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Poor-sleep is associated with slow recovery from lymphopenia and an increased need for ICU care in hospitalized patients with COVID-19: A retrospective cohort study

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ABSTRACT

Sleep is known to play an important role in immune function. However, the effects of sleep quality during hospitalization for COVID-19 remain unclear. This retrospective, single-center cohort study was conducted to investigate the effects of sleep quality on recovery from lymphopenia and clinical outcomes in hospitalized patients with laboratory-confirmed COVID-19 admitted to the West District of Wuhan Union Hospital between January 25 and March 15, 2020. The Richards-Campbell sleep questionnaire (RCSQ) and Pittsburgh Sleep Quality Index (PSQI) were used to assess sleep quality. The epidemiological, demographic, clinical, laboratory, treatment, and outcome data were collected from electronic medical records and compared between the good-sleep group and poor-sleep group. In all, 135 patients (60 in good-sleep group and 75 in poor-sleep group) were included in this study. There were no significant between-group differences regarding demographic and baseline characteristics, as well as laboratory parameters upon admission and in-hospital treatment. Compared with patients in the good-sleep group, patients in the poor-sleep group had lower absolute lymphocyte count (ALC) (day 14: median, 1.10 *vs* 1.32, $P = 0.0055$; day 21: median, 1.18 *vs* 1.48, $P = 0.0034$) and its reduced recovery rate (day 14: median, 56.91 *vs* 69.40, $P = 0.0255$; day 21: median, 61.40 *vs* 111.47, $P = 0.0003$), as well as increased neutrophil-to-lymphocyte ratio (NLR; day 14: median, 3.17 *vs* 2.44, $P = 0.0284$; day 21: median, 2.73 *vs* 2.23, $P = 0.0092$) and its associated deterioration rate (day 14: median, -39.65 *vs* -61.09, $P = 0.0155$; day 21: median, -51.40% *vs* -75.43, $P = 0.0003$). Nine [12.0%] patients in the poor-sleep group required ICU care ($P = 0.0151$); meanwhile, none of the patients in good-sleep group required ICU care. Patients in the poor-sleep group had increased duration of hospital stay (33.0 [23.0–47.0] days *vs* 25.0 [20.5–36.5] days, $P = 0.0116$) compared to those in the good-sleep group. An increased incidence of hospital-acquired infection (seven [9.3%] *vs* one [1.7%]) was observed in the poor-sleep group compared to the good-sleep group; however, this difference was not significant ($P = 0.1316$). In conclusion, poor sleep quality during hospitalization in COVID-19 patients with lymphopenia is associated with a slow recovery from lymphopenia and an increased need for ICU care.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly spread worldwide. COVID-19 is highly contagious and can result in acute respiratory distress, multiple organ failure, or death in severe cases (Huang et al., 2020a; Wang et al., 2020; Yang et al., 2020; Zhang et al., 2020). The reported mortality rate of COVID-19 is lower than that of severe acute respiratory syndrome (SARS) (Donnelly et al., 2003), or Middle East respiratory syndrome (MERS) (Ahmed, 2017). However, the number of patients needing urgent critical care is remarkably larger than previous outbreaks of SARS or MERS, which could lead to a critical shortage of intensive care unit (ICU) beds and specialized medical and nursing personnel, and, consequently, result in the collapse of local health care systems. Thus, timely and appropriate

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dynamic monitoring and treatment for non-ICU inpatients is urgent and necessary to reduce the risk of patients becoming critically ill and requiring ICU care.

Patients with COVID-19 typically present a decrease in absolute lymphocyte count (ALC) (Huang et al., 2020a; Wang et al., 2020). The dynamic profile of total circulating lymphocytes indicated that a continuous and sustained decrease in the ALC is closely associated with disease aggravation and death in COVID-19 patients (Wang et al., 2020; Zhou et al., 2020). Indeed, lymphopenia was associated with increased disease severity in COVID-19 (Tan et al., 2020). In addition, the neutrophil-to-lymphocyte ratio (NLR) can also serve as a simple complementary indicator to predict clinical severity and prognosis, and is an independent risk factor for mortality in patients with COVID-19 (Lagunas-Rangel, 2020; Qin et al., 2020; Liu et al., 2020). These studies indicate that promoting recovery from lymphopenia and slowing the deterioration based on an increased NLR may reduce the need for ICU care and improve the prognosis of patients with COVID-19.

To date, no specific drugs have been shown to be effective in alleviating lymphopenia in patients with COVID-19. Sleep is a physiological and behavioral process required for survival and plays an important role in metabolism and immune system homeostasis (Besedovsky et al., 2019; Haspel et al., 2020; Mukherjee et al., 2015); indeed, sleep and immunity are bidirectionally linked (Besedovsky et al., 2019). Sleep disturbance impairs innate and adaptive immune responses and activates inflammation, with an increase in circulating inflammatory cytokines due to disruption of the circadian rhythms (Haack et al., 2007; Irwin, 2015; Vgontzas et al., 2004). Short-term sleep deprivation is associated with compromised natural killer cell activity in the blood (Fondell et al., 2011). Disruption of the circadian rhythm of sleep, shorter sleep duration, or poor quality of sleep could increase susceptibility to upper respiratory infections (Cohen et al., 2009; Loef et al., 2019; Patel et al., 2012; Prather et al., 2015). In fact, septic patients with frequently disrupted sleep have higher mortality rates (Huang et al., 2014). Sleep impairment occurs frequent in patients with COVID-19 (Liguori et al., 2020), which may be due to isolated environment without family member' companion, physical discomfort caused by the illness, or psychological factor (fear, anxiety, helplessness and/or depression, etc.) (Guo et al., 2020). However, there are currently no reports of the effects of sleep quality during hospitalization on immune function recovery and prognosis in patients with COVID-19. In tour study, we aimed to describe the effects of self-reported sleep quality on recovery from lymphopenia, deterioration based on an increased NLR, and clinical outcomes in hospitalized patients with COVID-19.

2. Materials and methods

2.1. Study design and participants

For this single-center retrospective study, 449 hospitalized patients with laboratory confirmed COVID-19 admitted to the West District of Wuhan Union Hospital between January 25 and March 15, 2020 were screened using the following inclusion and exclusion criteria. The inclusion criteria included: (1) patients aged between 18 and 80 years; and (2) absolute counts of peripheral blood lymphocytes $< 1.1 \times 10^9$/L within 24 h of hospital admission. The exclusion criteria included: (1) duration of hospital stay $<$ 14 days or death during hospitalization; (2) pregnant or lactating women; (3) deterioration of the condition requiring ICU care within 14 days of admission; and (4) loss of consciousness during hospitalization. A total of 153 patients met these criteria and were included in the study (Fig. 1). The diagnosis, clinical classification, treatment, and discharge criteria of COVID-19 were based on the "Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (6th edition)" issued by the National Health and Family Planning Commission of China (NHPFC, 2020). COVID-19 was confirmed by real-time RT-PCR for throat-swab specimens from the upper respiratory tract. All the included patients had recovered from COVID-19.

The study was approved by the Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (Permission number: 0173). Informed consent for this retrospective study was waived due to the rapid emergence of this infectious disease.

2.2. Data collection

We reviewed the hospital's electronic medical records, nurse records, laboratory findings, and imaging examinations for all patients with confirmed COVID-19. All data were checked by two researchers.

