CLINICAL RESEARCH

e-ISSN 1643-3750 © Med Sci Monit, 2021; 27: e930447 DOI: 10.12659/MSM.930447

Received: 2020 Accepted: 2021 ble online: 2021 Published: 2021	.01.28 .02.10	Persistent Somatic Sym Sleep Disturbance in Pa During Hospitalization a A Prospective Cohort St	tients with COVID-19 and After Discharge:
Authors' Contribut Study Desig Data Collectio Statistical Analysi Data Interpretation Manuscript Preparatio Literature Searc Funds Collection	ABDEF 1,2 B BDF 3,4 D BD 3,4 D BCD 3,4 B BCD 3,4 B BC 3,4 CDE 5	Dongya Wang Lulu Zha Xi Xu Xiangdong Li Qiuling Shi Xin Shelley Wang	 Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong, P.R. China Shantou University Medical College, Shantou, Guangdong, P.R. China Huoshenshan Hospital, Wuhan, Hubei, P.R. China General Hospital of Southern Theater Command, Chinese People's Liberation Army, Guangzhou, Guangdong, P.R. China School of Public Health and Management, Chongqing Medical University, Chongqing, P.R. China Department of Symptom Research, The University of Texas MD Anderson Cance Center, Houston, TX, U.S.A. The Second School of Clinical Medicine, Southern Medical University, Guangzho Guangdong, P.R. China
	ponding Author: purce of support:	* Shujie Huang and Weitao Zhuang contributed equally to this Guibin Qiao, e-mail: guibinqiao@126.com This work was supported by a grant from the 2020-2021 Popu Guangdong Province of China (No. 2020A1414070007)	s work Ilarization of Science and Technology Innovation Special Project of
Mate	Background: erial/Methods:	quality over time in patients with COVID-19 and to it burden and sleep disturbance. Seventy-four patients with COVID-19 were prospective tom burden and sleep quality. We used the 8-item Sc Research Council (mMRC) scale for somatic symptom quality investigation. Univariate and multivariate and	cory of self-reported somatic symptom burden and sleep identify prognostic factors for greater somatic symptom ely followed for longitudinal assessment of somatic symp- omatic Symptom Scale (SSS-8) and the modified Medical burden and the Pittsburgh Sleep Quality Index for sleep lyses were performed to identify independent factors as-
	Results:	patients still experienced these problems to a certai that SSS-8 scores at admission (relative risk [RR] 1.234 charge (RR 2.420, 95% CI 1.251-4.682, <i>P</i> =0.009) were tom burden. In addition, muscle pain as a chief compl	ality. o quality issues tended to decline during self-quarantine, in degree. Univariate and multivariate analyses showed 4, 95% Cl 1.075-1.417, <i>P</i> =0.003) and mMRC scores at dis- e 2 independent prognostic indicators of somatic symp- laint (RR 4.682, 95% Cl 1.247-17.580, <i>P</i> <0.022) and histo- 0.749, <i>P</i> <0.019) were 2 independent indicators of patient
	Conclusions:	sleep quality during hospitalization. To the best of our knowledge, the present study was burden and sleep quality in patients with COVID-19 Patients with high somatic symptom burden at admi prone to having a higher physical burden and more s	s the first dynamic assessment of the somatic symptom during hospitalization and quarantine after discharge. ission, especially muscle pain as the chief complaint, are leep disturbance at discharge.
	Keywords: Full-text PDF:	COVID-19 • Signs and Symptoms • Sleep Disorders https://www.medscimonit.com/abstract/index/idArt	
			D 37



MEDICAL SCIENCE

MONITOR

Received: 2020.12.12 Accepted: 2021.01.28 Available online: 2021.02.10

e930447-1

Background

Numerous studies have revealed the initiation and development of different clinical manifestations of coronavirus disease 2019 (COVID-19) [1-12]. Huang et al described the clinical characteristics of clustered COVID-19 cases in early January 2020 [1] in one of the earliest studies of symptoms in patients with COVID-19. Subsequently, articles on various aspects of COVID-19 features, such as distinct regions [7,11], patient groups [2,6,12], symptoms in specific organ systems [4,5], and mortality rates [8-10], have been published. These studies have provided a better understanding of the evolution of clinical symptoms of COVID-19 and revealed different aspects of the physiological burden of common somatic symptoms (somatic symptom burden) in patients over time. How somatic symptom burden develops over time, however, is still unclear. Furthermore, there is a paucity of studies on the physiological status of patients with COVID-19 after they are discharged from the hospital [13-15].

Apart from the need to trace the development of somatic symptom burden, researchers should also pay attention to psychological stress in patients with COVID-19. Among the psychological factors that have been investigated [16,17], sleep quality has seldom been addressed [18,19]. No study has compared sleep disturbances during hospitalization versus the self-quarantine period.

Given the increase in the number of patients with COVID-19 who have been discharged from the hospital, it is important to study the trajectory of their rehabilitation during the selfquarantine period. There is a need to understand chronological changes in somatic symptom burden and sleep quality in patients with COVID-19 to improve post-discharge medical care and more easily identify patients in need of close follow-up.

