A biopsychosocial approach to persistent post-COVID-19 fatigue and cognitive complaints

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ORIGINAL RESEARCH

A Biopsychosocial Approach to Persistent Post-COVID-19 Fatigue and Cognitive Complaints: Results of the Prospective Multicenter NeNeSCo Study

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Abstract

Objective: To evaluate whether psychological and social factors complement biomedical factors in understanding post-COVID-19 fatigue and cognitive complaints. Additionally, to incorporate objective (neuro-cognitive) and subjective (patient-reported) variables in identifying factors related to post-COVID-19 fatigue and cognitive complaints.

Design: Prospective, multicenter cohort study.

Setting: Six Dutch hospitals.

Participants: 205 initially hospitalized (March-June 2020), confirmed patients with SARS-CoV-2, aged ≥18 years, physically able to visit the hospital, without prior cognitive deficit, magnetic resonance imaging (MRI) contraindication, or severe neurologic damage post-hospital discharge (N=205).

Interventions: Not applicable.

Main Outcome Measures: Nine months post-hospital discharge, a 3T MRI scan and cognitive testing were performed and patients completed questionnaires. Medical data were retrieved from medical dossiers. Hierarchical regression analyses were performed on fatigue severity (Fatigue Severity Scale; FSS) and cognitive complaints (Cognitive Consequences after Intensive Care Admission; CLC-IC; dichotomized into CLC-high/low). Variable blocks: (1) Demographic and premorbid factors (sex, age, education, comorbidities), (2) Illness severity (ICU/general ward, PROMIS physical functioning [PROMIS-PF]), (3) Neuro-cognitive factors (self-reported neurological symptoms, MRI abnormalities, cognitive

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performance), (4) Psychological and social factors (Hospital Anxiety and Depression Scale [HADS], Utrecht Coping List, Social Support List), and (5) Fatigue or cognitive complaints.

Results: The final models explained 60% (FSS) and 48% (CLC-IC) variance, with most blocks (except neuro-cognitive factors for FSS) significantly contributing. Psychological and social factors accounted for 5% (FSS) and 11% (CLC-IC) unique variance. Higher FSS scores were associated with younger age (P=.01), lower PROMIS-PF (P<.001), higher HADS-Depression (P=.03), and CLC-high (P=.04). Greater odds of CLC-high were observed in individuals perceiving more social support (OR=1.07, P<.05).

Conclusions: Results show that psychological and social factors add to biomedical factors in explaining persistent post-COVID-19 fatigue and cognitive complaints. Objective neuro-cognitive factors were not associated with symptoms. Findings highlight the importance of multidomain treatment, including psychosocial care, which may not target biologically-rooted symptoms directly but may reduce associated distress.

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Many individuals previously infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) experience persistent symptoms, with fatigue and cognitive complaints being the most common and debilitating.[1] These symptoms are also observed following other infectious (eg, Epstein-Barr virus, Coxiella burnetii bacteria, Ross River virus, Hepatitis C virus)[2,3] and non-infectious (eg, stroke,[4] traumatic brain injury[5]) conditions, potentially sharing underlying mechanisms. Research suggests that brain damage and also psychological and social factors contribute to these symptoms.[6-9]

Two magnetic resonance imaging (MRI) brain damage markers, cerebral microbleeds and white matter lesions (WML), may be connected to post-COVID-19 fatigue and cognitive complaints. Non-COVID-19 studies have established links between microbleeds and WML with fatigue[10] and cognitive complaints.[11-14] However, findings regarding associations between fatigue and WML are mixed.[15,16]

Psychological distress is recognized as a significant risk factor for post-infectious fatigue, with chronic fatigue syndrome often linked with stressful events and illness anxiety.[17,18] In the context of post-stroke cognitive complaints, psychological factors play a primary explanatory role,[8,17] with variables like anxiety, depression, social support, and coping being key contributors to persistent symptoms after neurologic conditions.[6,7,19]

Our knowledge on persistent post-COVID-19 symptoms is still incomplete. Evidence supports biological, psychological, and social influences on post-COVID-19 fatigue and cognitive complaints,[20] but their unique contributions have not yet been evaluated in an approach simultaneously examining subjective (self-reported) and objective (neuro-cognitive) measures. Knowledge about these associations give insight into potential risk factors.

