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Risk factors for fatigue and impaired function eight months after hospital admission with COVID-19

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ABSTRACT

Introduction. We aimed to evaluate post-COVID-19 fatigue, change in functional capacity and health-related quality of life (HRQoL) eight months after discharge from hospital due to COVID-19.

Methods. A total of 83 patients (35 women) admitted to the Copenhagen University Hospital – North Zealand Hospital, Denmark, for COVID-19 during the period from March to June 2020 were evaluated eight months after discharge using validated questionnaires quantifying fatigue, HRQoL and post-COVID-19 functional status. Follow-up data were correlated with measures of pre-COVID-19 status (anthropometrics, comorbidities) and measures of severity of the acute infection.

Results. A total of 22 (65%) women and 12 (26%) men reported excessive fatigue. In all, 20 women (67%) and 17 men (37%) reported decreased physical function. Female sex was associated with fatigue. Loss of physical function was associated with pre-COVID-19 presence of heart disease and absence of lung disease. Severity of the acute COVID-19 infection was not associated with fatigue or change in functional status. Fatigue and functional status were correlated with both generic HRQoL and lung disease-specific HRQoL.

Conclusions. Female sex was associated with a higher risk of fatigue eight months after hospitalisation with COVID-19 infection. Regarding loss of functional capacity after COVID-19, we found an apparently protective effect of pre-COVID-19 lung disease. Our findings underscore the urgent need for further research and the importance of evaluating those recovering from COVID-19 for symptoms of excessive fatigue and change in functional capacity irrespective of the severity of the initial infection.

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Trial registration. not relevant.

The COVID-19 pandemic caused by SARS-CoV-2 is the third known introduction of a highly pathogenic coronavirus into the human population within a period of 20 years, preceded by the Middle East Respiratory Syndrome (MERS) in 2012 and the Severe Acute Respiratory Syndrome (SARS) in 2002/2003 [1]. As of 9 July 2021, more than 185 million cases of COVID-19 and four million deaths have been registered worldwide [2]. Evidence is emerging describing a substantial number of both hospitalised and non-hospitalised COVID-19 patients suffering from persistent symptoms ("long COVID") with fatigue as a core symptom for up to six months of follow-up [2-4]. On follow-up of survivors after the previous outbreaks of SARS and MERS, clinically relevant fatigue was observed in a significant proportion of patients (up to 60%) 12 months after their acute infection [1].

Fatigue is associated with functional impairment and is a dominant symptom in a wide range of infectious and non-infectious diseases [5]. As a non-specific symptom, fatigue is difficult to evaluate. Limited information is available describing and quantifying fatigue as a long-term sequela in Danish patients after severe COVID-19 (requiring hospitalisation) with a follow-up time exceeding six months. Furthermore, a description of possible changes in functional status and health-related quality of life (HRQoL) and their association with fatigue is warranted.

Based on experiences from the previous SARS and MERS outbreaks and the growing concern regarding post-COVID-19 fatigue, we aimed to:

1: Study the burden of post-COVID-19 fatigue and evaluate changes in self-rated functional status as primary endpoints with HRQoL and lung disease-specific HRQoL and various aspects of fatigue as secondary endpoints eight months after discharge due to severe COVID-19 infection.

2: Explore risk factors for "long COVID" fatigue and impaired functional status in patients with severe COVID-19.

METHODS

Study population

Patients admitted to the Copenhagen University Hospital – North Zealand Hospital, Denmark (NZH) who had tested positive for SARS-CoV-2 between 1 March and 15 June 2020 were included as described previously [6]. Approximately eight months after discharge, patients who were not nursing home residents were offered a follow-up appointment in the outpatient clinic at the Department of Pulmonary and Infectious Diseases, NZH. All data were registered using an electronic data capture tool hosted by the Capital Region of Denmark. This study was approved by the Danish Patient Safety Authority (project ID 31-1521-266). Because of the retrospective nature of the study, the requirement for informed consent was waived.

Clinical data and variables from hospital stay

Data on demographic characteristics, admission findings and interventions during admission were collected from the electronic medical record system ("Sundhedsplatformen" by EPIC) [6].