The present prospective study was designed to assess the sequential development of somatic symptom burden and sleep disturbance in patients with COVID-19 and to identify clinicopathological factors associated with these issues.

Material and Methods

Study Design

A convenience sample of 74 patients with COVID-19 from Huoshenshan Hospital was enrolled in this prospective cohort study from February 4, 2020 to May 5, 2020. Well-designed and validated questionnaires were used to collect data from these patients on their physiological burden and sleep quality. In a nationwide, population-based study, the 8-item Somatic Symptom Scale (SSS-8), modified from the well-known 15-item Patient Health Questionnaire (PHQ-15) [20], was shown to have excellent item characteristics and reliability, with a Cronbach α value of 0.81 [21]. With advantages such as briefness, excellent practicality, and verified cutoff values, the SSS-8 has enabled researchers to identify individuals with mild, low, medium, high, and very high somatic symptom burdens [21]. Moreover, because respiratory symptoms are frequently reported in patients with COVID-19 [1,22,23], we assessed the severity of dyspnea using the modified Medical Research Council (mMRC) scale, which has been widely used in patients with chronic respiratory diseases [24]. The Pittsburgh Sleep Quality Index (PSQI) is effective in distinguishing individuals with distinct sleep quality [25-27] and was used in the present study to evaluate the sleep quality of patients with COVID-19.

All of the patients were required to complete the questionnaires at admission (T1), on discharge (T2), and 2 weeks (T3) and 1 month after discharge (T4). The SSS-8 and mMRC were completed at 4 time points. Because the PSQI was designed to evaluate sleep quality and mental health status over a period of time, it was only completed twice: during hospitalization (T2) and subsequent self-quarantine at home (T4). All of the questionnaires were distributed online. Patients who had 2 consecutive negative results on a nucleic acid test for severe acute respiratory syndrome coronavirus 2 virus were discharged from the hospital and underwent self-quarantine at home.

Institutional Review Board Approval

The present study was approved by the Ethics Committees of 3 hospitals: Huoshenshan Hospital (Wuhan, China), Guangdong Provincial People's Hospital (Guangzhou, China), and General Hospital of Southern Theater Command (Guangzhou, China). Informed consent was obtained from all patients when the online questionnaire was distributed. The authors are accountable for all aspects of the work and for ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved. The study conformed to the provisions of the Declaration of Helsinki (as revised in 2013).

Patient Diagnosis

All of the patients were diagnosed and treated according to the 6th edition of the Diagnosis and Treatment Guideline for COVID-19 issued by the National Health Commission of the People's Republic of China [28]. Patients with fever, respiratory symptoms, and evidence of pneumonia on imaging at admission were classified as having moderately severe cases, while severe cases were those that met any of the following criteria: dyspnea and respiratory rate \geq 30/min; oxygen saturation \leq 93% at resting state; or PaO₂/FiO₂ \leq 300 mmHg (1 mmHg=0.133 kPa).

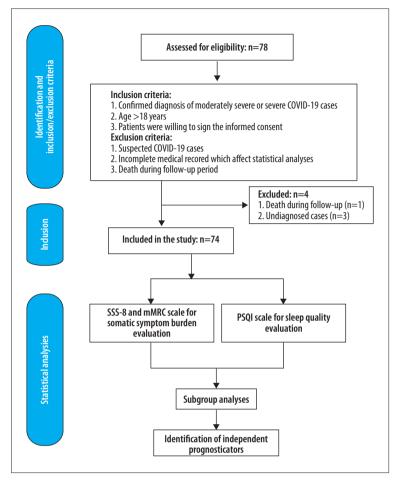


Figure 1. Study design and data analyses.

Patient Inclusion and Exclusion Criteria

The patients included in the study had a confirmed diagnosis of moderately severe or severe COVID-19, were aged ≥ 18 years, and were willing to sign the informed consent. Patients were excluded if they were suspected of having but not confirmed to have COVID-19, had incomplete medical records that could affect statistical analyses, or died during the follow-up period (**Figure 1**).

Statistical Analysis

For statistical purposes, the SSS-8 scores were divided into 2 groups: high and low somatic symptom burden. Patients with minimal (0-3) and low (4-7) physical discomfort were defined as the low somatic symptom burden group, while patients with SSS-8 scores from 7 to 32 were defined as the high somatic symptom burden group. Patients also were divided into groups for better (PSQI \leq 5) or worse (PSQI >5) sleep quality [29]. The SSS-8 scale, mMRC scale, and PSQI were validated by calculating the Kaiser-Meyer-Olkin Measure of Sampling Adequacy and with Bartlett's test of sphericity, whereas the reliability of the questionnaires was presented as Cronbach's