This prospective cohort study integrates neuroimaging, cognitive testing, questionnaires, and medical records to investigate post-COVID-19 fatigue and cognitive complaints from a biopsychosocial perspective considering objective and subjective factors. The study aims to determine the explanatory value of psychological and social variables beyond biological factors and identify specific factors associated with post-COVID-19 fatigue and cognitive complaints.

List of abbreviations:

APACHE-IV	**Acute Physiology And Chronic Health Evaluation IV**
CI	**confidence interval**
CLC-IC	**Checklist for Cognitive Consequences after Intensive Care Admission**
CLCE-24	**Checklist for Cognition and Emotion**
COVID-19	**Coronavirus disease 2019**
eg	**for example**
FSS	**Fatigue Severity Scale**
HADS	**Hospital Anxiety and Depression Scale**
ICU	**intensive care unit**
ISI	**Insomnia Severity Index**
MRI	**magnetic resonance imaging**
NeNeSCo	**Neurological and Neuropsychological Sequelae of COVID-19**
non-ICU	**non-intensive care unit (general ward)**
OR	**odds ratio**
PROMIS-PF	**Patient-Reported Outcomes Measurement Information System physical function**
PSQI	**Pittsburgh Sleep Quality Index**
SARS-CoV-2	**severe acute respiratory syndrome coronavirus 2**
SOFA	**sequential organ failure assessment**
SSL-12-L	**Social Support List**
UCL	**Utrecht Coping List**
WML	**white matter lesions**

Methods

Study design and participants

Cross-sectional data of the multicenter prospective cohort NeNeSCo (Neurological and Neuropsychological Sequelae of COVID-19) study (see Klinkhammer et al's 2021[21] and 2023[22] studies for more detail) were used. Participants were 205 intensive care unit (ICU) and general ward (non-ICU) COVID-19 survivors from 6 Dutch hospitals (see supplemental appendix S1, available online only at http://www.archives-pmr.org/) admitted during the first European infection wave (March to June 2020). Ethical approval was obtained, and the study was preregistered (ClinicalTrials.gov; NCT04745611).

Eligible participants were patients who had been admitted for confirmed SARS-CoV-2 treatment, 18 years or older, and proficient in Dutch. Exclusions included MRI contraindications, pre-existing cognitive impairment (based on medical records), severe post-hospital neurologic damage, or inability to visit the hospital for measurements. Recruitment occurred at least 6 months after hospital discharge, and patients underwent a 3T cranial MRI scan, cognitive tests, and completed questionnaires.

Procedure

Recruiting hospitals provided lists of COVID-19 patients. The order of lists was randomized and those meeting the criteria were contacted for participation until the intended sample size (for calculation see Klinkhammer et al[21]) was reached.

A 3T MRI scan and cognitive testing were performed during the same day at 1 of 3 university medical centers (ie, Amsterdam UMC, Maastricht UMC, UMC Utrecht). Brain abnormalities were evaluated by a clinical neuroradiologist using established criteria with good interrater reliability.[23] The cognitive test battery was carried out by trained research assistants. Questionnaires were completed on site during the visit (43% of patients) or at home, shortly after the visit (maximally 4 weeks), on paper or online. Medical data were retrieved from medical files or from the Dutch national COVID-19 database, CovidPredict.[24]

Measures

Dependent variable 1: fatigue

Fatigue was measured using the Fatigue Severity Scale (FSS), a 9-item self-report scale rated on a 7-point scale (total range 9-63), with higher scores indicating more fatigue. A score above 36 indicates severe fatigue.[25]

Dependent variable 2: cognitive complaints

Cognitive complaints were evaluated using the Checklist for Cognitive Consequences after Intensive Care Admission (CLC-IC; adapted from the Checklist for Cognition and Emotion; CLCE-24), a 10-item questionnaire assessing the presence of cognitive complaints (range 0-10).[26] CLC-IC scores were categorized as "CLC-low" (<4) and "CLC-high" (≥4) based on a mean score of 1.9 (SD=1.9) in healthy controls on the CLCE-24.[27]

Independent variables: Block 1 - Demographic and premorbid factors

Demographic variables (sex, age, and education) were collected through a paper-based questionnaire. Education level was categorized "high" (completed high-level secondary education or university) or "low", based on the Dutch education system (see supplemental appendix S2, available online only at http://www.archives-pmr.org/).