We collected data on age, sex, body mass index, education levels, marital status, comorbidities (chronic respiratory disease, cardiovascular and cerebrovascular diseases, and gastrointestinal, endocrine, urologic, and nervous system diseases), current smoking status, time from symptom onset to admission, signs and symptoms at disease onset, chest imaging abnormalities (unilateral or bilateral distribution of patchy shadows or ground glass opacity), vital signs on admission (respiratory rate, percutaneous oxygen saturation, heart rate, systolic blood pressure, and body temperature), laboratory parameters within 24 h of admission (blood routine, blood biochemistry and electrolytes, cardiac biomarkers, and coagulation parameters), treatment (oxygen therapy, vasoconstrictive agents, antiviral therapy, antibiotics, corticosteroids, immunoglobulin, and immunoregulatory therapy), and complications during hospitalization (acute kidney injury (AKI), acute liver dysfunction, acute cardiac injury, hyperglycemia, and hospital-acquired infection (HAI)). AKI was identified based on the definition in the Kidney Disease: Improving Global Outcomes statement (KDIGO, 2012). Cardiac injury was diagnosed when the levels of serum hypersensitive cardiac troponin I exceeded the upper limit of normal (ULN), measured in the laboratory of the Wuhan Union Hospital. Acute liver dysfunction was defined as an ALT $\geq 1 \times$ ULN. HAI was defined as infection acquired $>$ 48 h after hospital admission. For patient(s) with deterioration of the condition requiring ICU care, the subsequent data regarding laboratory parameters, treatment, and complications were not included in the final analysis.

2.3. Sleep assessment

The Richards-Campbell sleep questionnaire (RCSQ), a widely used subjective survey instrument (Nagatomo et al., 2020; Richards et al., 2000; Simons et al., 2018), was administered to assess sleep quality. Sleep assessment was performed by telephone within 30 days after hospital admission. The overall sleep quality was assessed within the first week (score one), second week (score two), and third week (score three) after admission using the RCSQ, since not all patients were able to accurately assess their daily sleep quality. The RCSQ assesses the following five items on a 0–100 mm visual analog scale: perceived sleep depth, sleep latency, frequency of awakenings, latency after awakenings, and sleep quality. The overall RCSQ score is the average value of these five items, with higher scores indicating better sleep quality. Self-reported factors associated with disruptive sleep were also recorded.

After assessment with the RCSQ, sleep quality within two or three weeks after hospital admission was further confirmed using the Chinese version of the Pittsburgh Sleep Quality Index (PSQI), which is reliable and valid for the Chinese population (Liu et al., 1996). The PSQI includes seven component scores: subjective sleep quality, sleep duration, sleep latency, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. The sum of the seven component scores (each ranging from 0 to 3) provides the global sleep quality score (ranging from 0 to 21), with a score greater than 7 indicating poor sleep quality (Liu et al., 1996). Patients were divided into two groups: good-sleep group (at least two RCSQ scores $\geq$ 70, and PSQI $\leq$ 7) and poor-sleep group (at least two RCSQ scores $\leq$ 50, and PSQI $>$ 7). Patients

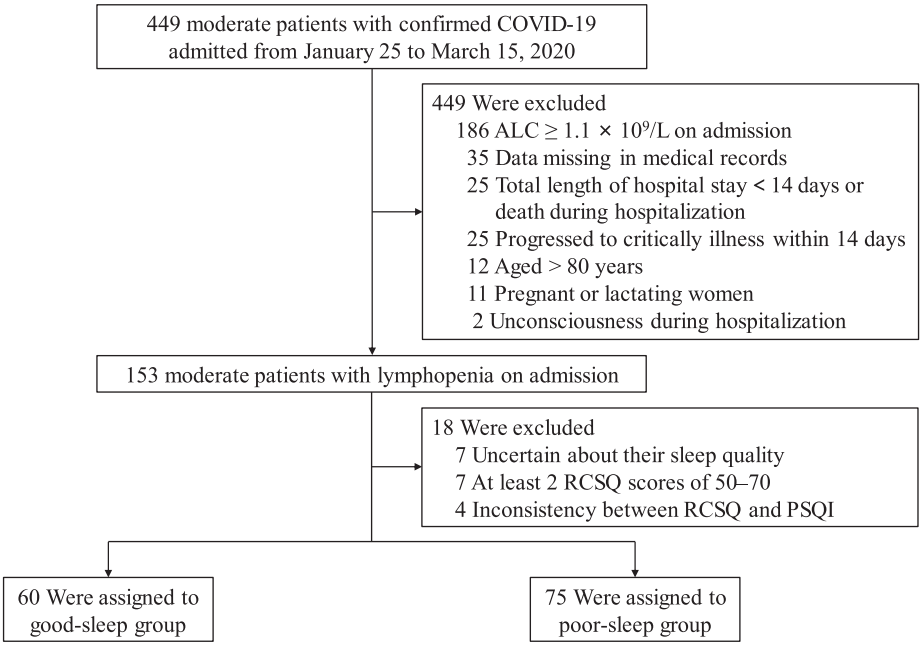

Fig. 1. Study flow diagram. ALC, absolute lymphocyte count; COVID-19, coronavirus disease-2019; ICU, intensive care unit; PSQI, Pittsburgh Sleep Quality Index; RCSQ, Richards-Campbell sleep questionnaire.

with deterioration of their health condition requiring ICU care, or those with a duration of hospital stay $<$ 21 days were assigned to one of the two groups based on the overall quality of their sleep within the first two weeks after hospital admission: patients with two RCSQ scores $\geq$ 70 and PSQI $\leq$ 7 were assigned to the good-sleep group and those with one RCSQ score $\leq$ 50 and PSQI $>$ 7 were assigned to the poor-sleep group.

2.4. Outcomes

The primary outcomes were: (1) recovery rate based on ALC and deterioration based on an increased NLR on day 7, 14, and 21 after admission; (2) need for ICU care within 14 days of hospital admission.

The absolute counts of peripheral blood lymphocytes and neutrophils within 24 h of hospital admission were set as baseline value. The formula for the recovery percentage or deteriorative percentage is described as:

$$\frac{\text{ALC or NLR(day 7, day 14 or day 21)} - -\text{ALC or NLR(baseline)}}{\text{ALC or NLR(baseline)}} \times 100\%$$

The secondary outcomes were: (1) HAI; and (2) total length of hospital stay.

2.5. Statistical analysis

Categorical variables were described as number (%). Continuous variables were described using mean (SD) if they were normally distributed, or median (interquartile range, IQR) if they were not. Continuous variables were compared using independent group t tests when the data were normally distributed; otherwise, the Mann-Whitney test was used. Proportions for categorical variables were compared using the χ^2 test, Yates' continuity corrected χ^2 test, or Fisher's exact test. A two-sided P value $<$ 0.05 was considered statistically significant. The data collected were all analyzed using SPSS version 20.0 software (SPSS, Tokyo, Japan).

3. Results

3.1. Patients

In all, 449 patients admitted to West District of Wuhan Union Hospital between January 25 and March 15, 2020 were included in the study. Subsequently, we excluded the following patients: 186 patients that did not have a decreased ALC upon hospital admission, 35 patients without relevant information in their medical records, 25 patients with duration of hospital stay less than 14 days or death during hospitalization, 25 patients with deteriorated condition requiring ICU care within 14 days after hospital admission, 12 patients aged $>$ 80 years, 11 pregnant or lactating women, two patients with loss of consciousness during hospitalization, seven patients who were uncertain about their sleep quality, seven patients with at least two RCSQ scores between 50 and 70, and four patients with inconsistency between RCSQ and PSQI. Therefore, we included 135 patients (60 in the good-sleep group and 75 in the poor-sleep group) in the final analysis (Fig. 1).