alpha. Descriptive statistics (frequency, mean, standard deviation, and median) were obtained for demographic, epidemiological, and clinical variables. The SSS-8 scores were stratified using previously validated cutoff values (0-3: no to minimal severity, 4-7: low severity; 8-11: medium severity; 12-15: high severity; 16-32: very high severity) [21]. Intergroup comparisons of continuous variables were conducted using the t test and one-way analysis of variance. Non-parametric tests were used for the variables that failed to meet the assumptions of normal distribution or equal variance. Categorical variables were compared by using a chi-square test when appropriate (expected frequency >5). Otherwise, the Fisher exact test was performed. Univariate and multivariate binary logistic regression were performed using the stepwise forward procedure to identify independent factors associated with stratified severity of physiological and psychological burden in patients with COVID-19. All statistical analyses were two-sided and P<0.05 was considered statistically significant. The analyses were carried out with IBM Statistical Package for Social Science (SPSS), version 26 for Windows (SPSS, Inc., Chicago, Illinois, United States). GraphPad Prism 8.0 (GraphPad Software, La Jolla, California, United States) was used to generate all of the figures.

 Table 1. Clinicopathological characteristics of COVID-19 patients.

Clinicopathological characteristics		n (%)
jex		
Male	44	(59.46)
Female	30	(40.54)
Age (mean±SD)	52	2.3±13.3
hief complaint		
Shortness of breath	27	(36.5)
Muscle pain	15	(20.3)
Fever	54	(73.0)
Chills	6	(8.1)
Fatigue	22	(29.7)
Headache	3	(4.1)
Dry mouth	1	(1.35)
Sore throat	1	(1.35)
Dyspnea	5	(6.8)
Cough (sputum production)	32	(43.2)
Dry cough	18	(24.3)
Palpitation	3	(4.1)
Chest tightness	10	(13.5)
Chest pain	3	(4.1)
Nausea	2	(2.7)
Diarrhea	5	(6.8)
uration of chief complain (mean±SD)	23	3.7±13.7
iagnosis		
Moderate cases	60	(81.08)
Severe cases	14	(18.92)
omorbidities		
Hypertension	21	(28.38)
Aneurysm	1	(1.35)
Hyperlipidemia	2	(2.70)
Coronary atherosclerotic heart disease	3	(4.05)
Cardiac insufficiency	1	(1.35)
Bradycardia	1	(1.35)
DVT	1	(1.35)
Hypothyroidism	2	(2.70)
Diabetes mellitus type II	11	(14.86)

Clinicopathological characteristics		n (%)
Bulla	3	(4.05)
COPD	2	(2.70)
Lung cancer	1	(1.35)
Hyperuricemia	1	(1.35)
Gouty arthritis	1	(1.35)
Chronic gastritis	1	(1.35)
Fatty liver	2	(2.70)
Hepatitis B	3	(4.05)
Gallstone	1	(1.35)
Kidney cyst	1	(1.35)
Chronic Kidney disease	1	(1.35)
Kidney cancer	1	(1.35)
Breast cancer	1	(1.35)
Length of hospital stay/median (IQR)	21	(12.0-34.3)
Multi-hospital admission history		
No	13	(17.57)
Yes	61	(82.43)
Drinking history		
No	71	(95.95)
Yes	3	(4.05)
Smoking history		
No	68	(91.89)
Yes	6	(8.11)
Antibiotics use during hospitalization		
No	32	(43.24)
Yes	42	(56.76)
Antiviral use during hospitalization		
No	43	(58.11)
Yes	31	(41.89)
Glucocorticoid use during hospitalization		
No	61	(82.43)
Yes	13	(17.57)
Hypnotic use during hospitalization		
No	46	(62.2)
Yes	28	(37.8)

e930447-4

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Clinicopathological characteristics	n (%)
Key lab results on admission (mean±SD)	
WBC (×10 ⁹ /L)	6.14±1.94
RBC (×10 ¹² /L)	4.14±0.59
Hemoglobin (g/L)	128.36±16.92
Platelet (×10º/L)	244.14±78.69
Neutrophil (×10º/L)	3.98±1.80
Lymphocyte (×10 ⁹ /L)	1.55±0.57
Monocyte (×10º/L)	0.46±0.17

Table 1 cotinued. Clinicopathological characteristics of COVID-19 patients.

Results

Clinicopathological Characteristics of Patients with COVID-19

We included 74 patients with COVID-19 (44 men [59.46%] and 30 women [40.54%]; median age, 56 years). To shorten the time it took to distribute the questionnaires, we combined them at different time points. At T1 and T3, we combined the SSS-8 with the mMRC, while at T2 and T4, we combined the SSS-8, mMRC, and the PSQI. The overall response rates for the guestionnaires at the T1, T2, T3, and T4 time points were 100%, 100%, 98.6%, and 94.5%, respectively. Of the 74 enrolled patients, 60 were diagnosed with moderately severe COVID-19. Common chief complaints included shortness of breath (36.5%), muscle pain (20.3%), fever (73.0%), fatigue (29.7%), productive cough (43.2%), and dry cough (24.3%) (Table 1). The median length of hospital stay was 21 days. Eighty-three percent of the patients (n=61) had a previous history of COVID-19related admission. Further detailed clinicopathological information is provided in Table 1.