Comorbidities retrieved from medical files included diabetes mellitus, hypertension, overweight (body-mass-index ≥25), chronic pulmonary, and chronic cardiac disease; common risk factors for cognitive decline.[28] To reduce the number of predictors, a comorbidity compound score was created, assigning 1 point per comorbidity (range: 0-5). The score was then dichotomized into "low" (<2) and "high" (≥2).

Independent variables: Block 2 — Illness severity

Because of the lack of a COVID-19 illness severity measure at the time of data collection, illness severity was determined based on initial hospitalization in either the ICU or the general ward (non-ICU). Since critical COVID-19 is associated with reduced physical functioning after hospital discharge,[29] the Patient-Reported Outcomes Measurement Information System Physical Function (PROMIS-PF) (short form 8b), was included.[30] The PROMIS-PF is a 6-item self-report questionnaire rated on a 5-point scale, where higher scores indicate better physical functioning. Normalized *t*-values of the total score were used for analysis.

Independent variables: Block 3 — Neuro-cognitive factors

Neurological symptoms were assessed with a self-report questionnaire that recorded the presence of common symptoms after infection: changes in taste, smell, or vision, (neuropathic) pain, headaches, reduced sensation in hands or feet, and loss of muscle strength.

Cerebral microbleeds and WML were assessed using the 3T MRI scan with a standardized protocol including T1- and T2-weighted, fluid-attenuated inversion recovery, susceptibility-, and diffusion-weighted images. The number of cerebral microbleeds, defined as small hypointensities on T2-weighted images, was categorized into (scores 0-6): no microbleeds, 1 microbleed, 2-4 microbleeds, 5-9 microbleeds, 10-19 microbleeds, and ≥20 microbleeds.

WML were expressed as Fazekas scores[31] (scores 0-3): no WML, punctuate/non-confluent WML, starting confluent WML, and confluent WML. Analyses initially evaluated Fazekas score and microbleeds independently. Non-significant associations led to their consolidation into a compound brain abnormality score. A score of 1 was assigned if both Fazekas and microbleed scores were >1; otherwise, it was set to 0.

Cognitive dysfunction was assessed using a battery of internationally recognized and validated neuropsychological tests. These tests evaluated mental speed, attention, executive function, (working) memory, visuospatial-, and language abilities (see supplemental appendix S3, available online only at http://www.archives-pmr.org/). Initially, analyses examined associations with separate cognitive domains (see supplemental appendix S4, available online only at http://www.archives-pmr.org/). As neither showed significant associations, all test scores were averaged into 1 T score.[32]

Independent variables: Block 4 — Psychological and social factors

Anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS), with 7 self-report items for each anxiety and depression (subscale score range: 0-21). Higher scores indicate higher levels of the anxiety/depression.

Passive coping tendencies were assessed using the passive coping subscale of the Utrecht Coping List (UCL), consisting of 7 items (score range: 7-28).[33] Higher scores indicate a greater tendency for passive coping.

Social support was measured using the Social Support List (SSL-12-I), which includes 12 self-report items (score range: 12-48). Higher scores indicate greater perceived social support.[34]

Block 5 — Fatigue and cognitive complaints

The FSS was entered in the final cognitive complaints model. The (dichotomized) CLC-IC was entered in the final fatigue model.

Analyses

Missing data imputation

Missing data were imputed through multiple imputation by chained equation, using Van Buuren, Boshuizen, and Knook's approach, executed with the MICE package in R.[35,36] Results were pooled using Rubin's rule (most used method to pool parameter estimates[37]). For details, see supplemental appendix S5 (available online only at http://www.archives-pmr.org/).