3.2. Demographic and baseline characteristics, as well as laboratory parameters upon hospital admission and treatment

The median age of patients was 63 years (IQR, 55–69 years), and 57.8% of patients were men (Table 1). The median interval time from symptom onset to admission was 11.0 days (IQR, 9.0–13.5 days). A total of 83 (61.5%) patients had comorbidities, and 134 (99.3%) patients had bilateral distribution of patchy shadows or ground glass opacity on chest x-ray or CT imaging. There were no significant between-group differences in demographic and baseline characteristics (Table 1), as well as laboratory parameters upon hospital admission and treatment during hospitalization (Table 3).

3.3. Self-reported sleep quality

Patients in the poor-sleep group had lower RCSQ scores in the first week (median, 40.0 [IQR, 30.0–50.0] *vs* 75.0 [IQR, 70.0–82.0], P $<$ 0.0001), second week (median, 45.0 [IQR, 40.0–50.0] *vs* 80.0 [IQR, 75.5–86.0], P $<$ 0.0001) and third week (median, 45.0 [IQR, 40.0–50.5] *vs* 80.0 [IQR, 75.0–88.0], P $<$ 0.0001) than those in the

Table 1
Demographics and baseline characteristics of patients with COVID-19.

	Total (n = 135)	Good sleep (n = 60)	Poor sleep (n = 75)	*P* value
Age, median (IQR), years	63 (55–69)	61 (51–68)	64 (56–70)	0.1126
< 50 years	22 (16.3)	14 (23.3)	9 (12.0)	0.0818
50–70 years	83 (61.5)	36 (60.0)	46 (61.3)	0.8747
≥ 70 years	30 (22.2)	10 (16.7)	20 (26.7)	0.1649
Sex:				
Male	78 (57.8)	40 (66.7)	38 (50.7)	0.0614
Female	57 (42.2)	20 (33.3)	37 (49.3)	
BMI, median (IQR), kg/m^2	23.9 (22.3–25.6)	23.8 (22.5–25.3)	24.2 (22.0–25.7)	0.7886
Marital status:				
Married	129 (95.6)	57 (95.0)	72 (96.0)	0.7794
Unmarried	3 (2.2)	2 (3.3)	1 (1.3)	0.8447
Death of a spouse	3 (2.2)	1 (1.7)	2 (2.7)	0.8447
Education level:				
≤ High school	96 (71.1)	39 (65.0)	57 (76.0)	0.1612
University or college	32 (23.7)	17 (28.3)	15 (20.0)	0.2579
Master or doctor	7 (5.2)	4 (6.7)	3 (4.0)	0.4875
Current smoking	4 (3.0)	0 (0)	4 (5.3)	0.1918
Comorbidities:	83 (61.5)	34 (56.7)	49 (65.3)	0.3038
Cardiovascular and cerebrovascular diseases	42 (31.1)	19 (31.7)	23 (30.7)	0.9008
Endocrine disease	38 (28.1)	16 (26.7)	22 (29.3)	0.7321
Malignancy	13 (9.6)	4 (6.7)	9 (12.0)	0.2966
Chronic respiratory disease	6 (4.4)	1 (1.7)	5 (6.7)	0.3268
Gastrointestinal disease	4 (3.0)	1 (1.7)	3 (4.0)	0.7766
Urologic diseases	2 (1.5)	0 (0)	2 (2.7)	0.5025
Onset of symptom to hospital admission, median (IQR), days	11.0 (9.0–13.5)	11.0 (9.0–15.0)	11.0 (8.5–13.0)	0.5954
Signs and symptoms at disease onset:				
Fever	123 (91.1)	53 (88.3)	70 (93.3)	0.3104
Cough	92 (68.1)	38 (63.3)	54 (72.0)	0.2828
Shortness of breath	75 (55.6)	31 (51.7)	44 (58.7)	0.4160
Fatigue	68 (50.4)	32 (53.3)	36 (48.0)	0.5380
Expectoration	37 (27.4)	14 (23.3)	23 (30.7)	0.3425
Myalgia or arthralgia	34 (25.2)	15 (25.0)	19 (25.3)	0.9646
Diarrhoea	18 (13.3)	7 (11.7)	11 (14.7)	0.6104
Chills	18 (13.3)	8 (13.3)	10 (13.3)	> 0.9999
Nausea or Vomiting	15 (11.1)	9 (15.0)	6 (8.0)	0.1984
Anorexia	12 (8.9)	7 (11.7)	5 (6.7)	0.3104
Headache	10 (7.4)	5 (8.3)	5 (6.7)	0.9707
Dizziness	5 (3.7)	2 (3.3)	3 (4.0)	0.7989
Chest pain	5 (3.7)	2 (3.3)	3 (4.0)	0.7989
Pharyngalgia	3 (2.2)	3 (5.0)	0 (0)	0.1704
Rhinorrhoea	2 (1.5)	1 (1.7)	1 (1.3)	> 0.9999
Haemoptysis	2 (1.5)	2 (3.3)	0 (0)	0.1957
Abdominal pain	2 (1.5)	2 (3.3)	0 (0)	0.1957
Vital signs on admission:				
Body tempreture, median (IQR), ℃	36.9 (36.5–38.0)	36.9 (36.6–38.0)	36.8 (36.5–37.9)	0.4967
Systolic pressure, median (IQR), mmHg	131.0 (120.0–143.0)	131.5 (117.5–145.0)	131.0 (120.0–142.5)	0.5040
Heart rate, median (IQR), beat per minute	85.0 (75.5–100.0)	80.5 (74.5–99.0)	87.0 (77.5–100.5)	0.2444
Respiratory rate, median (IQR), breaths per minute	20.0 (20.0–24.5)	20.0 (20.0–24.0)	21.0 (20.0–25.0)	0.2136
Percutaneous oxygen saturation, median (IQR), %†	95 (92–96)	95 (91–96)	94 (92–96)	0.9816
Bilateral distribution of patchy shadows or ground glass opacity on chest x-ray or CT imaging:	134 (99.3)	59 (98.3)	75 (100%)	0.2618

Values are numbers (percentages) unless stated otherwise. Abbreviations: IQR, interquartile range; n, number. *P* values indicate differences between good-sleep and poor-sleep patients. $P < 0.05$ was considered statistically significant.
†Data were missing for the measurement of percutaneous oxygen saturation in eight patients (13.3%) of the good-sleep group, and nine patients (12.0%) of the poor-sleep group.

good-sleep group (Table 2). The PSQI scores were higher in patients in the poor-sleep group than those in the good-sleep group (median, 12.0 [IQR, 11.0–14.0] *vs* 5.0 [IQR, 4.0–6.0], $P < 0.0001$). Among the etiological causes of poor-sleep during hospitalization, these included environmental factors, psychosocial factors, discomfort caused by the illness, and chronic insomnia for 85.3%, 60.0%, 56.0%, and 32.0% of patients, respectively (Table 2).

