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Sleep and Circadian Health of Critical Survivors: A 12-Month Follow-Up Study*

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OBJECTIVES: To investigate the sleep and circadian health of critical survivors 12 months after hospital discharge and to evaluate a possible effect of the severity of the disease within this context.

DESIGN: Observational, prospective study.

SETTING: Single-center study.

PATIENTS: Two hundred sixty patients admitted to the ICU due to severe acute respiratory syndrome coronavirus 2 infection.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: The cohort was composed of 260 patients (69.2% males), with a median (quartile 1–quartile 3) age of 61.5 years (52.0–67.0 yr). The median length of ICU stay was 11.0 days (6.00–21.8 d), where 56.2% of the patients required invasive mechanical ventilation (IMV). The Pittsburgh Sleep Quality Index (PSQI) revealed that 43.1% of the cohort presented poor sleep quality 12 months after hospital discharge. Actigraphy data indicated an influence of the disease severity on the fragmentation of the circadian rest-activity rhythm at the 3- and 6-month follow-ups, which was no longer significant in the long term. Still, the length of the ICU stay and the duration of IMV predicted a higher fragmentation of the rhythm at the 12-month follow-up with effect sizes (95% CI) of 0.248 (0.078–0.418) and 0.182 (0.005–0.359), respectively. Relevant associations between the PSQI and the Hospital Anxiety and Depression Scale (rho = 0.55, anxiety; rho = 0.5, depression) as well as between the fragmentation of the rhythm and the diffusing lung capacity for carbon monoxide (rho = −0.35) were observed at this time point.

CONCLUSIONS: Our findings reveal a great prevalence of critical survivors presenting poor sleep quality 12 months after hospital discharge. Actigraphy data indicated the persistence of circadian alterations and a possible impact of the disease severity on the fragmentation of the circadian rest-activity rhythm, which was attenuated at the 12-month follow-up. This altogether highlights the relevance of considering the sleep and circadian health of critical survivors in the long term.

KEYWORDS: circadian rhythms; critical survivors; intensive care unit; severe acute respiratory syndrome coronavirus 2; sleep

Patients referred to the ICU present with sleep and circadian alterations that often persist after the acute phase of the critical illness. Estimations reveal that up to 64.3% of the survivors report poor sleep quality 1–3 months after hospital discharge along with substantial fragmentation of the circadian rest-activity rhythm (1–5). Potential causative factors include mistimed and excessive artificial light exposure, nighttime patient care interventions, and noise from alarms and staff conversations. Additionally, other critical illness-related events such as the presence of symptoms of pain, increased inflammatory processes, sleep-altering medication intake, and the use of invasive mechanical ventilation (IMV) can be relevant contributors to this scenario (1,

*See also p. 1308.

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KEY POINTS

Question: Do sleep and circadian alterations persist in the long term?

Findings: There is poor sleep quality among a great percentage of critical survivors 12 months after hospital discharge. The circadian alterations persist in the long term and the fragmentation of the circadian rest-activity rhythm is further influenced by the severity of the disease.

Meanings: This highlights the necessity of strategies aiming to prevent and/or reverse the disruption of sleep and circadian health after the ICU stay.

2, 6). Nevertheless, there is a paucity of evidence on whether the sleep and circadian alterations associated with the ICU stay persist in the long term.

Further explorations within this context are imperative for several reasons. First, compromised sleep and circadian health are associated with a wide range of outcomes in the short and long term, including a decrease in the quality of life and the occurrence or aggravation of conditions such as depression and anxiety (7). Also, the respiratory and immune functions are paramount for critical survivors' recovery and both are under the constant influence of sleep and circadian rhythms (8, 9). Furthermore, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic led to an unprecedented escalation in the number of critical survivors in a short period, which potentiates the impact of such context on society.