Data analyses

Hierarchical regression analyses were conducted to determine the proportion of variance explained by the previously described variable blocks. Linear regression was used for FSS scores, while logistic regression was used for dichotomized CLC-IC scores. Blocks were entered in the following order: (1) Demographic and premorbid factors, (2) Illness severity, (3) Neuro-cognitive factors, (4) Psychological and social factors, and (5) Fatigue/Cognitive complaints. The final model consisted of all 5 variable blocks.

Explained variance was expressed as R^2 for linear regression and Nagelkerke R^2 for logistic regression. Model improvements were analyzed using the F-statistic for linear regression and likelihood ratio chi-square test for logistic regression. Associations between independent variables and FSS/CLC-IC scores were expressed using standardized regression coefficients (Betas) for linear regression and odds ratios (OR) for logistic regression along with their 95% confidence intervals (CIs).

Sensitivity analyses were conducted to test the robustness of findings. The first analysis compared results based on the imputed dataset to those from the non-imputed dataset. The second examined the use of ICU/general ward hospitalization and physical functioning as proxies for illness severity, with the highest sequential organ failure assessment (SOFA) and Acute Physiology And Chronic Health Evaluation IV (APACHE IV). These are recognized measures of illness-severity in ICU patients. Because of multicollinearity, only the variable correlating stronger with the outcome variable was included. The third analysis explored the contribution of sleep-related variables (Insomnia Severity Index [ISI] and Pittsburgh Sleep Quality Index [PSQI]) as an additional block. All sensitivity analyses followed the same approach as the primary analyses.

For all analyses, significance was assessed at a 2-sided alpha-level of 0.05. To enhance between-study comparability, significance is additionally reported at the most used alpha-levels (ie, 0.1, 0.05, 0.01, 0.001). Analyses were executed using R version 4.2.2.

Table 1 Patient characteristics (N=205)

Demographic and premorbid factors	
Sex (women); n (%)	62/205 (30.2)
Age (years); median [IQR]	63 [53-69]
Education (high);* n (%)	82/205 (40.0)
Comorbidities† (>1); n (%)	55/120 (45.8)
Diabetes; n (%)	25/183 (13.6)
Hypertension; n (%)	61/183 (33.3)
Chronic cardiac disease; n (%)	38/183 (20.8)
BMI ≥25; n (%)	102/124 (82.3)
Chronic pulmonary disease; n (%)	17/183 (9.29)
Illness severity	
Hospitalization (ICU); n (%)	101/205 (50.9)
PROMIS physical function; mean ± SD‡	45.8 (17.6)
Neuro-cognitive factors	
Neurological symptoms (number); median [IQR]	2 [0-4]
Brain abnormalities, n (%)	22/198 (11.1)
Microbleeds (>1); n (%)	66/198 (33.3)
Fazekas (>1); n (%)	52/198 (26.2)
Cognitive function; median [IQR]§	0.9 [0.6-1.3]
Psychosocial factors	
HADS-Anxiety; median [IQR]	3 [1-6]
HADS-Depression; median [IQR]	2 [1-5]
Utrecht Coping List - passive coping; median [IQR]	9 [7-11]
Social Support List; median [IQR]	31 [26-36]
Outcome variables	
Fatigue Severity Scale; mean ± SD	37.7 (19.8)
Cognitive complaints (≥4); n (%)	96/196 (49.0)

* Completed high level secondary education or university degree.
† Compound score consisting of diabetes, hypertension, chronic cardiac disease, BMI≥25, and chronic pulmonary disease.
‡ Normalized *t*-values of the total score.
§ Average T score across all cognitive tests.

Results

A total of 205 patients were included in this analysis. Their characteristics are shown in table 1. Assessments were performed 9 months post-hospital discharge.

Fatigue

The mean FSS score was 37.4 (*SD*=13.3), 51% of patients had an FFS score above the clinical cutoff. Table 2 displays the results of the FSS regression analyses.