3.4. Complications, HAI, and duration of hospital stay

During hospitalization, there were no important between-group differences in organ function damage, including acute liver injury (47 [62.7%] *vs* 37 [61.7%], $P = 0.9052$), hyperglycemia (33 [44.0%] *vs* 31 [51.7%], $P = 0.3754$), acute kidney injury (three [4.0%] *vs* 0 [0%], $P = 0.3275$), and acute cardiac injury (two [2.7%] *vs* one [1.7%], $P = 0.8447$) in the good-sleep group and poor-sleep group (Table 3). Patients in the poor-sleep group had an increased incidence of HAI (seven [9.3%] *vs* one [1.7%]) compared to those in the good-sleep group; however, this difference was not significant ($P = 0.1316$) (Table 3). One patient with HAI in the good-sleep group had pulmonary infection of extended-spectrum β-lactamase (EBSL)-positive *klebsiella pneumoniae*. Meanwhile, HAI in the poor-sleep group included the following: two patients had pulmonary infection of carbapenem-resistant *Acinetobacter Baumanii* and *Candida tropicalis*, two patients had urinary tract infection, one patient had blood stream infection of EBSL-positive *klebsiella pneumoniae,* one patient had both pulmonary infection of *Candida tropicalis* and blood stream infection of *bacillus*, and one patient had pulmonary infection of *Stenotrophomonas maltophilia* and

Table 2
Sleep quality assessment in patients with COVID-19.

	Median (IQR)		*P* value
	Good sleep (n = 60)	Poor sleep (n = 75)	
RCSQ scores in the first week, median (IQR)			
All ages	75.0 (70.0–82.0)	40.0 (30.0–50.0)	< 0.0001
< 50 years	76.0 (71.0–84.0)	44.5 (40.0–47.5)	< 0.0001
50–70 years	75.0 (70.0–80.5)	40.0 (30.0–50.0)	< 0.0001
≥ 70 years	78.5 (72.0–80.0)	45.0 (32.5–50.0)	< 0.0001
RCSQ scores in the second week, median (IQR)			
All ages	80.0 (75.5–86.0)	45.0 (40.0–50.0)	< 0.0001
< 50 years	86.0 (76.0–87.0)	46.0 (42.5–50.0)	< 0.0001
50–70 years	80.0 (75.0–85.0)	45.0 (40.0–50.0)	< 0.0001
≥ 70 years	78.5 (76.0–82.0)	44.0 (35.0–50.0)	< 0.0001
RCSQ scores in the third week, median (IQR)			
All ages	80.0 (75.0–88.0)	45.0 (40.0–50.5)	< 0.0001
< 50 years	80.0 (75.0–89.0)	51.5 (45.0–60.0)	0.0002
50–70 years	81.0 (75.0–89.0)	45.0 (40.0–55.0)	< 0.0001
≥ 70 years	80.0 (75.0–82.0)	45.0 (40.0–50.0)	< 0.0001
PSQI scores, median (IQR)			
All ages	5.0 (4.0–6.0)	12.0 (11.0–14.0)	< 0.0001
< 50 years	6.0 (4.0–6.0)	12.0 (10.5–15.0)	< 0.0001
50–70 years	5.0 (4.5–6.0)	12.0 (11.0–13.0)	< 0.0001
≥ 70 years	5.0 (4.0–7.0)	13.0 (12.0–15.0)	< 0.0001
Factors affecting sleep quality			
Environmental factor, n (%)	–	61 (85.3)	–
Psychosocial factor, n (%)[a]	–	45 (60.0)	–
Discomfort caused by the illness, n (%)	–	42 (56.0)	–
Chronic insomnia, n (%)	–	24 (32.0)	–

Values are median (IQR [range]) unless stated otherwise. [a]Psychological factors include fear, anxiety, helplessness and depression. Abbreviations: IQR, interquartile range; n, number; PSQI, Pittsburgh Sleep Quality Index; RCSQ, Richards Campbell sleep questionnaire. *P* values indicate differences between the good-sleep and the poor-sleep patients. $P < 0.05$ was considered statistically significant.

carbapenem-resistant *Acinetobacter baumannii*. The health condition of nine [12.0%] patients in the poor-sleep group deteriorated and required ICU care ($P = 0.0151$); meanwhile, none of the patients in the good-sleep group needed ICU care. In addition, patients in the poor-sleep group had an increased hospital stay (median, 33.0 [IQR, 23.0–47.0] days *vs* 25.0 [IQR, 20.5–36.5] days, $P = 0.0116$) compared to those in the good-sleep group.

3.5. Absolute lymphocyte count and neutrophil-to-lymphocyte ratio

Compared to patients in the good-sleep group, patients in the poor-sleep group had significantly decreased ALC on day 14 (median, 1.10 [IQR, 0.88–1.35] *vs* 1.32 [IQR, 1.04–1.59], $P = 0.0055$) and day 21 after hospital admission (median, 1.18 [IQR, 0.92–1.45] *vs* 1.48 [IQR, 1.10–1.98], $P = 0.0034$). Patients in the poor-sleep group also had an increased NLR on day 14 (median, 3.17 [IQR, 2.27–4.66] *vs* 2.44 [IQR, 2.05–3.75], $P = 0.0284$) and day 21 (median, 2.73 [IQR, 2.10–5.90] *vs* 2.23 [IQR, 1.63–2.92], $P = 0.0092$) than those in the good-sleep group (Fig. 2). The recovery rate based on ALC was higher in patients in the good-sleep group on day 14 (median, 56.91 [IQR, 8.67–94.54] *vs* 69.40 [IQR, 43.67–132.40], $P = 0.0255$) and day 21 (median, 61.40 [IQR, 26.81–102.82] *vs* 111.47 [IQR, 65.38–183.05], $P = 0.0003$) than those in the poor-sleep group; similar results were found regarding the deterioration based on an increased NLR on day 7 (median, −15.01 [IQR, −43.02–0.82] *vs* −39.24 [IQR, −60.34–-0.24], $P = 0.0314$), day 14 (median, −39.65 [IQR, −62.06–-12.94] *vs* −61.09 [IQR, −70.87—23.50], $P = 0.0155$), and day 21 (median, −51.40% [IQR, −61.08—22.36] *vs* −75.43 [IQR, −82.19–-47.77], $P = 0.0003$) (Fig. 2).

4. Discussion

To our knowledge, this report is the first case series to study the effects of sleep quality on the recovery from lymphopenia, deterioration based on an increased NLR, and clinical outcomes in hospitalized patients with COVID-19. Among the 135 patients included in this study, 44.4% of patients reported at least two weeks of good-sleep, and 55.6% patients reported at least two weeks of poor-sleep within three weeks after hospital admission. There were no significant between-group differences regarding demographic and baseline characteristics, as well as laboratory parameters upon admission and in-hospital treatment. Also, no significant differences between the good-sleep group and poor-sleep groups were detected regarding ALC and its recovery rate, as well as NLR on day 7 after hospital admission, indicating an equivalent immune function and its recovery rate between the two groups during the early phase of hospital admission. However, at least 2 weeks of poor sleep during hospitalization was associated with a slow recovery from lymphopenia and an increase in the deterioration of NLR. On day 14 and day 21 after hospital admission, patients in the poor-sleep group had reduced ALC and associated recovery rate, as well as increased NLR and associated deterioration percentage compared to patients in the good-sleep group, suggesting detrimental effects of a sustained period of poor sleep on recovery of immune function in patients with COVID-19. Furthermore, patients in the poor-sleep group had an increased incidence of HAI (seven [9.3%] *vs* one [1.7%]) compared to those in the poor-sleep group, which may be due to a slower recovery from lymphopenia in the poor-sleep group; however, this difference was not significant. Additionally, the health condition of 12.0% of patients with COVID-19 with poor-sleep deteriorated, requiring ICU care, whereas none of the patients in the good-sleep group required ICU care. Patients in the poor-sleep group spent an average of eight days longer in the hospital than those in the good-sleep group. Our present study confirms recent studies showing that a continuous and sustained decrease in the ALC, or increase in NLR, is closely associated with the disease aggravation in patients with COVID-19 (Tan et al., 2020; Wang et al., 2020; Zhou et al., 2020). However, SARS-CoV-2 could be detected in the cerebrospinal fluid by PCR in a case of COVID-19 encephalitis (Huang et al., 2020b), and neurologic syndrome was found after the onset of COVID-19, including Guillain-Barré Syndrome, polyneuritis cranialis, and stroke (Toscano et al., 2020; Gutierrez-Ortiz et al., 2020;

Table 3
Laboratory parameters on hospital admission as well as complications, treatments and outcomes of patients with COVID-19.

