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Early View

Research letter

Negative association between fatigue and signs of sleep apnoea in patients after COVID-19

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Negative association between fatigue and signs of sleep apnoea in patients after COVID-19

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Take home message:

Compared to the general population, there are increased scores of the apnoea-hypopnoea-index in patients recovering from COVID-19. Yet, there is a negative correlation to symptoms of fatigue and no significant correlation to daytime sleepiness.

Introduction

Both during and after the acute phase, COVID-19 is associated with a variety of clinical symptoms, many of which may persist even several months after the infection [1, 2]. One of the most common symptoms that is likely to persist is fatigue [1, 3]. Despite intensive research, little is known about the factors that contribute to the development and persistence of fatigue during and after COVID-19 [3]. Since sleep apnoea and particularly more severe forms are commonly associated with tiredness and exertion, an increased rate of sleep apnoea may explain at least in part the commonly mentioned fatigue symptoms.

Various studies have shown associations between COVID-19 and sleep apnoea [4]. Besides similar risk factors, there are indications that patients affected by sleep apnoea are at a greater risk of developing more severe forms of COVID-19, of being hospitalized, and of dying of the disease [5]. On the other hand, COVID-19 may also increase the risk of developing sleep apnoea due to thrombotic effects and fibrotic changes [4]. There are few studies that examined the prevalence of sleep apnoea in COVID-19 patients, suggesting higher rates than in the general population [6]. However, the link to persistent symptoms of fatigue has so far not been studied yet.

Therefore, the current investigation was conducted with two goals:

a) Determining the risk for sleep apnoea in form of an increased apnoea-hypopnoea-index (AHI) in patients recovering from COVID-19
b) Investigating the associations between the AHI and symptoms of fatigue

Methods

The patients were investigated at the Klinik Bad Reichenhall, Germany, in the framework of a research project on effects of a 3–6-week inpatient pulmonary rehabilitation on Long-COVID symptoms. The study protocol was approved by the ethics committee of the medical faculty of

the Ludwig-Maximilians-Universität München, Germany (No. 20-326) and is registered in the German register of clinical studies (DRKS00023180). Participation in the study was voluntary and all participants gave their written informed consent. The recruiting time lasted from April 2020 until April 2021 [7]. All participants were asked to undergo polygraphy screening (Miniscreen, Löwenstein Medical Diagnostics or SOMNOtouch RESP, SOMNOmedics). If the screening detected an AHI of ≥15, a more detailed examination using polysomnography (Alice, Löwenstein Medical Diagnostics or SOMNO HD eco, SOMNOmedics) was conducted. Furthermore, we assessed the daytime sleepiness with the Epworth Sleepiness Scale (ESS) [8] and symptoms of fatigue with the Brief Fatigue Inventory (BFI) [9]. These data were intercorrelated along with the body mass index (BMI), sociodemographic variables, and symptom rating scales for dyspnoea, both at rest and under exertion. For an advanced examination, we used a linear regression analysis with fatigue as criterion and all variables that were significantly correlated as predictors to investigate whether bivariate correlations between AHI- and BFI-scores depend on associations between BFI-scores and other variables.

Results

143 patients (39.9% ♀; mean age = 54.1±10.4 years; mean BMI 30.2±5.9 kg/m²) underwent polygraphy screening. Comorbidities were common, with only 11 patients (7.7%) having no comorbidity at all. The most common comorbidities were cardiovascular disease (58.0%) and metabolic disorders (53.8%). Only 25.2% of the sample revealed an AHI of <5, indicating no clinically relevant sleep apnoea. The percentages for mild (5≤AHI<15), moderate (15≤AHI<30), and severe sleep apnoea (AHI≥30) were 39.9%, 21.7%, and 13.3%, respectively.

The results of the correlation and regression analyses are presented in Table 1. There was no significant correlation between the AHI and the ESS. Furthermore, symptoms of fatigue were

negatively correlated with the AHI. Subgroup analyses did not reveal any divergences for age groups, sex, or clusters of the most common comorbidities (cardiovascular disease, metabolic disorders, obesity, orthopaedic disorders, pulmonary diseases, and psychiatric disorders). An additional screening of the scatter plot did not indicate non-linear associations. The regression model was significant with about 34% of variance explained (R^2=0.371, corrected R^2=0.339, $F(6, 126)=11.793$, $p<0.001$).

Discussion

As expected, data revealed increased AHI-scores in the sample, with three quarters of the patients having an AHI of ≥5 and a third of the patients having an AHI of ≥15. Interestingly, the association between the AHI and fatigue turned out to be negative and the AHI scores were not intercorrelated with self-perceived daytime sleepiness.