Reliability and Factorial Validity of the SSS-8 and mMRC Scales and PSQI

The reliability ratings for the SSS-8 and mMRC scales and PSQI in patients with COVID-19 patients, as assessed by Cronbach α , were 0.926, 0.837, and 0.877, respectively. In addition, the 3 scales showed high factorial validity (SSS-8: Kaiser-Meyer-Olkin [KMO]=0.737, X₂=1881.762, *P*<0.001; mMRC: KMO=0.772, X₂=142.033, *P*<0.001; PSQI: KMO=0.776, X₂=522.820, *P*<0.001).

Change in Somatic Symptom Burden and Sleep Quality Over Time

The overall somatic symptom burden decreased significantly over time. Results of all intergroup comparisons of the SSS-8 and mMRC scores at different time points (T1, T2, T3, and T4)

Clinicopathological characteristics	n (%)
Eosinophil (×10 ⁹ /L)	0.12±0.11
Basophil (×10 ⁹ /L)	0.02±0.01
C-reactive protein (mg/L)	14.65±33.03
hs-C-reactive protein (mg/L)	3.00±2.49
PCT (ng/ml)	0.07±0.09
Additional key lab results during hospitalization (mean±SD)	
SARS-CoV-IgM antibody	76.46±97.14
SARS-CoV-IgG-antibody	143.97±46.11

were statistically significant (P<0.001). The rates of remission for the investigated symptoms were much more pronounced during hospitalization than during the self-quarantine period (**Figure 2**).

Moreover, the residual somatic symptom burden was observed at the time of discharge and during the self-quarantine period. At discharge, nearly one-third of the patients were still experiencing a high somatic symptom burden (SSS-8 score >7).

The median total SSS-8 scores at 2 and 4 weeks after discharge were 4 and 3, respectively. Chest pain and trouble sleeping were the 2 most pronounced complaints among those assessed.

A Wilcoxon signed rank test revealed a significantly decreased PSQI score during the self-quarantine period compared to that during hospitalization (P<0.001) (**Figure 3**). However, the median score of 6 was relatively high (interquartile range [IQR]=3.0 to 9.0), indicating that more than 50% of the patients were disturbed by poor sleep quality. Subjective sleep quality and sleep latency were the 2 main components that accounted for the high PSQI score.

Assessment of Prognostic Indicators of Somatic Symptom Burden at Discharge

The median SSS-8 and mMRC scores at discharge were 5 (IQR: 3-8) and 2 (IQR: 1-3), respectively. The SSS-8 total scores at discharge were classified into low and high somatic symptom burden groups. Univariate analyses revealed that the severity of disease (severe vs moderate: RR 4.821, 95% CI 1.418-16.390, P<0.012), SSS-8 score at admission (RR 2.709, 95% CI 1.551-4.733, P<0.001), mMRC scores at admission (RR 2.018, 95% CI 1.338-3.043, P=0.001), mMRC scores at discharge (2.804, 95% CI 1.558-5.046, P=0.001), and PSQI scores during hospitalization (RR 1.195, 95% CI 1.059-1.347, P=0.004) were significantly associated with higher somatic symptom burden (**Figure 4**). Furthermore, multivariate analyses suggested that

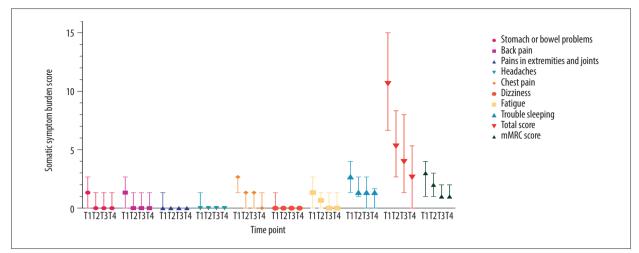


Figure 2. Changes in somatic symptom burden over time in patients with COVID-19. Median scores of for somatic symptom burdens were evaluated using the Somatic Symptom Score (SSS-8) and modified Medical Research Council (mMRC) scales at 4 time points (T1, T2, T3, and T4). The baseline score for each symptom recorded at admission was the highest. A declining trend in the scores was observed throughout hospitalization and quarantine.

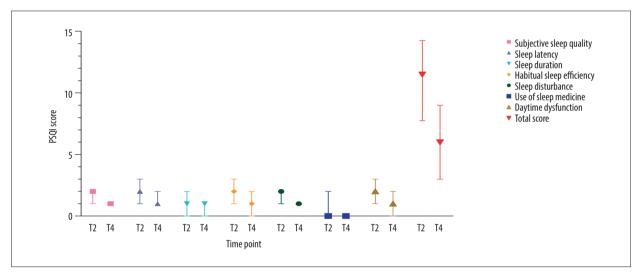


Figure 3. Alterations in sleep quality over time in patients with COVID-19. Sleep quality during hospitalization and self-quarantine was assessed via median Pittsburgh Sleep Quality Index (PSQI) scores. Overall, sleep disturbances were more serious during hospitalization than during self-quarantine. Pronounced sleep quality issues (PSQI >5) were observed during self-quarantine.

the SSS-8 scores at admission (RR 1.234, 95% Cl 1.075-1.417, P=0.003) and the mMRC scores at discharge (RR 2.420, 95% Cl 1.251-4.682, P=0.009) were 2 independent prognostic indicators of somatic symptom burden.