	Normal range	Total (n = 135)	Good-sleep (n = 60)	Poor-sleep (n = 75)	*P* value
Blood routine:					
White blood count, $\times 10^9$/L	3.50–9.50	5.36 (4.16–7.18)	6.06 (4.77–7.57)	5.16 (4.09–6.78)	0.1260
Neutrophil count, $\times 10^9$/L	1.80–6.30	4.23 (2.98–5.99)	4.60 (3.30–6.61)	3.92 (2.92–5.54)	0.1700
Neutrophil percentage, %	40.0–75.0	78.9 (72.1–86.7)	79.7 (73.6–86.9)	76.5 (71.9–85.9)	0.1515
Lymphocyte count, $\times 10^9$/L	1.10–3.20	0.75 (0.55–0.95)	0.72 (0.55–0.93)	0.81 (0.55–0.96)	0.5126
Lymphocyte percentage, %	20.0–50.0	14.5 (8.5–18.1)	11.8 (8.1–17.8)	14.8 (8.9–19.2)	0.2271
Platelet count, $\times 10^9$/L	125–350	207.0 (153.0–258.0)	207.0 (145.0–264.5)	207.0 (154.5–247.0)	0.9358
Coagulation parameters†:					
Activated partial thromboplastin time, S	27.0–45.0	38.0 (34.8–42.2)	38.6 (35.4–42.9)	37.9 (34.7–41.6)	0.7342
Prothrombin time, S	11.0–16.0	13.5 (12.6–14.2)	13.4 (12.7–14.2)	13.5 (12.6–14.2)	
D-dimer ≥ 0.5, μg/mL, n (%)	0.0–0.5	72 (53.3)	29 (48.3)	43 (57.3)	0.2976
Blood biochemistry and electrolyte‡:					
Albumin, g/L	33.0–55.0	29.7 (26.8–32.6)	30.4 (27.5–34.2)	28.7 (26.1–32.0)	0.0386
Alanine transaminase, U/L	5–40	38.0 (24.5–58.5)	42.5 (29.0–72.5)	33.0 (23.0–54.0)	0.0424
Total bilirubin, μmol/L	3.0–20.0	10.7 (7.3–14.0)	11.7 (8.6–14.0)	10.1 (6.7–14.0)	0.1305
Blood urea nitrogen, mmol/L	2.90–8.20	4.77 (3.63–6.47)	5.52 (3.52–7.42)	4.65 (3.64–5.83)	0.1422
Serum creatinine, μmol/L	57.0–111.0	69.3 (58.5–85.0)	69.7 (58.7–86.3)	68.0 (57.3–82.6)	0.9991
Creatine kinase, U/L‡	24–194	69.0 (47.0–130.0)	81.0 (52.0–165.0)	64.5 (40.0–105.5)	0.0288
Lactate dehydrogenase, U/L	109–245	305.0 (224.5–380.5)	326.0 (225.0–402.0)	277.0 (224.5–367.0)	0.1233
Glucose, mmol/L	3.90–6.10	6.40 (5.53–8.63)	6.37 (5.77–9.78)	6.55 (5.47–8.20)	0.3565
Total carbon dioxide, mmol/L	20.0–29.0	24.1 (21.6–28.0)	23.6 (21.7–27.6)	24.6 (21.6–28.4)	0.3503
Sodium, mmol/L	137.0–147.0	138.2 (135.9–140.3)	137.8 (135.3–140.1)	138.5 (136.5–140.4)	0.2621
Potassium, mmol/L	3.50–5.30	3.75 (3.41–4.11)	3.82 (3.50–4.17)	3.65 (3.39–4.07)	0.1872
Cardiac biomarkers§:					
Creatine kinase-MB ≥ 6.6, ng/mL	< 6.6	0 (0)	0 (0)	0 (0)	–
Hypersensitive cardiac troponin I ≥ 26.2, ng/L	< 26.2	7 (5.2)	5 (8.3)	2 (2.7)	0.2779
Complications					
Acute liver dysfunction	–	84 (62.2)	37 (61.7)	47 (62.7)	0.9052
Hyperglycaemia	–	64 (47.4)	31 (51.7)	33 (44.0)	0.3754
Hospital-acquired infection	–	8 (5.9)	1 (1.7)	7 (9.3)	0.1316
Acute kidney injury	–	3 (2.2)	0 (0)	3 (4.0)	0.3275
Acute cardiac injury	–	3 (2.2)	1 (1.7)	2 (2.7)	0.8447
Treatment:					
Oxygen therapy					
Nasal cannula	–	102 (75.6)	48 (80.0)	64 (85.3)	0.4128
Oxygen mask	–	32 (23.7)	16 (26.7)	16 (21.3)	0.4690
Without oxygen	–	3 (2.2)	1 (1.7)	2 (2.7)	0.8447
Antiviral therapy	–	132 (97.8)	59 (98.3)	73 (97.3)	0.6953
Antibiotics	–	105 (79.5)	44 (73.3)	61 (81.3)	0.2666
Immunoregulatory therapy	–	79 (58.5)	37 (61.7)	42 (56.0)	0.5067
Corticosteroids	–	74 (54.8)	32 (53.3)	42 (56.0)	0.7570
Immunoglobulin	–	39 (28.9)	21 (35.0)	18 (24.0)	0.1612
Vasoconstrictive agents	–	13 (9.6)	6 (10.0)	7 (9.3)	0.8962
Requring ICU care	–	9 (6.7)	0 (0)	9 (12.0)	0.0151
Total length of hospital stay, median (IQR), d	–	29.0 (21.0–45.0)	25.0 (20.5–36.5)	33.0 (23.0–47.0)	0.0116

Values are median (IQR [range]) or numbers (percentages). Abbreviations: IQR, interquartile range; n, number. [a]*P* values indicate differences between good-sleep and poor-sleep patients. $P < 0.05$ was considered statistically significant.
†Data were missing for the measurement of activated partial thromboplastin time, prothrombin time, or D-dimer in five patients (8.3%), five patients (8.3%), and 10 patients (16.6%) in the good-sleep group, and six patients (8.0%), six patients (8.0%), and 10 patients (13.3%) in the poor-sleep group, respectively.
‡Data regarding creatine kinase were missing for seven patients (11.7%) in the good-sleep group, and 11 patients (14.7%) in the poor-sleep group.

Oxley et al., 2020). Therefore, bidirectional causality might exist between poor sleep quality during hospitalization and worse clinical outcomes in patients with COVID-19.