Model 1 showed that demographic and premorbid factors explained 13% of the variance in FSS scores. Model 2, adding illness severity, accounted for an additional 39% of variance, leading to a significant improvement of the model (*P*<.001). An extra 2% of variance was explained by model 3, entering neuro-cognitive factors, which did not improve the model fit significantly (*P*=.098). Adding psychological and social factors in model 4 increased the proportion of explained variation significantly (*P*<.001) by 5%. CLC-IC explained 1%, significantly contributing to a total explained variation of 60%. In the final model, lower age (β=-0.13, 95% CI [-0.23, -0.03], *P*=.015), lower PROMIS-PF score (β=-0.49, 95% CI [-0.62, -0.36], *P*<.001), higher HADS-Depression score (β=0.16, 95% CI [0.02, 0.31], *P*=.048), and being in the high CLC-IC group (β=0.28, 95% CI [0.05, 0.50], *P*=.018) were associated with higher levels of fatigue.

Cognitive complaints

The median CLC-IC score was 3 (interquartile range=1-7), 48% of patients were in the CLC-high group. Table 3 displays the results of the CLC-IC regression analyses.

Model 1 showed that demographic and premorbid factors explained 6% of the variance in the CLC-IC. Model 2, adding illness-severity, explained 24% of variance in the CLC-IC (*P*<.001). Adding neuro-cognitive factors in model 3 led to a significant increase in explained variance (*P*=.008) of 6%. Including psychological and social factors increased the explained variation by another 11% significantly (*P*<.001). Adding CLC-IC did not improve the model (*P*=.080). The full model explains 47% of variation, with significantly higher odds for CLC-high with increasing social support (OR=1.07, 95% CI [1.01-1.14], *P*=.031). At a less conservative alpha of 0.1, the odds of CLC-high increased with a higher UCL score (OR=1.20, 95% CI [0.97-1.47], *P*=.086) and having higher FSS scores (OR=1.04, 95% CI [0.99-1.08], *P*=.096).

Table 2 Linear regression model for fatigue severity (Fatigue Severity Scale)

Independent Variables	Model 1			Model 2			Model 3			Model 4			Model 5		
	Beta	SE	95% CI	Beta	SE	95% CI	Beta	SE	95% CI	Beta	SE	95% CI	Beta	SE	95% CI
Demographic and premorbid factors															
Sex (women)*	0.49‡	0.15	0.20-0.78	0.11	0.12	-0.13 to 0.35	0.11	0.11	-0.11 to 0.33	0.13	0.11	-0.09 to 0.35	0.12	0.11	-0.10 to 0.34
Age	-0.08	0.07	-0.22 to 0.06	-0.17‡	0.05	-0.27-(-0.07)	-0.15†	0.06	-0.27-(-0.03)	-0.13	0.06	-0.25-(-0.01)	-0.13†	0.05	-0.23-(-0.03)
Education (high)*	-0.29†	0.14	-0.56-(-0.02)	-0.11	0.11	-0.33 to 0.11	-0.08	0.11	-0.30 to 0.14	-0.03	0.11	-0.25 to 0.19	-0.04	0.11	-0.26 to 0.18
Comorbidities (high)*	0.42‡	0.15	0.13-0.71	0.09	0.12	-0.15 to 0.33	0.05	0.12	-0.19 to 0.29	0.13	0.12	-0.11 to 0.37	0.13	0.11	-0.09 to 0.35
Illness severity															
Hospitalization (non-ICU)*				0.04	0.10	-0.16 to 0.24	0.03	0.10	-0.17 to 0.23	-0.05	0.10	-0.25 to 0.15	-0.05	0.10	-0.25 to 0.15
PROMIS physical function				-0.70§	0.06	-0.82-(-0.58)	-0.62§	0.06	-0.74-(-0.50)	-0.52§	0.07	-0.66-(-0.38)	-0.49§	0.07	-0.63-(-0.35)
Neuro-cognitive factors															
Neurological symptoms (number)							0.13•	0.06	0.01-0.25	0.02	0.07	-0.12 to 0.16	0.00	0.07	-0.14 to 0.14
Brain abnormalities (high)*							-0.16	0.17	-0.49 to 0.17	-0.13	0.16	-0.44 to 0.18	-0.14	0.16	-0.45 to 0.17
Cognition (average T score)							-0.04	0.06	-0.16 to 0.08	-0.01	0.06	-0.13 to 0.11	-0.01	0.06	-0.13 to 0.11
Psychological and social factors															
HADS-Anxiety										0.07	0.09	-0.11 to 0.25	0.06	0.09	-0.12 to 0.24
HADS-Depression										0.18†	0.08	0.02-0.34	0.16†	0.08	0.00-0.32
Utrecht Coping List - passive coping										0.10	0.08	-0.06 to 0.26	0.08	0.08	-0.08 to 0.24
Social Support List										0.04	0.05	-0.06 to 0.14	0.01	0.05	-0.09 to 0.11
Cognitive complaints															
CLC-IC (high)*													0.28†	0.12	0.04-0.52
R^2	0.13			0.52			0.54			0.59			0.60		
Adjusted R^2	0.11			0.51			0.52			0.56			0.55		
ΔF				81.95§			2.12•			6.30§			6.06†		