Assessment of Prognostic Indicators of Sleep Quality During Hospitalization

The median PSQI scores were 11.5 (IQR 7.75-14.25) and 6 (IQR 3.00-9.00) during hospitalization and 1-month self-quarantine, respectively. Univariate analyses indicated that muscle pain as the chief complaint (RR 4.287, 95% CI 1.264-14.541, P=0.019) was significantly associated with worse sleep quality than in

patients who did not have that complaint. Use of hypnotic drugs during hospitalization (RR 0.159, 95% CI 0.033-0.760, P=0.021) was identified as a protective factor (**Figure 5**). A multivariate regression model suggested that muscle pain as the chief complaint (RR 4.682, 95% CI 1.247-17.580, P=0.022) and use of hypnotic drugs (RR 0.148, 95% CI 0.029-0.749, P=0.019) were 2 independent prognostic indicators of sleep quality.

Discussion

Despite the substantial number of studies of COVID-19 that have been ongoing in the last 7 months, little is known about

Subgroup	Lower somatic symptom burden (mean score)	Higher somatic symptom burden (mean score)		Risk ratio (95% CI)
Sex				
Male	3.4	9.9	+	0.386 (0.137-1.085)
Female	4.0	11.4	•• •	2.593 (0.921-7.295)
Age				
60 years	3.4	11.0	•	1.286 (0.426-3.879)
>60 yeras	4.1	10.0	•	0.778 (0.258-2.347)
SOB as chief complaint				
Yes	3.8	11.0	•	1.101 (0.388–3.129)
No	4.5	10.7	•	0.908 (0.32-2.581)
Dyspnea as chief complaint				
Yes	6.7	8.0		1.754 (0.272-11.332)
No	3.4	11.0		0.57 (0.088-3.682)
Use of antivirais				
Yes	3.5	10.2	4	0.448 (0.151-1.332)
No	3.7	11.0		2.232 (0.751-6.636)
Diagnosis				
Moderate cases	3.5	10.4		0.207 (0.061-0.705)
Severe cases	4.7	11.5		4.821 (1.418-16.39)
SS-8 acore at admission	9.2	15.9	•	2.709 (1.551-4.733)
mMRC acore at admission	2.3	3.7	•	2.018 (1.338-3.043)
mMRC score at discharge	1.7	2.7	•	2.804 (1.558-5.046)
PSQI score during hospitalization	9.9	14.1		1.195 (1.059–1.347)
			0 2 4 6 8 10 13 16	. ,
			The estimates	

Figure 4. Forest plot of prognostic indicators for somatic symptom burden at discharge. The severity of the disease, Somatic Symptom Score-8 and modified Medical Research Council scores at admission and Pittsburgh Sleep Quality Index score during hospitalization were significantly associated with patient self-reported physical outcomes. (Purple squares and diamonds indicate relative risk.)

the overall evolution of somatic symptom burden and sleep quality in patients with the virus. To address this issue, we conducted a 3-month prospective follow-up study of 74 patients with COVID-19. By tracing patient self-reported physiological and psychological burdens at 4 consecutive time points, we were able to record the development of somatic symptom burden and sleep quality in these patients. Furthermore, independent prognostic indicators associated with somatic symptom burden and sleep disturbance were identified.

More than half of the patients recruited for this study were older than age 50 years. Fever and productive cough were the 2 most common chief complaints, which is in keeping with previous findings [1,6,22]. We observed an overall declining trend in both somatic symptom burden and sleep quality in patients with COVID-19. It was worth noting that the residual somatic symptom burden and sleep disturbance persisted throughout the 1-month self-quarantine period. These results suggest that early close follow-up should be initiated and treatment of symptoms should be recommended to lessen the physiological and psychological burden for patients. Lack of regular follow-up could lead to worse clinical outcomes. Wang et al reported that although readmission is uncommon, the risk is higher in patients who have been discharged and have a latent or recurring physiological burden [30]. In a 4-week follow-up of elderly patients with COVID-19, individuals with dyspnea, cardiovascular disease, and chronic obstructive pulmonary disease had poor clinical outcomes after discharge [31]. To date, few studies have investigated the post-discharge status of patients with COVID-19. However, evidence from the present study underscores the value that physicians and other caregivers should place on post-discharge surveillance. To date, more than 83 million cases of COVID-19 have been confirmed and the moderate and severe cases account for a considerably large proportion [32]. Therefore, if post-discharge surveillance were initiated among patients with COVID-19 who are self-quarantining, a significant number of individuals would stand to benefit from the lessened somatic symptom burden and improved sleep quality.