The objective of this study was to investigate the sleep and circadian health of critical survivors in the long term and to evaluate a possible influence of the severity of the disease within this context. To accomplish this, we took advantage of the natural research opportunity provided by the SARS-CoV-2 pandemic, recruiting critical COVID-19 patients during the ICU stay. Additional analyses were performed to further understand this setting. First, we explored the evolution of sleep and circadian health during the 12-month follow-up. In the sequence, we identified baseline predictors for sleep and circadian alterations in the long term. Finally, we evaluated the associations between such alterations and other relevant factors for the recovery of critical patients such as mental health, quality of life, cognitive function, and respiratory function.

MATERIALS AND METHODS

Study Population

This is a prospective, observational, single-center study. The inclusion criteria comprised: 1) age 18 years old or older, 2) admission to the ICU due to SARS-CoV-2 infection, and 3) availability of subjective sleep data (Pittsburgh Sleep Quality Index [PSQI]) related to the 12-month follow-up. The exclusion criteria included: 1) patients in palliative care and 2) patients with severe mental and/or physical disabilities that could prevent the proposed evaluations. This study was approved by the Medical Ethics Committee (CEIC-2510; "The impact of COVID-19 and its context on sleep and circadian rhythms"; June 22, 2021) and conducted according to the principles outlined by the Declaration of Helsinki. Informed consent was acquired for all patients.

Study Design

Patients were recruited during the ICU stay (baseline) and scheduled for the first (3 mo), second (6 mo), and third (12 mo) medical appointments after hospital discharge. In each visit, a respiratory evaluation was performed followed by subjective assessments of sleep, mental health, quality of life, and cognitive function.

The objective analysis of sleep and circadian rest-activity rhythm included a subgroup of patients randomly selected at the 3-month follow-up, who were later evaluated during the following visits, excepting those not willing to participate for a second and/or third time (**Fig. 1**). Additional patients (who underwent the subjective but not the objective assessment at the 3-mo follow-up) were randomly selected for the objective evaluations at the following visits (a detailed description is present in the **Supplemental Digital Content**, http://links.lww.com/CCM/H536).

Data Obtained During the ICU Stay

Sociodemographic and anthropometric data including age, sex, body mass index (BMI), and comorbidities were obtained using the available medical records. Daily figures related to the state of the patients were

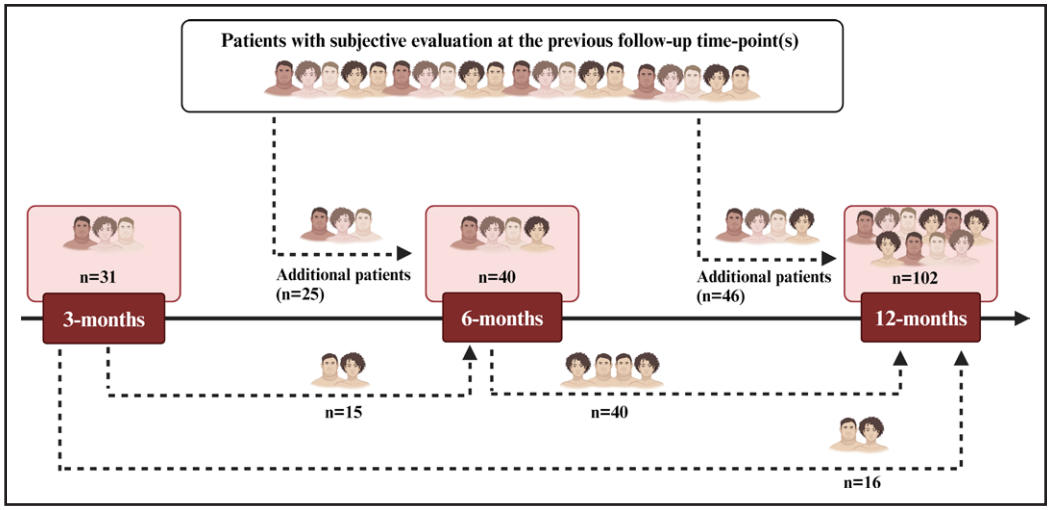

Figure 1. Patients included in the objective evaluation of sleep and circadian rest-activity rhythm (actigraphy) over the three follow-up time points. A subgroup of patients was randomly selected at the 3-mo follow-up and later evaluated during the following visits, excepting those who were not willing to participate for a second and/or third time. Additional patients (who underwent the subjective but not the objective assessment at the 3-mo follow-up) were randomly selected for the objective evaluations at the following visits. (The figure was created with BioRender.com.)