Pre-COVID-19 status

Participants were characterised with respect to age at admission, sex, BMI and multi-morbidity categorised as 0, 1 or ≥ 2 [7] of the following: cancer, hypertension, coronary artery disease, congestive heart failure, diabetes, cerebrovascular disease, asthma, chronic obstructive pulmonary disease (COPD) and chronic kidney disease [6].

Severity of the acute infection

Severity was assessed by admission length (days), inflammatory load estimated as highest measure of ferritin during the admission [8], maximum oxygen supply during admission (categorised into two groups: 1) maximum oxygen supply ≤ 2 l/min.; or 2) > 2 l/min. including high flow ventilation, non-invasive ventilation and mechanical ventilation) and presence of bacterial co-infection.

Follow-up

Data from questionnaires were collected from the electronic medical record system.

Fatigue Assessment Scale

A general ten-item fatigue questionnaire with good psychometric qualities for an array of diseases was used. A total score and a mental and a physical score were calculated. The total score defines three subgroups: no fatigue (total score < 22), fatigue (total score 22-34) and extreme fatigue (total score ≥ 35) [9]. As primary endpoint, excessive fatigue operalisationalised as a Fatigue Assessment Scale (FAS) score ≥ 22 was used.

The Post-COVID-19 Functional Status Scale

A questionnaire developed for the evaluation of the ultimate consequences of COVID-19 on functional status was employed using a five-step ordinal scale (0-4) with higher values indicating poorer functional status [10]. The patients were asked to evaluate their functional status at follow-up approximately eight months after discharge and to quantify their functional capacity immediately prior to contracting COVID-19.

EQ-5D-5L

The EQ-5D-5L is a self-reported, generic HRQoL questionnaire consisting of two parts: (A) A descriptive system based on five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) with five levels of severity in each dimension. Based on a profile score in each of the five domains, a single index score describing a patient's HRQoL is derived. (B) The EQ visual analogue scale (EQ-VAS) recording the patient's self-rated health on a vertical visual analogue scale [11].

The King's Brief Interstitial Lung Disease questionnaire

Finally, the study comprised the King's Brief Interstitial Lung Disease questionnaire (K-BILD); 15-item validated self-completed lung disease-specific HRQoL questionnaire yielding scores in three domains (breathlessness and activities (K-BILD BA), chest symptoms (K-BILD CH), and psychological (K-BILD PS)) [12].

Statistical analysis

The patients' characteristics and clinical variables were tested for associations with the two outcome variables fatigue and decreased function in unadjusted linear regression analyses. Variables that were associated ($p < 0.1$) with the outcome were included in multiple linear regression analyses (general linear model) of the associations between included independent variables and outcomes. Interactions between sex and other categorical independent variables were tested.

The statistical analyses were conducted using the IBM SPSS 25 programme. Data are presented as number (percentage), median (interquartile range), mean ± standard deviation) or β (95% confidence interval). Results were considered significant (two-tailed) when $p < 0.05$.

For further information see https://ugeskriftet.dk/files/a08210633_-_supplementary.pdf.

Trial registration: not relevant.

RESULTS

Among 172 eligible patients (76 females), 39 (22.6%) died during or after admission, 14 were excluded as they were residents at nursing homes, seven were followed up at other hospitals and therefore not invited, and 29 declined the offer of follow-up, leaving 83 patients for further analysis (see **Table 1**). The included patients were comparable to the ones lost to follow up with regard to gender, age at admission, presence of co-morbidities and admission length. The included 83 patients (35 females) were admitted to the NZH with COVID-19 during the study period. They were evaluated at the out-patient clinic 8.5 ± 1.5 months after their discharge and had a median age of 67 (55-75) years. Mean admission length was 9.5 ± 15.2 days. Twenty-seven patients (33%) were diagnosed with bacterial coinfection during admission and ten patients (12%) were admitted to the intensive care unit (ICU).

TABLE 1 Characteristics of the participants (N = 83).