The somatic symptom burden in patients with COVID-19 has been investigated in several studies [2,6,11,12]. Unfortunately, these descriptive studies did not stratify the severity of the overall somatic symptom burden; therefore, the information was insufficient on which to base the development of personalized intervention and prevention for individuals who are currently hospitalized. Also, few articles have specifically targeted mental health and sleep quality in patients with COVID-19

Subgroup	Worse sleep quality (mean score)	Better sleep qua (mean score)	lity	Risk ratio (95% CI)
Sex				
Male	12.61	3.54	H	2.726 (0.792-9.381)
Female	14.23	4.00	+	0.67 (0.107-1.263)
Age				
\leq 60 years	13.61	3.79	•	2.722 (0.7-10.585)
> 60 yeras	12.90	3.00	+	0.367 (0.094–1.429)
Muscle pain as chief con	nplaint			
Yes	12.13	3.86		4.289 (1.264-14.541)
No	13.55	3.50	4	0.233 (0.069–0.791)
SOB as chief complaint				
Yes	12.20	3.86	•	1.295 (0.427-3.924)
No	13.97	3.50	•	0.772 (0.255-2.34)
Productive cought as ch	ief complaint			
Yes	13.88	3.38		1.222 (0.412-3.628)
No	12.97	3.89	.	0.816 (0.276-2.428)
Dray cought as chief cor	nplaint			
Yes	12.33	4.33	•	2.045 (0.628-6.664)
No	13.62	3.27	.	0.489 (0.15-1.593)
Palpitation as chief com	plaint			
Yes	11.00	5.00	—	1.719 (0.146-20.202)
No	13.44	3.56		0.582 (0.05-6.839)
Chest pain as chief com	plaint			
Yes	13.50	4.00	→	1.719 (0.146–20.202)
No	13.35	3.63	• •	0.582 (0.0506.839)
Hypertension				
Yes	14.38	3.60	—	1.719 (0.146-20.202)
No	12.95	3.67	• •	0.582 (0.05-6.839)
Type II diabetes mellitu	S			
Yes	13.14	3.75	•	2.198 (0.558-8.664)
No	13.38	3.62	•	0.455 (0.11501.794)
HX of hpnotics use				
Yes	14.31	4.50	+	0.159 (0.033–0.76)
No	12.55	3.53	H B I	6.29 (1.316–30.087)
			0 2 4 6 8 101316	

Figure 5. Forest plot of prognostic indicators for sleep quality during hospitalization. Muscle pain as the chief complaint was identified as a risk factor for sleep quality. A history of use of hypnotic drugs during hospitalization was a protective factor for ensuring better sleep quality. (Purple squares and diamonds indicate relative risk.)

who have no preexisting psychiatric problems. Bo et al showed that posttraumatic stress syndrome occurs in more than 95% of patients who are hospitalized [33]. Nearly 30% of patients who recover from COVID-19 develop depressive episodes [34]. However, neither of these studies stratified the severity of the psychological problem nor did they identify patients at higher risk of suffering from prolonged psychological problems, such as depressive episodes and sleep disturbances. In the present study, we performed binary logistic analyses to identify patients with COVID-19 who had a potentially high somatic symptom burden and sleep disturbance. A univariate and multivariate binary logistic regression model revealed that SSS-8 score at admission and mMRC score at discharge were 2 independent predictors of somatic symptom burden at discharge. Our data suggest that the patients with a higher somatic symptom burden at admission were prone to poor recovery. The severity of dyspnea significantly contributed to the degree of somatic symptom burden. Hence, treatment of dyspnea symptoms during the self-quarantine period could be beneficial.

Our results further indicate that muscle pain as the chief complaint and use of hypnotic drugs during hospitalization were independent prognostic indicators for sleep quality. Previous reports of the close association between muscle pain and sleep

e930447-8

disturbance [35] were echoed by our findings in patients with COVID-19. Moreover, patients with severe COVID-19 and comorbidities reportedly are likely to have muscle pain [1,22,35-37]. In this regard, we suggest close monitoring of patients with COVID-19 who have muscle pain on admission. So far, data on the protective effects of hypnotic drugs on sleep quality in patients with COVID-19 have not been captured in the documented reports, likely because few studies have investigated sleep disturbance in patients with COVID-19. Our findings on the beneficial effects of hypnotic drugs could provide evidence for early initiation of these agents in patients who have sleep disturbance during hospitalization and suggest a need to further investigate the specific timing and duration of use of the drugs.

The present prospective study was the first to establish the overall trend in both somatic symptom burden and sleep quality in patients with COVID-19, and to identify independent prognostic indicators for them. Identification of factors that significantly increase and decrease risk would facilitate timely psychological intervention during hospitalization and post-discharge follow-up, at an early stage.

Although our findings about patient-reported outcomes over time were significant, the present study had some limitations. The assessment had a small sample size of only 74 patients. Furthermore, because it was the first study to explore somatic symptom burden and sleep quality in patients with COVID-19, we are cautious about drawing any conclusions based on the findings. Therefore, future prospective studies, based on large sample sizes, are required to confirm the results of the present study.

Supplementary Data

Supplementary Table 1. The Somatic Symptom Scale-8 (SSS8).