In patients with COVID-19 with poor-sleep, the most important etiological causes of poor-sleep were environmental and psychosocial factors, which accounted for 85.3% and 60.0%, respectively. Physical discomfort caused by illness was another major factor that contributed to poor-sleep during hospitalization in patients with COVID-19. These factors are also the major causal factors of sleep disturbance in ICU patients and could negatively affect recovery from critical illness (Delaney et al., 2015; Devlin et al., 2018; Friese, 2008; Kamdar et al., 2012; Pulak and Jensen, 2016). Therefore, psychological treatment (spiritual encouragement, psychological comfort, emotional support, psychotropic drug therapy, etc.), improving the ward environment (reducing noise, improving lighting, segregating patients from each other by curtains, etc.), and interventions to alleviate psychological comfort (adequate analgesia, proper sedation, relieving breathing difficulty, etc.) are essential to improve the sleep quality of patients with COVID-19 in non-ICU wards.

As a retrospective study, there were no objective tools for sleep assessment in patients with COVID-19. The RCSQ is empirically valid and the most widely used subjective survey instrument for assessing the quality of ICU patients' sleep (Nagatomo et al., 2020; Richards et al., 2000; Simons et al., 2018). In a clinical study of 70 ICU patients, the RCSQ was validated against polysomnography (PSG) (Richards et al., 2000), which is considered the gold standard method for evaluating sleep. We chose the RCSQ for assessing the sleep quality of patients with COVID-19 in non-ICU wards, since the frequent shifting of duty during ward-rounds, and the isolated environment without family member' companion in non-ICU ward for patients with COVID-19, are similar to that in the ICU wards for patients who are recovering from critical illness. Since not all patients were able to accurately recollect and assess their daily sleep quality during their hospitalization, we broadened the application scope of the RCSQ and only assessed the overall sleep quality within the first week, second week, and third week after hospital admission. In order to minimize different forms of bias,

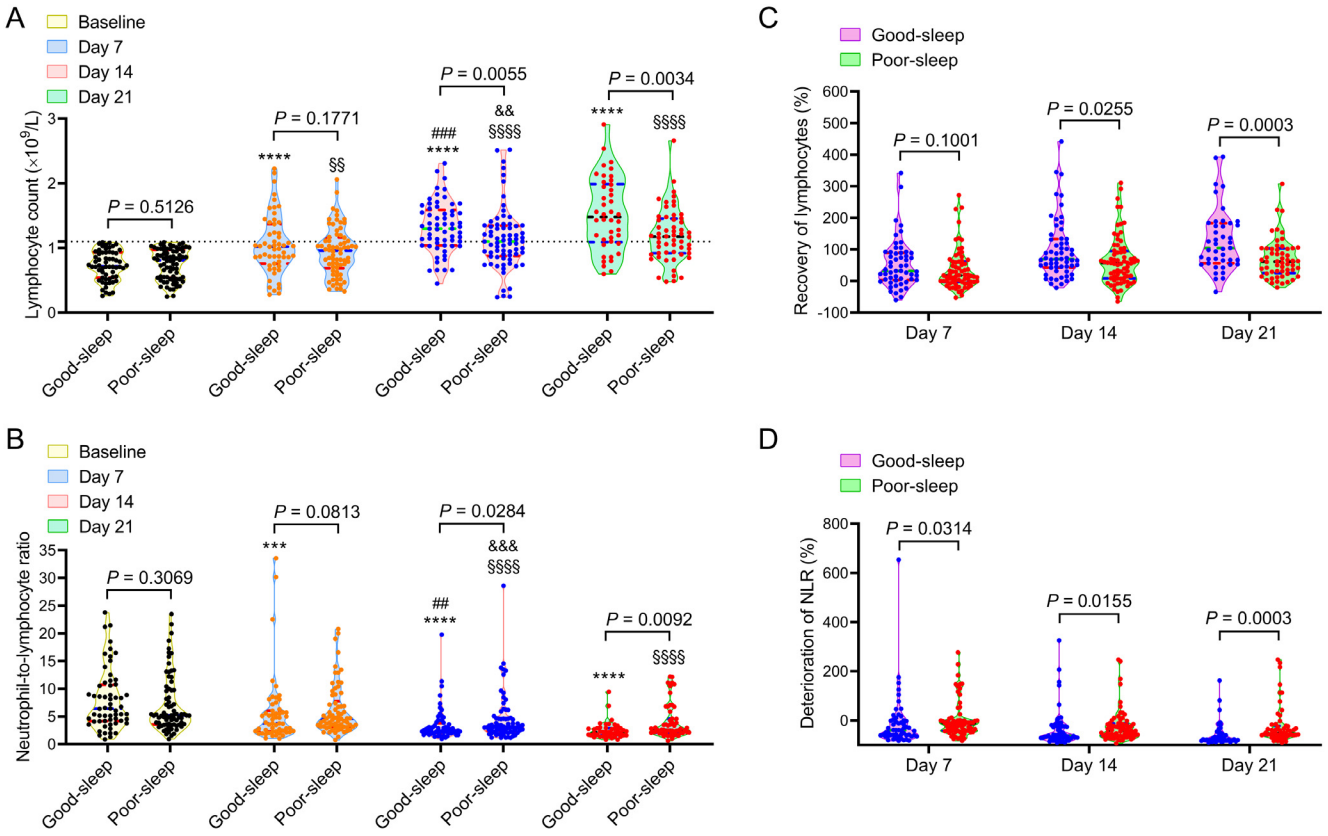

Fig. 2. Effects of self-reported sleep quality on recovery from lymphopenia. Dynamic changes in absolute lymphocyte count (ALC; A) and neutrophil-to-lymphocyte ratio (NLR; B) within 24 h (baseline value), on day 7, 14, and 21 after hospital admission in patients with COVID-19 in the good-sleep and poor-sleep groups. Dynamic changes in the ALC recovery rate (C) and NLR deterioration rate (D) on day 7, 14, and 21 after hospital admission in patients with COVID-19 in the good-sleep and poor-sleep groups. Data were missing in five patients (8.3%) on day 7, and three patients (5.0%) on day 21 in the good-sleep group. Data were missing in five patients (6.6%) on day 7, three patients (4.0%) on day 14, and four patients (5.3%) on day 21 in the poor-sleep group. $^{***}P < 0.001$ and $^{****}P < 0.0001$ when compared to the baseline value of the good-sleep group; $^{§§}P < 0.01$ and $^{§§§§}P < 0.0001$ when compared to baseline values of the poor-sleep group; $^{\#\#}P < 0.01$ and $^{\#\#\#}P < 0.001$ when compared to values on day 7 in the good-sleep group; $^{\&\&}P < 0.01$ and $^{\&\&\&\&}P < 0.001$ when compared to values on day 7 in the poor-sleep group; N.S., not significant. $P < 0.05$ was considered statistically significant.

including recollection and response bias, patients with COVID-19 who were unsure of their sleep quality were excluded from the study. We also lowered the upper limit of the RCSQ score that defines poor-sleep quality (≤50) to minimize bias, while the cut-off point differentiating good and poor sleep was 70/100 in previous studies (Mannion et al., 2019; McKinley et al., 2013). Patients with at least two RCSQ scores of 50–70 were also excluded. After assessment with the RCSQ, overall sleep quality was further confirmed using the Chinese version of the PSQI, which has been shown to be reliable and valid for the Chinese population (Liu et al., 1996). The PSQI could discriminate between poor and good sleep quality over the preceding 30-days and has been widely used in clinical and non-clinical settings (Mollayeva et al., 2016). In our study, we used both the RCSQ and the PSQI to better reflect the subjective sleep quality of patients with COVID-19 during hospitalization. Furthermore, patients were excluded in cases of inconsistency between the RCSQ and PSQI scores. In addition, after patients' self-reported sleep assessment, we further checked patients' overall sleep quality by asking their hospital roommates, as well as the doctors and nurses responsible for their treatment.