collected, including vital signs, information related to arterial blood gases (Pao_2, FIO_2), and clinical requirements (non-IMV [NIMV], IMV, prone position, pharmacological treatment). The Acute Physiology and Chronic Health Evaluation-II score was determined based on previous reports (10, 11).

Data Obtained During the Follow-Up

Questionnaires. The questionnaires included the PSQI to evaluate sleep quality (12, 13), the Epworth Sleepiness Scale (ESS) to evaluate excessive daytime somnolence (14–16), the Hospital Anxiety and Depression Scale (HADS) to assess signs of anxiety and depression (17–19), the 12-item Short Form Survey (SF-12) to evaluate the quality of life (20, 21), and the British Columbia Cognitive Complaints Inventory (BC-CCI) to assess the cognitive function (22–24). Detailed information is present in the Supplemental Digital Content (http://links.lww.com/CCM/H536).

Actigraphy. Patients who arrived for the medical appointments after hospital discharge were randomly selected for the objective assessment of sleep and circadian rest-activity rhythm through the use of a wrist-mounted actigraph (Actiwatch 2; Philips Respironics, Murrysville, PA) for 7 days (Supplemental Digital Content, http://links.lww.com/CCM/H536; and Fig. 1 for further information). Sleep logs were delivered to be completed during the period in which the patients were with the actigraph. Activity counts of 60-second epochs were obtained and distinct variables that describe the circadian rest-activity rhythm were estimated using the "nparACT" package for R (https://cran.r-project.org/web/packages/nparACT/index.html). The intradaily variability represents the fragmentation of the circadian rest-activity rhythm within each 24-hour period. The interdaily stability represents the similarity among the 24-hour periods. The mean activity of the 5 consecutive hours with the lowest activity (L5) and the mean activity of the 10 consecutive hours with the highest activity (M10) were used to calculate the relative amplitude (M10 – L5/M10 + L5). The relative amplitude represents the robustness of the circadian rest-activity rhythm. The average of intradaily variability, interdaily stability, and relative amplitude was used to estimate the circadian function index (CFI) (25). Finally, the Midline Estimating Statistic Of Rhythm (MESOR) represents the mean value for the investigated oscillation. The complete description is present in the Supplemental Digital Content (http://links.lww.com/CCM/H536).

Other Assessments. The diffusing lung capacity for carbon monoxide (DLCO) was the variable used to represent the respiratory function and the CT of the chest was performed to evaluate the severity of lung affectation (26). The 6-minute walking test (6MWT) was performed to evaluate the aerobic capacity (27, 28). Detailed information is present in the Supplemental Digital Content (http://links.lww.com/CCM/H536).

The Severity of the Disease and Groups of Study

The determination of the severity of the disease and consequent establishment of the groups of study was

based on the seven-category ordinal scale. This scale defines the severity of the disease based on the resumption of normal activities, hospital/ICU admission, supplemental oxygen requirement, high-flow nasal cannula requirement, NIMV requirement, extracorporeal membrane oxygenation requirement, IMV requirement, and death (29–31). Given the characteristics of the cohort (ICU patients) and previous findings demonstrating that the use of IMV predicts an increased fragmentation of the rhythm 3 months after hospital discharge (4), two main groups were established: 1) ICU, representing the patients admitted to the ICU, but without IMV and 2) ICU + IMV, representing the patients admitted to the ICU who required the IMV.

