the PCFS. However, the suitability of this measure is questionable since it may not be entirely objective. Consequently, this outcome measure is potentially biased as it solely reflects the patient's own assessment of their functioning. Nevertheless, we will consider it as an objective measure in this context, but we recommend that future research should aim to objectify this measure when using it as an outcome.

A potential suggestion for future research is to incorporate a time factor. In the current study, appointments were scheduled based on the availability of both the researcher and the participant. As previously mentioned, PEM significantly affects patients with PCS. This study did not account for the time of day when the measurements were conducted. Future research should consider including a time factor in the statistical analysis, as individuals with PCS who

participate in the morning may experience fewer symptoms compared to those who participate in the afternoon after engaging in various activities.

Another limitation of our study lies in the varied utilization of questionnaires and measurement tools, some of which have not been fully validated specifically for PCS-populations. Therefore, caution should be taken when extrapolating results to broader PCS-cohorts. Moving forward, future research should prioritize the validation and standardization of assessment measures tailored specifically for PCS. This will ensure greater accuracy and reliability in assessing the multifaceted aspects of PCS and ultimately advance the development of targeted interventions and treatment strategies.

Conclusion

Reflecting on the hypothesis, fatigue is indeed an important indicator for functioning and quality of life in individuals with PCS. However, it is crucial to recognize that fatigue is not the sole determinant. Other significant factors impacting our outcome measures include BMI, the number of walks post-COVID, overall health, anxiety levels, burnout, and hyperventilation symptoms. These findings underscore the complex and interconnected nature of physical and mental health challenges in PCS and highlight the need for comprehensive, multidisciplinary approaches to treatment and rehabilitation. Future research should focus on developing interventions specifically aimed at reducing fatigue and improving overall well-being in PCS-patients.

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