Age, yrs, median (IQR)/mean ± SD	67 (55-75)/64 ± 15
Female/male, n (%)	35 (42)/48 (58)
BMI, kg/m², median (IQR)/mean ± SD	26.5 (23.2-30.9)/27.6 ± 6.0
Comorbidities, n (%)	
0	45 (55)
1	23 (28)
≥ 2	14 (17)
Heart disease: CAD and/or CHD, n (%)	19 (23)
Lung disease: COPD and/or asthma, n (%)	16 (20)
Admission days, n, median (IQR)	4 (2-10)
Ferritin concentration[a]	
Highest concentration, µg/l, mean ± SD	1,112 ± 1,091
0-822.5 µg/l, n (%)	38 (50)
≥ 822.6 µg/l, n (%)	38 (50)
Oxygen administered	
Highest amount administered, l/min., median (IQR)	3 (2-5)
≤ 2 l/min., n (%)	47 (57)
> 2 l/min., n (%)	36 (43)
Bacterial coinfection, n (%)	27 (33)

CAD = coronary artery disease; CHD = congestive heart failure; IQR = interquartile range; SD = standard deviation.
a) Only 76 participants.

A total of 34 (41% of 80 patients) patients reported excessive fatigue at follow-up (women n = 22 (65%); men n = 12 (26%)) of whom seven women (21%) and three men (7%) reported suffering from extreme fatigue. Female sex and a high levels of ferritin and oxygen demand during admission were associated with fatigue in unadjusted analyses (**Table 2**). A loss of functional status after the COVID-19 illness was reported by 37 (49% of 76 patients) patients (women n = 20 (67%); men n = 17 (37%)). Female sex was associated with a reduction in functional status at follow-up (Table 2).

TABLE 2 Unadjusted associations between independent variables and the outcomes fatigue and decreased physical function.

	Fatigue		Decreased function	
	β (95% CI)	p-value	β (95% CI)	p-value
Age: yrs	0.01 (–0.15-0.16)	0.940	0.01 (–0.01-0.02)	0.538
Sex: female	7.86 (3.70-12.02)	< 0.001	0.59 (0.13-1.05)	0.013
BMI: kg/m²	0.24 (–0.16-0.64)	0.241	0.03 (–0.02-0.07)	0.215
Comorbidities: n				
0	1		1	
1	4.49 (–0.63-9.61)	0.085	0.40 (–0.16-0.96)	0.157
≥ 2	5.87 (–0.15-11.88)	0.056	0.18 (–0.49-0.85)	0.590
Heart disease: CAD and/or CHD	2.78 (–2.43-7.99)	0.291	0.52 (–0.05-1.09)	0.071
Lung disease: COPD and/or asthma	3.34 (–2.23-8.91)	0.236	–0.53 (–1.13-0.07)	0.084
Admission days: n	0.01 (–0.20-0.21)	0.954	0.01 (–0.01-0.03)	0.419
Highest ferritin concentration: > 822.5 µg/l	–6.22 (–10.65–1.80)	0.007	–0.44 (–0.92-0.03)	0.066
Highest amount oxygen administered: > 2 l/min.	5.65 (0.47-10.84)	0.033	0.49 (–0.08-1.06)	0.090
Bacterial coinfection: yes	–1.23 (–5.94-3.49)	0.606	0.08(–0.43-0.59)	0.745
Attached to labour market: no	2.00 (–2.46-6.45)	0.376	0.41 (–0.06-0.87)	0.085
EQ-5D				
Index	–28.13 (–37.46–-18.80)	< 0.001	–2.28 (–3.41–-1.15)	< 0.001
VAS	–0.30 (–0.38–-0.22)	< 0.001	–0.03 (–0.04–-0.02)	< 0.001
Lung HRQoL (K-BILD): scores				
PS	–0.29 (–0.40–-0.19)	< 0.001	–0.03 (–0.04-4–-0.02)	< 0.001
BA	–0.21 (–0.28–-0.14)	< 0.001	–0.02 (–0.02–-0.01)	0.001
CH	–0.27 (–0.38–-0.16)	< 0.001	-0.02 (–0.03–-0.01)	< 0.001
Total	–0.32 (–0.42–-0.21)	< 0.001	–0.03 (–0.04–-0.01)	< 0.001
FAS: score	-		0.05 (0.03-0.07)	< 0.001
Decreased physical function: score	4.88 (2.90-6.87)	< 0.001	-	

BA = breathlessness and activities; CAD = coronary artery disease; CH = chest symptoms; CHD = congestive heart failure; CI = confidence interval; EQ-5D = EuroQol-5 Domaine-5; FAS = Fatigue Assessment Scale; HRQoL = health-related quality of life; IQR = interquartile range; K-BILD = King's Brief Interstitial Lung Disease questionnaire; PS = psychological; SD = standard deviation; VAS = visual analogue scale.