Statistical Analysis

Descriptive statistics were performed to describe the baseline characteristics. Absolute and relative frequencies were used for qualitative data, whereas means (SD) or medians (quartile 1 [Q1]–quartile 3 [Q3]) were estimated for quantitative variables. The normality of the distribution was assessed by the Shapiro-Wilk test.

The comparison of baseline characteristics between the groups was accomplished with a chi-square test or Fisher exact test (when the expected frequencies were < 5) for qualitative variables and with a *t* test or Wilcoxon signed-rank test (when variables presented a nonparametric distribution) for quantitative variables.

The comparison of the main outcomes (PSQI score, intradaily variability, interdaily stability, relative amplitude, CFI, and MESOR) at the 12-month follow-up between the groups of study was accomplished with unadjusted and adjusted (for age and sex) generalized linear models. The same approach was used for the comparisons related to the secondary outcomes (individual components of the PSQI, ESS, and other variables of actigraphy).

Sleep and circadian-related data were assessed at three different time points (3, 6, and 12 mo after hospital discharge). Changes in the values of the main outcomes over time stratified by the groups of study were assessed using generalized linear mixed-effect models. Potential confounders (age and sex) were introduced as fixed effects and patients were included as a random effect. Differences between the groups of study at each time point were assessed considering the interaction between group and time (with time included as a fixed effect).

The presence of associations between baseline characteristics (data obtained during the ICU stay) and main outcomes collected 12 months after hospital discharge was evaluated using generalized linear models adjusted for age and sex after standardization of continuous variables. Possible associations between main outcomes and other relevant factors assessed 12 months after hospital discharge (depression and anxiety [HADS], physical and mental domains of quality of life [SF-12], cognitive function [BC-CCI], DL_{CO}, lung affectation [CT scan], and aerobic capacity [6MWT]) were evaluated using Pearson coefficient tests.

The *p* value threshold defining statistical significance was set at less than 0.05. All statistical analyses were performed using R software, Version 4.0.2 (R Core Team, Vienna, Austria).

RESULTS

Baseline Characteristics

The cohort was composed of 260 patients (69.2% males), with a median (Q1–Q3) age of 61.5 years (52.0–67.0 yr) and a BMI of 29.9 kg/m^2 (26.9–33.5 kg/m^2) (**Table 1**). The most prevalent comorbidities were obesity (47.7%) and hypertension (46.5%). The median length of hospital stay was 21.0 days (14.0–35.0 d), of which 11.0 (6.00–21.8) were spent at the ICU.

The group of patients who received IMV during the ICU stay constituted 56.2% of the cohort, presented a higher percentage of males (76.0% vs. 60.5%) and a higher age (62.0 yr [53.2–68.0 yr] vs. 59.5 yr [49.0–65.0 yr]). IMV patients spent more days at the hospital (31.0 [21.0–44.0] vs. 14.0 [11.0–18.0]) and at the ICU (19.0 [13.0–32.0] vs. 6.00 [4.00–8.00]).

The baseline characteristics of the subpopulation randomly selected for the objective assessment of sleep and circadian rest-activity rhythm (n = 102) were similar to the global population (n = 260) (**Table S1**, http://links.lww.com/CCM/H536). Furthermore, no relevant differences were observed among patients included at distinct time points (**Table S2**, http://links.lww.com/CCM/H536).

Sleep and Circadian Health 12 Months After Hospital Discharge

According to the PSQI, 43.1% of the population presented with poor sleep quality 12 months after hospital discharge (**Table S3**, http://links.lww.com/CCM/H536). The comparison between patients who received