A little bit Not at all Somewhat Quite a bit Very much 1. Stomach or bowel problems 0 1 2 3 4 2. Back pain 0 1 2 3 4 3. Pain in your arms, legs, or joints 0 1 2 3 4 0 2 3 4. Headaches 1 4 3 6. Dizziness 0 1 2 4 5. Chest pain or shortness of breath 0 2 3 4 1 7. Feeling tired or having low energy 0 1 2 3 4 0 2 3 4 8. Trouble sleeping 1

Conclusions

To the best of our knowledge, the present study is the first dynamic assessment of somatic symptom burden and sleep quality in patients with COVID-19 during hospitalization and the quarantine period after discharge. Persistent somatic symptoms and sleep disturbance were detected in a considerable number of patients despite their discharge from the hospital. Patients with high somatic symptom burden at admission, especially muscle pain as the chief complaint, were prone to have sleep disturbance. This suggests to us that symptomspecific treatment, such as a painkiller for muscle pain, should be considered to manage sleep disturbance before hypnotic drugs are prescribed.

Availability of Data and Material

All data needed to evaluate the conclusions in the paper are present in the paper and/or the **Supplementary Tables 1-3**.

Acknowledgments

We are grateful to the Freescience Editing Service for English language editing.

Conflict of Interest

None.

CLINICAL RESEARCH

Supplementary Table 2. The modified Medical Research Council scale (mMRC).

	Severity	Grade
Dyspnea only with strenuous exercise	No dyspnea	0
Dyspnea when hurrying or walking up a slight hill	Slight dyspnea	1
Walks slower than people of the same age because of dyspnea or has to stop for breath when walking at own pace	Moderate dyspnea	2
Stops for breath after walking 100 yards (91m) or after a few minutes	Severe dyspnea	3
Too dyspneic to leave house or breathless when dressing	Very severe dyspnea	4

Supplementary Table 3. Pittsburgh Sleep Quality Index (PSQI).

Instructions: The following questions were designed to investigated your sleep quality during your hospitalization and selfquarantine period. **Please answer all questions**.

1. During the past month, what time have you usually gone to bed at night?

2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night? _____

3. During the past month, what time have you usually gotten up in the morning? ____

4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.)

	None	Less than once a week	Once or twice a week	Three or more times a week
5. During hospitalization/self-quarantine period, how often have you had trouble sleeping because you				
a. Cannot get to sleep within 30 minutes				
b. Wake up in the middle of the night or early morning				
c. Have to get up to use the bathroom				
d. Cannot breathe comfortably				
e. Cough or snore loudly				
f. Feel too cold				
g. Feel too hot				
h. Have bad dreams				
i. Have pain				
j. Other reason(s), please describe:				
6. During hospitalization/self-quarantine period, how often have you taken medicine to help you sleep (prescribed or "over the counter")?				
7. During hospitalization/self-quarantine period, how often have you had trouble staying awake while eating meals?				

	No problem at all	Only a very slight problem	Somewhat of a problem	A very big problem
8. During hospitalization/self-quarantine period, how much of a problem has it been for you to keep up enough enthusiasm to get things done?				
	Very good	Fairly good	Fairly bad	Very bad
9. During hospitalization/self-quarantine period, how would you rate your sleep quality overall?				
	No bed partner or room mate	Partner/room mate in other room	Partner in same room but not same bed	Partner in same bed
10. Do you have a bed partner or roommate?				
	None	Less than once a	Once or twice a	Three or more
		week	week	times a week
If you have a roommate or bed partner, ask him/her how often in hospitalization/self-quarantine period, you have had:		week	week	times a week
how often in hospitalization/self-quarantine period,		week	week	times a week
how often in hospitalization/self-quarantine period, you have had:		week	week	times a week
how often in hospitalization/self-quarantine period, you have had: a. Loud snoring		week	week	times a week
how often in hospitalization/self-quarantine period, you have had: a. Loud snoring b. Long pauses between breaths while asleep		week	week	times a week

References:

- 1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506
- Chen T, Dai Z, Mo P, et al. Clinical characteristics and outcomes of older patients with coronavirus disease 2019 (COVID-19) in Wuhan, China (2019): A single-centered, retrospective study. J Gerontol A Biol Sci Med Sci. 2020;75(9):1788-95
- 3. Zu ZY, Jiang MD, Xu PP, et al. Coronavirus disease 2019 (COVID-19): A perspective from China. Radiology. 2020;296(2):E15-25
- Han C, Duan C, Zhang S, et al. Digestive symptoms in COVID-19 patients with mild disease severity: Clinical presentation, stool viral RNA testing, and outcomes. Am J Gastroenterol. 2020;115(6):916-23
- Jin X, Lian JS, Hu JH, et al. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. Gut. 2020;69(6):1002-9
- 6. Wang Y, Lu X, Li Y, et al. Clinical course and outcomes of 344 intensive care patients with COVID-19. Am J Respir Crit Care Med. 2020;201(11):1430-34
- 7. Young BE, Ong SWX, Kalimuddin S, et al. Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. JAMA. 2020;323(15):1488-94
- Weiss P, Murdoch DR. Clinical course and mortality risk of severe COVID-19. Lancet. 2020;395(10229):1014-15
- Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet. 2020;395(10229):1054-62
- Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: A single-centered, retrospective, observational study. Lancet Respir Med. 2020;8(5):475-81
- Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: A prospective cohort study. Lancet. 2020;395(10241):1919-26