Putting the results into context, the prevalence of increased AHI-scores that we detected, exceed the prevalence in the German general population of 46% for an AHI ≥5 and of 21% for an AHI ≥ 15 [10]. Regarding daytime sleepiness, it is important to consider that previous research has suggested that some patients suffering from sleep apnoea do not suffer from daytime sleepiness [11]. For example, in the Sleep Heart Health Study, a majority of participants with moderate to severe sleep disordered breathing did not report sleepiness [12]. Despite these results, an non-significant correlation of $r<0.1$ diverges from the norm, since the severity of sleep apnoea is one of the most important predictors for excessive daytime sleepiness and the AHI is known to correlate with both subjective and objective daytime sleepiness [11]. Similar to the aforementioned analysis, the negative association between the AHI and symptoms of fatigue that we detected in our sample, is hard to interpret. Both included analyses indicate that higher scores of the AHI go along with fewer self-perceived symptoms of fatigue. Even though several studies have highlighted various links between COVID-19 and sleep apnoea, such as similar risk factors or the risk of reciprocal

intensification [4, 5], to the best of our knowledge, a negative correlation between the two constructs has not been reported before. It is important to consider possible publication biases, yet the results appear counter-intuitive. Influences of selection bias and non-linear associations are rather unlikely, since further investigations of the data did not reveal any indications of these two common factors of influence. Nevertheless, sampling effects in the referral to pulmonary rehabilitation may be a possible confounding variable. Furthermore, another explanation may be that commonly used screening instruments, such as the BFI, are not suitable for the detection of COVID-related symptoms of fatigue. Therefore, future analyses should evaluate our results, using broader assessment strategies than only patient reported outcomes. In addition, it is advisable for future studies to focus on possible confounding variables.

In summary, our results confirm previously reported increased rates of the AHI in patients after COVID-19, yet they suggest negative associations to symptoms of fatigue and no associations to daytime sleepiness. Considering the heterogeneous burden of disease that is associated with COVID-19, a closer investigation of the interaction with sleep apnoea and symptoms of fatigue, including an analysis of potential moderators and mediators, is highly advisable.

Disclosure Statement

Financial Disclosure: none. (The study was carried out with the Bad Reichenhall Clinic's regular financial resources without any additional external funding.)

Non-financial Disclosure: none.

The study has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). Participation in the study was voluntary and all

participants gave their written informed consent. The study protocol was approved by the ethics committee of the medical faculty of the Ludwig-Maximilians-Universität München, Germany (No. 20-326) and is registered in the German register of clinical studies (DRKS00023180).

Table 1: Correlation matrix and regression coefficients

Correlation

	BFI	ESS	BMI	Dyspnoea at rest	Dyspnoea on exertion	Age	Gender
AHI	**r_s = -0.188 p = 0.033**	r_s = 0.022 p = 0.797	**r_s = 0.367 p < 0.001**	r_s = -0.070 p = 0.431	r_s = -0.063 p = 0.473	**r_s = 0.165 p = 0.048**	**r_s = -0.170 p = 0.043**
BFI		**r_s = 0.183 p = 0.039**	**r_s = 0.183 p = 0.039**	**r_s = 0.495 p < 0.001**	**r_s = 0.521 p < 0.001**	r_s = -0.148 p = 0.096	**r_s = 0.205 p = 0.020**
ESS			r_s = 0.054 p = 0.524	**r_s = 0.371 p < 0.001**	r_s = 0.097 p = 0.272	**r_s = -0.201 p = 0.017**	r_s = 0.017 p = 0.844
BMI				r_s = 0.064 p = 0.469	**r_s = 0.217 p = 0.013**	r_s = -0.060 p = 0.478	r_s = -0.022 p = 0.790
Dyspnoea at rest					**r_s = 0.507 p < 0.001**	r_s = -0.101 p = 0.252	r_s = 0.154 p = 0.081
Dyspnoea on exertion						r_s = -0.029 p = 0.743	r_s = 0.042 p = 0.632
Age							r_s = -0.097 p = 0.251

Regression

Predictor	b	95% CI	β	p
Dyspnoea on exertion	**0.250**	**0.103 – 0.396**	**0.291**	**0.001**
Dyspnoea at rest	**0.290**	**0.116 – 0.463**	**0.290**	**0.001**
AHI	**-0.031**	**-0.056 – 0.006**	**-0.193**	**0.016**
BMI	0.051	-0.005 – 0.107	0.147	0.074
Gender	0.568	-0.043 – 1.118	0.136	0.068
ESS	0.008	-0.063 – 0.080	0.017	0.821

95% CI = 95% confidence interval; b = regression coefficient; β = standardized regression coefficient.
AHI = apnoea-hypopnea-index; BFI = Brief Fatigue Inventory; BMI = body mass index; ESS = Epworth Sleepiness Scale.
Values in bold indicate statistically significant results of p < 0.05 (two-sided).

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