Female sex was associated with a poorer outcome in all aspects of fatigue (mental and physical domains) and all evaluated aspects of HRQoL than male sex (**Table 3**). Stratifying for menopausal status did not change this.

TABLE 3 Outcome by sex.

	Women (N = 48)	Men (N = 38)	p-value
FAS scores			
Total fatigue, mean ± SD	26.3 ± 10.0	18.4 ± 8.6	< 0.001
Mental fatigue, mean ± SD	11.5 ± 5.4	8.5 ± 4.7	0.011
Physical fatigue, mean ± SD	14.6 ± 5.4	9.9 ± 4.6	< 0.001
Fatigue, total score > 22, n (%)	22 (64.7)	12 (26.1)	0.001
Decreased physical function, n (%)	20 (66.7)	17 (37.0)	0.011
EQ-5D-5L, mean ± SD			
Index score	0.76 ± 0.25	0.91 ± 0.13	0.003
VAS 0-100	66.9 ± 23.4	80.4 ± 17.8	0.008
K-BILD scores, mean ± SD			
PS	76.3 ± 18.3	86.8 ± 18.1	0.014
BA	56.2 ± 23.7	73.0 ± 26.6	0.004
CH	74.3 ± 17.7	89.7 ± 16.3	< 0.001
Total	68.6 ± 15.8	80.9 ± 18.6	0.002

BA = breathlessness and activities; CH = chest symptoms; EQ-5D-5L = EuroQol-5 Domaine-5 Level; FAS = Fatigue Assessment Scale; K-BILD = King's Brief Interstitial Lung Disease questionnaire; PS = psychological; SD = standard deviation; VAS = visual analogue scale.

Women had near-significant lower maximum levels of ferritin during admission than men (women 826 ± 950 µg/l; men 1,301 ± 1,135 µg/l (p = 0.056)). The highest measured level of CRP during admission did not differ between men and women (p = 0.517) and was not associated with fatigue (p = 0.319) or changes in functional status (p = 0.847) at follow-up.

Female sex was associated with fatigue when the analysis included the independent variables age, follow-up time, comorbidities, ferritin level and oxygen level (**Table 4**). Heart disease and absence of lung disease were associated with loss of functional status when the regression analysis model also included age, gender, follow-up time, ferritin and oxygen levels (Table 4). No interactions were observed between sex and other independent categorical variables in the multiple regression models.

TABLE 4 Multivariate linear regressions of the associations between independent variables and fatigue and decreased function.

	Fatigue		Decreased function	
	β (95% CI)	p-value	β (95% CI)	p-value
Age: yrs	−0.06 (−0.23-0.11)	0.488	−0.003 (−0.021-0.015)	0.777
Sex: female	5.67 (0.88-10.46)	0.021	0.44 (−0.07-0.95)	0.090
Follow-up time: mo.s	0.44 (−1.18-2.06)	0.589	0.11 (−0.08-0.29)	0.250
Comorbidities: n				
0	1		-	
1	2.10 (−3.14-7.33)	0.426	-	
≥ 2	4.45 (−2.32-11.22)	0.193	-	
Heart disease: CAD and/or CHD	-		0.67 (0.07-1.28)	0.029
Lung disease: COPD and/or asthma	-		−0.89 (−1.58-−0.20)	0.012
Highest ferritin concentration: > 822.5 µg/l	−4.50 (−9.53-0.54)	0.079	−0.37 (−1.58-−0.41)	0.403
Highest amount oxygen administered: > 2 l/min.	2.46 (−1.98-6.89)	0.272	0.41 (−0.90-0.16)	0.163

CAD = coronary artery disease; CHD = congestive heart failure; CI = confidence interval.

Both fatigue and decreased functional status were significantly correlated withboth generic HRQoL (EQ-5D-5L-VAS: Fatigue ($R = –0.57$; $p < 0.001$), functional status ($R = 0.515$; $p < 0.001$)) and lung disease-specific HRQoL (K-BILD: Fatigue ($R = –0.582$; $p < 0.001$); functional status ($R = –0.435$; $p < 0.001$)).