- 12. Lee LYW, Cazier JB, Starkey T, et al. COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: A prospective cohort study. Lancet. 2020;395(10241):1919-26
- Liu HQ, Yuan B, An YW, et al. Clinical characteristics and follow-up analysis of 324 discharged COVID-19 patients in Shenzhen during the recovery period. Int J Med Sci. 2021;18(2):347-55
- 14. Zhao YM, Shang YM, Song WB, et al. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. EClinicalMedicine. 2020;25:100463
- 15. George PM, Barratt SL, Condliffe R, et al. Respiratory follow-up of patients with COVID-19 pneumonia. Thorax. 2020;75(11):1009-16
- Guo Q, Zheng Y, Shi J, et al. Immediate psychological distress in quarantined patients with COVID-19 and its association with peripheral inflammation: A mixed-method study. Brain Behav Immun. 2020;88:17-27
- 17. Vindegaard N, Eriksen Benros M. COVID-19 pandemic and mental health consequences: Systematic review of the current evidence. Brain Behav Immun. 2020;89:531-42
- Liu K, Chen Y, Wu D, et al. Effects of progressive muscle relaxation on anxiety and sleep quality in patients with COVID-19. Complement Ther Clin Pract. 2020;39:101132
- Vitale JA, Perazzo P, Silingardi M, et al. Is disruption of sleep quality a consequence of severe Covid-19 infection? A case-series examination. Chronobiol Int. 2020;37(7):1110-14
- Kroenke K, Spitzer RL, Williams JBW. The PHQ-15: Validity of a new measure for evaluating the severity of somatic symptoms. Psychosom Med. 2002;64(2): 258-66.
- Gierk B, Kohlmann S, Kroenke K, et al. The somatic symptom scale-8 (SSS-8): A brief measure of somatic symptom burden. JAMA Intern Med. 2014;174(3):399-407

e930447-11

- 22. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708-20
- 23. Li T, Lu H, Zhang W. Clinical observation and management of COVID-19 patients. Emerg Microbes Infect. 2020;9(1):687-90
- Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-69
- Carney S, Koetters T, Cho M, et al. Differences in sleep disturbance parameters between oncology outpatients and their family caregivers. J Clin Oncol. 2011;29(8):1001-6
- Crum-Cianflone NF, Roediger MP, Moore DJ, et al. Prevalence and factors associated with sleep disturbances among early-treated HIV-infected persons. Clin Infect Dis. 2012;54(10):1485-94
- 27. Ghabril M, Jackson M, Gotur R, et al. Most Individuals with advanced cirrhosis have sleep disturbances, which are associated with poor quality of life. Clin Gastroenterol Hepatol. 2017;15(8):1271-1278.e1276
- National Health Commission of the People's Republic of China. 6th edition of Diagnosis and Treatment Guideline of COVID-19. 2020; http://www.nhc. gov.cn/yzygj/s7653p/202002/8334a8326dd94d329df351d7da8aefc2/files/ b218cfeb1bc54639af227f922bf6b817.pdf [in Chinese]
- 29. Shorofsky M, Bourbeau J, Kimoff J, et al. Impaired sleep quality in COPD Is associated with exacerbations: The CanCOLD Cohort Study. Chest. 2019;156(5):852-63

- Wang X, Xu H, Jiang H, et al. Clinical features and outcomes of discharged coronavirus disease 2019 patients: A prospective cohort study. QJM. 2020;113(9):657-65
- Wang L, He W, Yu X, et al. Coronavirus disease 2019 in elderly patients: Characteristics and prognostic factors based on 4-week follow-up. J Infect. 2020;80(6):639-45
- World Health Organization: Weekly epidemiological update
 5 January 2021. https://www.who.int/publications/m/item/ weekly-epidemiological-update---5-january-2021
- 33. Bo HX, Li W, Yang Y, et al. Posttraumatic stress symptoms and attitude toward crisis mental health services among clinically stable patients with COVID-19 in China. Psychol Med. 2020 [Online ahead of print]
- Zhang J, Lu H, Zeng H, et al. The differential psychological distress of populations affected by the COVID-19 pandemic. Brain Behav Immun. 2020;87:49-50
- 35. Geneen LJ, Moore RA, Clarke C, et al. Physical activity and exercise for chronic pain in adults: An overview of Cochrane Reviews. Cochrane Database Syst Rev. 2017;4(4):CD011279
- 36. Wan S, Xiang Y, Fang W, et al. Clinical features and treatment of COVID-19 patients in northeast Chongqing. J Med Virol. 2020;92(7):797-806
- Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with Coronavirus disease 2019 in Wuhan, China. JAMA Neurol. 2020;77(6):1-9