There were some notable limitations in our study. First, a few cases had incomplete documentation of the laboratory parameters at each specific time point, due to lack of necessity for continuous daily tests. Second, it was a single-center retrospective study with a small sample size. Future prospective studies with large patient cohorts are needed to validate the results. Third, although multiple criteria for grouping based on the RCSQ and the PSQI was strictly defined in this study, there could still be recollection and response bias. Therefore, objective sleep monitoring is needed in future studies.

5. Conclusions

Poor-sleep quality in patients with COVID-19 was associated with a slow recovery from lymphopenia, an increased risk of becoming critically ill and requiring ICU care, and prolonged duration of hospital stay. It is important to adopt comprehensive treatment measures during hospitalization to improve the sleep quality of patients with mild or moderate lymphopenia in the early stage of COVID-19 infection to promote recovery of immune function and prevent the need for ICU care, thereby reducing the great risk posed by the COVID-19 crisis regarding critical care resources.

Author contributions

SY and JZ had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: SY, KH, and YS. Acquisition, analysis, or interpretation of data: JZ, DX, BX, YZ, HH, HL, HC, and YBS. Drafting of the manuscript: JZ. Critical revision of the manuscript for important intellectual content: KH. Statistical analysis: JZ. Administrative, technical, or material support: DX, YS, and SY. Supervision: YS and SY.

7. Data visualization

After publication, the data supporting the findings of this study can

be provided by the corresponding author upon reasonable request. Participant data without names and identifiers can be provided by the corresponding author and the Wuhan Union Hospital after approval. The research team will provide an email address for communication purposes once approval is obtained regarding sharing the data with others. The proposal with detailed description of the study objectives and statistical analysis plan will be needed for evaluation of the purpose for the data request. Additional materials may also be required during the process of evaluation.

Declaration of interests

The authors declare no competing interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2020.05.075.

References

Ahmed, A.E., 2017. The predictors of 3- and 30-day mortality in 660 MERS-CoV patients. BMC Infect. Dis. 17, 615.

Besedovsky, L., Lange, T., Haack, M., 2019. The Sleep-Immune Crosstalk in Health and Disease. Physiol. Rev. 99, 1325–1380.

Cohen, S., Doyle, W.J., Alper, C.M., Janicki-Deverts, D., Turner, R.B., 2009. Sleep habits and susceptibility to the common cold. Arch Intern Med 169, 62–67.

Delaney, L.J., Van Haren, F., Lopez, V., 2015. Sleeping on a problem: the impact of sleep disturbance on intensive care patients - a clinical review. Ann Intensive Care 5, 3.

Devlin, J.W., Skrobik, Y., Gelinas, C., Needham, D.M., Slooter, A., Pandharipande, P.P., Watson, P.L., Weinhouse, G.L., Nunnally, M.E., Rochwerg, B., Balas, M.C., van den Boogaard, M., Bosma, K.J., Brummel, N.E., Chanques, G., Denehy, L., Drouot, X., Fraser, G.L., Harris, J.E., Joffe, A.M., Kho, M.E., Kress, J.P., Lanphere, J.A., McKinley, S., Neufeld, K.J., Pisani, M.A., Payen, J.F., Pun, B.T., Puntillo, K.A., Riker, R.R., Robinson, B., Shehabi, Y., Szumita, P.M., Winkelman, C., Centofanti, J.E., Price, C., Nikayin, S., Misak, C.J., Flood, P.D., Kiedrowski, K., Alhazzani, W., 2018. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. Crit. Care Med. 46, e825–e873.

Donnelly, C.A., Ghani, A.C., Leung, G.M., Hedley, A.J., Fraser, C., Riley, S., Abu-Raddad, L.J., Ho, L.M., Thach, T.Q., Chau, P., Chan, K.P., Lam, T.H., Tse, L.Y., Tsang, T., Liu, S.H., Kong, J.H., Lau, E.M., Ferguson, N.M., Anderson, R.M., 2003. Epidemiological determinants of spread of causal agent of severe acute respiratory syndrome in Hong Kong. Lancet 361, 1761–1766.

Fondell, E., Axelsson, J., Franck, K., Ploner, A., Lekander, M., Balter, K., Gaines, H., 2011. Short natural sleep is associated with higher T cell and lower NK cell activities. Brain Behav. Immun. 25, 1367–1375.

Friese, R.S., 2008. Sleep and recovery from critical illness and injury: a review of theory, current practice, and future directions. Crit. Care Med. 36, 697–705.

Gutierrez-Ortiz, C., Mendez, A., Rodrigo-Rey, S., San, P.E., Bermejo-Guerrero, L., Gordo-Manas, R., de Aragon-Gomez, F., Benito-Leon, J., 2020. Miller Fisher Syndrome and polyneuritis cranialis in COVID-19. Neurology. https://doi.org/10.1212/WNL.0000000000009619.

Guo, Q., Zheng, Y., Shi, J., Wang, J., Li, G., Li, C., Fromson, J.A., Xu, Y., Liu, X., Xu, H., Zhang, T., Lu, Y., Chen, X., Hu, H., Tang, Y., Yang, S., Zhou, H., Wang, X., Chen, H., Wang, Z., Yang, Z., 2020. Immediate psychological distress in quarantined patients with COVID-19 and its association with peripheral inflammation: a mixed-method study. Brain Behav Immun. https://doi.org/10.1016/j.bbi.2020.05.038.

Haack, M., Sanchez, E., Mullington, J.M., 2007. Elevated inflammatory markers in response to prolonged sleep restriction are associated with increased pain experience in healthy volunteers. Sleep 30, 1145–1152.

Haspel, J.A., Anafi, R., Brown, M.K., Cermakian, N., Depner, C., Desplats, P., Gelman, A.E., Haack, M., Jelic, S., Kim, B.S., Laposky, A.D., Lee, Y.C., Mongodin, E., Prather, A.A., Prendergast, B.J., Reardon, C., Shaw, A.C., Sengupta, S., Szentirmai, E., Thakkar, M., Walker, W.E., Solt, L.A., 2020. Perfect timing: circadian rhythms, sleep, and immunity - an NIH workshop summary. JCI. Insight 5.

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., Cheng, Z., Yu, T., Xia, J., Wei, Y., Wu, W., Xie, X., Yin, W., Li, H., Liu, M., Xiao, Y., Gao, H., Guo, L., Xie, J., Wang, G., Jiang, R., Gao, Z., Jin, Q., Wang, J., Cao, B., 2020a. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395, 497–506.

Huang, C.Y., Chen, Y.T., Wu, L.A., Liu, C.J., Chang, S.C., Perng, D.W., Chen, Y.M., Chen, T.J., Lee, Y.C., Chou, K.T., 2014. Sleep apnoea patients have higher mortality when confronting sepsis. Eur. J. Clin. Invest. 44, 38–45.

Huang, Y.H., Jiang, D., Huang, J.T., 2020b. SARS-CoV-2 Detected in Cerebrospinal Fluid by PCR in a Case of COVID-19 Encephalitis. Immun Brain Behav. https://doi.org/10.1016/j.bbi.2020.05.012.