DISCUSSION

We identified female sex as the primary risk factor related to long-lasting fatigue among individuals previously hospitalised with COVID-19. Eight months after discharge from the NZH hospital due to COVID-19 illness, two thirds of the women reported excessive fatigue and a perceived loss of functional status compared with their functional status levels before COVID-19 infection. The proportion of men reporting excessive fatigue and impaired functional status was lower.

Whereas male sex was identified as a risk factor for a more severe COVID-19 illness including a higher risk of ICU admission and death, women seems to have a higher risk of "long COVID" with fatigue and decreased functional capacity [3, 13, 14]. This sex difference may partly be attributed to general sex differences in both prevalence and reporting of fatigue and symptoms in general and gender differences in medical healthcare utilisation. However, long-term effects including fatigue following a viral infection may, in many cases, be caused by a prolonged and inexpedient host response to the virus in women [15, 16]. Sex differences in immune responses lead to different susceptibility between the sexes. This applies both to infectious diseases and post-infectious autoimmune disease [16]. Women tend to have a higher prevalence of autoimmune conditions and are more prone to post-viral fatigue than men [16, 17].

A striking similarity exists between "long COVID" and other manifestations of post-viral fatigue including chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). In both CFS/ME and "long COVID", an array of autoantibodies have been detected at increased levels compared with healthy controls [17]. To what degree these autoantibodies are specific, clinically relevant and potential targets for specific treatment modalities currently remains unknown [17].

Female sex was the primary risk factor for reduced functional status after COVID-19 in the crude analysis. In the adjusted analysis, the association between female sex and reduced functional status was insignificant ($p = 0.09$). Heart disease was found to be associated with increased risk for reduced functional status eight months after COVID-19 in the adjusted analysis. It may not be surprising that preexisting heart disease may render patients more susceptible to long-lasting functional impairment after COVID-19. More surprisingly, we found that

patients with chronic lung disease before a COVID-19 diagnosis were less likely to have a reduced functional status in the long term. This finding may be influenced by confounders, such as lower functional levels before admission and immunological characteristics of patients and medications, among others. Similar observations have been reported in other studies [18].

In accordance with others, we failed to establish a clear association between measures of the severity of the initial COVID-19 disease and change in functional capacity or fatigue [19]. A Danish population-based study of routinely collected registry data found a low risk of severe sequela after COVID-19 illness that did not require hospitalisation [4]. However, the study was conducted before the specific International Classification of Diseases (ICD)-10 code for post-acute sequelae of COVID-19 was implemented in October 2020. Fatigue may not lead to new prescriptions, healthcare contacts or new diagnoses, and may therefore be underestimated in studies based on such data. We suspect that we may be looking into a pervasive problem affecting a marked proportion of COVID-19 survivors who will suffer from fatigue for an unknown period of time after the infection. Future studies including larger groups of patients and with a longer follow-up period will show. Our findings of a strong association between fatigue and impaired functional status and measures of HRQoL underscores the severity of "long COVID".

We recognise several sources of bias in our study including recall bias related to the evaluation of pre-COVID-19 levels of function at follow-up eight months after discharge, as well as selection bias (exclusion of nursing homes residents, loss to follow-up) and a small sample size. However, our findings of fatigue and loss of functional status after COVID-19 are comparable to what was seen after SARS and MERS epidemics [1, 3, 4] and underscore the importance of evaluating those recovering from COVID-19 for symptoms of excessive fatigue and changes in functional capacity irrespective of the trajectory and severity of their initial infection.

CONCLUSIONS

We found a strong female sex preponderance – unaffected by menopausal status – among patients suffering from "long COVID"-associated fatigue. Regarding loss of functional capacity post-COVID-19, we found an apparent protective effect of pre-COVID-19 lung disease. Further investigation into the gender difference in the trajectory of COVID-19 illness and its long-term effects and the underlying biological mechanisms is warranted.

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Conflicts of interest Potential conflicts of interest have been declared. Disclosure forms provided by the authors are available with the article at ugeskriftet.dk/dmj

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