Abbreviations: CLC-IC, Checklist for Cognitive Consequences after Intensive Care Admission; HADS, Hospital Anxiety and Depression Scale; non-ICU, non-intensive care unit.

* Dichotomous variable with reference category given in brackets.

• $P<.1$.

† $P<.05$.

‡ $P<.01$.

§ $P<.001$.

Table 3 Logistic regression model for cognitive complaints (Cognitive Consequences after Intensive Care Admission)

Independent Variables	Model 1			Model 2			Model 3			Model 4			Model 5		
	B	SE	OR (95% CI)	B	SE	OR (95% CI)	B	SE	OR (95% CI)	B	SE	OR (95% CI)	B	SE	OR (95% CI)
Demographic and premorbid factors															
Sex (women)*	0.70	0.33	2.02† (1.06-3.83)	0.23	0.37	1.26 (0.61-2.63)	0.21	0.39	1.23 (0.57-2.63)	0.22	0.43	1.25 (0.54-2.90)	0.14	0.44	1.15 (0.48-2.73)
Age (years)	0.00	0.01	1.01 (0.98-1.03)	0.00	0.01	1.00 (0.97-1.03)	0.00	0.02	1.00 (0.97-1.03)	0.01	0.02	1.01 (0.97-1.04)	0.01	0.02	1.02 (0.98-1.05)
Education (high)*	-0.34	0.31	0.71 (0.39-1.31)	-0.08	0.34	0.92 (0.47-1.81)	0.06	0.37	1.06 (0.51-2.19)	0.28	0.41	1.32 (0.59-2.96)	0.27	0.41	1.31 (0.58-2.95)
Comorbidities (high)*	0.36	0.33	1.43 (0.74-2.74)	-0.14	0.38	0.87 (0.41-1.83)	-0.22	0.39	0.80 (0.37-1.74)	0.04	0.43	1.04 (0.44-2.45)	-0.05	0.44	0.95 (0.40-2.27)
Illness severity															
Hospitalization (non-ICU)*				0.04	0.33	1.04 (0.54-2.01)	0.08	0.35	1.09 (0.54-2.17)	-0.05	0.39	0.96 (0.45-2.05)	-0.03	0.39	0.97 (0.45-2.09)
PROMIS physical function				-0.15	0.03	0.86§ (0.82-0.91)	-0.11	0.03	0.89§ (0.84-0.95)	-0.08	0.03	0.92 (0.87-0.98)	-0.05	0.03	0.95 (0.89-1.02)
Neuro-cognitive factors															
Neurological symptoms (number)							0.27	0.09	1.30‡ (1.09-1.55)	0.16	0.10	1.17 (0.95-1.43)	0.16	0.10	1.17 (0.95-1.44)
Brain abnormalities (high)*							0.14	0.57	1.15 (0.38-3.51)	0.19	0.59	1.20 (0.37-3.87)	0.25	0.59	1.28 (0.40-4.11)
Cognitive function							-0.01	0.03	0.99 (0.94-1.05)	-0.01	0.03	1.00 (0.94-1.06)	0.00	0.03	1.00 (0.94-1.06)
Psychological and social factors															
HADS-Anxiety										0.03	0.09	1.03 (0.87-1.23)	0.03	0.09	1.03 (0.86-1.23)
HADS-Depression										0.19	0.09	1.21† (1.01-1.44)	0.15	0.09	1.16 (0.96-1.39)
Utrecht Coping List - passive coping										0.20	0.11	1.23• (0.99-1.51)	0.18	0.10	1.20• (0.97-1.47)
Social Support List										0.07	0.03	1.07† (1.01-1.14)	0.07	0.03	1.07† (1.01-1.14)
Fatigue															
Fatigue Severity Scale													0.04	0.02	1.04• (0.99-1.08)
Nagelkerke R^2			0.06			0.30			0.36			0.47			0.48
-2 Log Likelihood			274.37			231.57			219.83			195.68			192.62
χ^2						42.80§			11.74‡			24.15§			3.06