Irwin, M.R., 2015. Why sleep is important for health: a psychoneuroimmunology perspective. Annu. Rev. Psychol. 66, 143–172.

Kamdar, B.B., Needham, D.M., Collop, N.A., 2012. Sleep deprivation in critical illness: its role in physical and psychological recovery. J Intensive Care Med 27, 97–111.

National Health and Family Planning Commission of China (NHPFC), 2020. New coronavirus pneumonia prevention and control program (6th edition). http://www.nhc.gov.cn/jkj/s3577/202003/4856d5b0458141fa9f376853224d41d7/files/4132bf035bc242478a6eaf157eb0d979.pdf (accessed Mar 7, 2020).

KDIGO AKI Work Group, 2012. KDIGO clinical practice guideline for acute kidney injury. Kidney Int. Suppl. 2, 1–138.

Lagunas-Rangel, F.A., 2020. Neutrophil-to-lymphocyte ratio and lymphocyte-to-C-reactive protein ratio in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis. J. Med. Virol. https://doi.org/10.1002/jmv.25819.

Liguori, C., Pierantozzi, M., Spanetta, M., Sarmati, L., Cesta, N., Iannetta, M., Ora, J., Genga, M. G., Puxeddu, E., Balbi, O., Pezzuto, G., Magrini, A., Rogliani, P., Andreoni, M., and Biagio, M. N., 2020. Subjective neurological symptoms frequently occur in patients with SARS-CoV2 infection. Brain Behav. Immun. doi: 10.1016/j.bbi.2020.05.037.

Liu, X., Tang, M., Hu, L., Wang, A., Wu, H., Zhao, G., Gao, C., Li, W., 1996. Reliability and validity of the Pittsburgh sleep quality index. Chin. J. Psychiatry. 29, 103–107.

Liu, Y., Du, X., Chen, J., Jin, Y., Peng, L., Wang, H., Luo, M., Chen, L., Zhao, Y., 2020. Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. J. Infect. https://doi.org/10.1016/j.jinf.2020.04.002.

Loef, B., van Baarle, D., van der Beek, A.J., Sanders, E., Bruijning-Verhagen, P., Proper, K.I., 2019. Shift Work and Respiratory Infections in Health-Care Workers. Am. J. Epidemiol. 188, 509–517.

Mannion, H., Molloy, D.W., O'Caoimh, R., 2019. Sleep Disturbance in Older Patients in the Emergency Department: Prevalence, Predictors and Associated Outcomes. Int J Environ Res Public Health 16.

McKinley, S., Fien, M., Elliott, R., Elliott, D., 2013. Sleep and psychological health during early recovery from critical illness: an observational study. J. Psychosom. Res. 75, 539–545.

Mollayeva, T., Thurairajah, P., Burton, K., Mollayeva, S., Shapiro, C.M., Colantonio, A., 2016. The Pittsburgh sleep quality index as a screening tool for sleep dysfunction in clinical and non-clinical samples: A systematic review and meta-analysis. Sleep Med. Rev. 25, 52–73.

Mukherjee, S., Patel, S.R., Kales, S.N., Ayas, N.T., Strohl, K.P., Gozal, D., Malhotra, A., 2015. An Official American Thoracic Society Statement: The Importance of Healthy Sleep. Recommendations and Future Priorities. Am J Respir Crit Care Med 191, 1450–1458.

Nagatomo, K., Masuyama, T., Iizuka, Y., Makino, J., Shiotsuka, J., Sanui, M., 2020. Validity of an under-mattress sensor for objective sleep measurement in critically ill patients: a prospective observational study. J. Intensive Care 8, 16.

Oxley, T.J., Mocco, J., Majidi, S., Kellner, C.P., Shoirah, H., Singh, I.P., De Leacy, R.A., Shigematsu, T., Ladner, T.R., Yaeger, K.A., Skliut, M., Weinberger, J., Dangayach, N.S., Bederson, J.B., Tuhrim, S., Fifi, J.T., 2020. Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. N Engl. J. Med. 382, e60.

Patel, S.R., Malhotra, A., Gao, X., Hu, F.B., Neuman, M.I., Fawzi, W.W., 2012. A prospective study of sleep duration and pneumonia risk in women. Sleep 35, 97–101.

Prather, A.A., Janicki-Deverts, D., Hall, M.H., Cohen, S., 2015. Behaviorally assessed sleep and susceptibility to the common cold. Sleep 38, 1353–1359.

Pulak, L.M., Jensen, L., 2016. Sleep in the intensive care unit: a review. J. Intensive Care Med. 31, 14–23.

Qin, C., Zhou, L., Hu, Z., Zhang, S., Yang, S., Tao, Y., Xie, C., Ma, K., Shang, K., Wang, W., Tian, D.S., 2020. Dysregulation of immune response in patients with COVID-19 in Wuhan. Clin. Infect. Dis China. https://doi.org/10.1093/cid/ciaa248.

Richards, K.C., O'Sullivan, P.S., Phillips, R.L., 2000. Measurement of sleep in critically ill patients. J. Nurs. Meas. 8, 131–144.

Simons, K.S., Verweij, E., Lemmens, P., Jelfs, S., Park, M., Spronk, P.E., Sonneveld, J., Feijen, H.M., van der Steen, M.S., Kohlrausch, A.G., van den Boogaard, M., de Jager, C., 2018. Noise in the intensive care unit and its influence on sleep quality: a multicenter observational study in Dutch intensive care units. Crit. Care 22, 250.

Tan, L., Wang, Q., Zhang, D., Ding, J., Huang, Q., Tang, Y.Q., Wang, Q., Miao, H., 2020. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. Signal. Transduct. Target Ther. 5, 33.

Toscano, G., Palmerini, F., Ravaglia, S., Ruiz, L., Invernizzi, P., Cuzzoni, M.G., Franciotta, D., Baldanti, F., Daturi, R., Postorino, P., Cavallini, A., Micieli, G., 2020. Guillain-Barre Syndrome Associated with SARS-CoV-2. N Engl. J. Med. https://doi.org/10.1056/NEJMc2009191.

Vgontzas, A.N., Zoumakis, E., Bixler, E.O., Lin, H.M., Follett, H., Kales, A., Chrousos, G.P., 2004. Adverse effects of modest sleep restriction on sleepiness, performance, and inflammatory cytokines. J. Clin.. Endocrinol. Metab. 89, 2119–2126.

Wang, D., Hu, B., Hu, C., Zhu, F., Liu, X., Zhang, J., Wang, B., Xiang, H., Cheng, Z., Xiong, Y., Zhao, Y., Li, Y., Wang, X., Peng, Z., 2020. Clinical Characteristics of 138

Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. doi: 10.1001/jama.2020.1585.
Yang, X., Yu, Y., Xu, J., Shu, H., Xia, J., Liu, H., Wu, Y., Zhang, L., Yu, Z., Fang, M., Yu, T., Wang, Y., Pan, S., Zou, X., Yuan, S., Shang, Y., 2020. 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. 8, 475–481.
Zhang, J., Xie, B., Hashimoto, K., 2020. Current status of potential therapeutic candidates for the COVID-19 crisis. Brain Behav. Immun. doi: 10.1016/j.bbi.2020.04.046.
Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., Xiang, J., Wang, Y., Song, B., Gu, X., Guan, L., Wei, Y., Li, H., Wu, X., Xu, J., Tu, S., Zhang, Y., Chen, H., Cao, B., 2020. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 395, 1054–1062.