Abbreviations: HADS, Hospital Anxiety and Depression Scale; non-ICU, non-intensive care unit.

* Dichotomous variable with reference category given in brackets.

• $P<.1$.

† $P<.05$.

‡ $P<.01$.

§ $P<.001$.

Sensitivity analyses

A comparison of models based on the imputed and non-imputed datasets showed that for the FSS, significant variables in the final model did not change except for the CLC-IC only being marginally significant. The final CLC-IC model showed no significant variables but similar trends as the imputed data.

Sensitivity analyses including the APACHE IV (FSS: $r_{FSSxSOFA}$=.037; $r_{FSSxAPACHE}$ =-.074) for FSS and SOFA (CLC-IC: $r_{CLCxSOFA}$=.032; $r_{CLCxAPACHE}$=-.026) for the CLC-IC only marginally differed from the main analyses and neither showed a significant association with the outcome variable.

An analysis including a sixth predictor block containing sleep (ISI sumscore and PSQI sleep efficiency) did not explain a significant amount of variance in FSS or CLC-IC but the odds of high CLC-IC increased with a higher ISI sumscore (OR: 1.11, *P*=.027). Detailed sensitivity analyses results can be found in the supplemental material (supplemental tables S1-S6, available online only at http://www.archives-pmr.org/).

Discussion

This study confirms that persistent post-COVID-19 fatigue and cognitive complaints in hospitalized patients are prevalent and linked to biological, psychological, and social factors. The final models explained substantial variance, consistent with similar studies.[38-40] Psychological and social variables accounted for small but significant amounts of variance when controlling for biomedical factors. Younger age, poorer physical functioning, depressive symptoms, and increased cognitive complaints were associated with higher fatigue. Cognitive complaints were linked to more social support. Passive coping and fatigue showed significance at a less conservative alpha threshold.

Fatigue

Younger individuals experienced more severe fatigue, fitting the overall post-COVID-19 profile and likely attributable to higher daily life demands such as active careers or family management.[41-43] Physical functioning showed the strongest association with fatigue. This can be explained by compensatory mechanisms, where functional loss and deconditioning lead to increased physical effort and thus higher levels of fatigue.[44] Fatigue then reduces daily activity, leading to further deconditioning, causing a self-reinforcing cycle.[45] This similarly has been observed in other diseases and after general critical illness.[46-48] Self-reported fatigue and physical functioning can be influenced by factors beyond symptom severity, such as personality and introspective ability, thereby increasing their association.[49] Further, while fatigue has both physical and cognitive/mental components, the FSS emphasizes the physical component, explaining the strong connection to physical functioning.[50] Consequently, future research should assess results using a mental fatigue measure.

Neuro-cognitive factors did not significantly explain fatigue-variance. In line with this, fatigue after traumas not involving the brain, such as orthopedic injuries, suggests other contributing factors.[51] We report a significant association between fatigue and depressive symptoms, frequently observed across various medical conditions (eg, Hepatitis C, human immunodeficiency virus [HIV], or general critical illness), suggesting a common underlying factor, potentially immune system activation.[3,52-54] Yet, preliminary Hepatitis C evidence shows persistent fatigue despite viral remission, suggesting secondary or additional consequences.[52,54]

The association between fatigue and cognitive complaints may result from individuals perceiving cognitive shortcomings exerting additional effort, leading to increased fatigue.[44] Conversely, fatigue can make cognitive tasks more effortful. Depressive symptoms may contribute via rumination and catastrophizing thoughts.[55]

Biological, psychological, and social variables are interconnected. Psychological factors can affect bodily functions, potentially mitigating biological symptoms.[56] Although fatigue may have a biological component, psychological treatment may be able to alleviate the perceived burden. Cognitive behavioral therapy effectiveness in managing post-COVID-19 fatigue supports this.[57] Therefore, despite modest contribution, psychological and social factors may offer modifiable treatment targets.

Cognitive complaints

Our findings suggest that post-COVID-19 cognitive complaints are not linked to cognitive dysfunctions or brain damage, as defined by the variables examined in this study. This discrepancy is common, also in research beyond COVID-19.[58-60] Instead, mental health factors such as anxiety, depression, and personality traits like neuroticism, inverse openness, and conscientiousness frequently predict cognitive complaints.[61,62] In a model not yet including fatigue, we observe an association with depressive symptoms. The absence of significance in the final model is likely due to the overlap between fatigue and depression, suggesting an interrelation between the 3 factors. Depressive symptoms, rather than cognitive dysfunctions, may underlie the attentional problems and mental slowness.[59] Maladaptive coping, linked to depression, like symptom monitoring and catastrophic thinking, may also influence cognitive beliefs.[63] Though cognitive complaints are not linked to cognitive functioning now, they could predict future decline.[64]

Although counterintuitive, the link between cognitive complaints and increased perceived social support may result from governmental restrictions that reduced social interactions. This may have been especially limiting for pre-pandemic socially active individuals. The sensitivity analysis, including insomnia, revealed links to increased cognitive complaints, consistent with prior findings, offering additional treatment possibilities.[65]

In general, there seems to be overlap and distinct characteristics among factors associated with cognitive complaints and fatigue, potentially requiring different treatment. Insights from conditions such as traumatic brain injury,[66] HIV,[67] and multiple sclerosis[68] support our data by indicating effectiveness of a multidomain treatment approach.

Fatigue and cognitive complaints are not exclusive to hospitalized patients but are also prevalent in non-hospitalized COVID-19 individuals. Our results are potentially transferable to non-hospitalized individuals. The absence of association with brain abnormalities and cognitive dysfunction in severely ill patients suggests that a similar pattern may hold for less-severely ill individuals. However, explicit investigation in future research is essential.

Strengths and weaknesses

Our study, evaluating associations of objective and subjective variables in a non-preselected sample (ie, not preselected on

neurological, cognitive, or fatigue symptomatology), and a multicenter recruitment generated input for future research and clinical practice. The use of advanced imputation methods prevented a potential bias caused by listwise-deletion, while sensitivity analyses showed robustness of results. Though unique contributions of psychological and social variables were modest, findings were limited by the available data. This is the result of limited knowledge about the disease at the time of study design (beginning of 2020) and led to interesting variables not being considered (eg, personality traits, inflammation severity, COVID-19-specific illness-severity measure, pre-pandemic mental health, health-promoting variables such as diet or exercise).

However, the early study execution likely reduced the participation bias, as post-COVID-19 syndrome was not yet in the center of attention, and little was known about persistent consequences. Inclusion of non-hospitalized individuals would have been of added value, but individuals were often not formally tested on SARS-CoV-2. Most variables were measured at the same timepoint, allowing for identification of associations between variables but not for timely prediction.

Conclusion/Implications

Persistent post-COVID-19 fatigue and cognitive complaints are associated with a complex interplay of biological, psychological, and social factors. Our study shows that psychological and social factors add to biomedical factors in explaining the occurrence of persistent post-COVID-19 fatigue and cognitive complaints, either directly or indirectly via subjective physical function, depressive symptoms, and social support. Objective neuro-cognitive factors were not associated with either fatigue or cognitive complaints. Treatment of post-COVID-19 symptoms should include psychosocial care, which may not be able to target biologically rooted symptoms directly but may reduce associated distress and disease effect. Evidence for this is found in cognitive behavioral therapy reducing symptoms without the need of biomedical changes.

Keywords

Cognitive complaints; Fatigue; Infection; Long COVID; Post-COVID; Rehabilitation; SARS-CoV-2

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