TABLE 1.
Baseline Characteristics of the Cohort

Characteristics	Global, *n* = 260	ICU, *n* = 114	ICU + Invasive Mechanical Ventilation, *n* = 146	*p*
	n (%) or Median (Quartile 1–Quartile 3)			
Sociodemographic and anthropometric data				
Sex, male	180 (69.2%)	69 (60.5%)	111 (76.0%)	0.011
Age, yr	61.5 (52.0–67.0)	59.5 (49.0–65.0)	62.0 (53.2–68.0)	0.03
Body mass index, kg/m^2	29.9 (26.9–33.5)	29.5 (26.3–33.9)	30.0 (27.1–33.0)	0.617
Comorbidities				
Hypertension	121 (46.5%)	46 (40.4%)	75 (51.4%)	0.101
Obesity	124 (47.7%)	51 (44.7%)	73 (50.0%)	0.473
Diabetes mellitus	54 (20.8%)	14 (12.3%)	40 (27.4%)	0.005
Asthma	17 (6.54%)	7 (6.14%)	10 (6.85%)	1
Chronic obstructive pulmonary disease	15 (5.77%)	8 (7.02%)	7 (4.79%)	0.621
Hospitalization, d				
Duration	21.0 (14.0–35.0)	14.0 (11.0–18.0)	31.0 (21.0–44.0)	< 0.001
Before ICU admission	1.00 (0.00–2.00)	1.00 (0.00–3.00)	0.00 (0.00–2.00)	0.002
After ICU discharge	7.00 (4.00–11.0)	6.00 (4.00–9.00)	8.00 (4.00–12.0)	0.092
ICU stay				
Duration, d	11.0 (6.00–21.8)	6.00 (4.00–8.00)	19.0 (13.0–32.0)	< 0.001
Acute Physiology and Chronic Health Evaluation-II score	11.0 (9.00–13.0)	11.0 (9.00–12.0)	11.0 (8.00–13.0)	0.773
Pao_2 to Fio_2 ratio	119 (86.2–166)	118 (90.0–155)	120 (83.2–181)	0.931
Procedures				
Mechanical ventilation				
Invasive	146 (56.2%)	0 (0.00%)	146 (100%)	< 0.001
Duration, d	13.0 (7.00–25.0)	0.00 (0.00–0.00)	13.0 (7.00–25.0)	< 0.001
Noninvasive	201 (77.3%)	87 (76.3%)	114 (78.1%)	0.851
Duration, d	2.00 (1.00–4.00)	3.00 (1.00–5.75)	2.00 (1.00–4.00)	0.01
Prone position	136 (52.7%)	19 (16.8%)	117 (80.7%)	< 0.001
Duration, hr	0.00 (0.00–36.0)	0.00 (0.00–0.00)	31.0 (8.50–71.0)	< 0.001
Pharmacotherapy				
Antibiotics	205 (79.8%)	68 (60.2%)	137 (95.1%)	< 0.001
Corticosteroids	237 (91.2%)	102 (89.5%)	135 (92.5%)	0.533
Tocilizumab	187 (71.9%)	84 (73.7%)	103 (70.5%)	0.675
Remdesivir	28 (10.8%)	19 (16.7%)	9 (6.16%)	0.012
Hydroxychloroquine	61 (23.5%)	21 (18.4%)	40 (27.4%)	0.122

Missings: prone position, 2; antibiotics, 3.

IMV and those who did not revealed no differences in relation to the PSQI and ESS in both adjusted and unadjusted analyses (**Table 2**).

The qualitative analysis of the actograms suggested distinct patterns of circadian rest-activity rhythm between the groups of study, especially in terms of

TABLE 2.
Subjective Evaluations (Questionnaires) at the 12-Month Follow-Up

Questionnaires	Global, *n* = 260	ICU, *n* = 114	ICU + Invasive Mechanical Ventilation, *n* = 146	Model 1 (Unadjusted Analysis)		Model 2 (Adjusted for Age and Sex)	
	Mean (SD)			Mean Difference (95% CI)	*p*	Mean Difference (95% CI)	*p*
Pittsburgh Sleep Quality Index	5.75 (4.03)	5.84 (3.91)	5.68 (4.13)	−0.16 (−1.15 to 0.83)	0.754	0.09 (−0.92 to 1.09)	0.868
Subjective sleep quality	1.09 (0.63)	1.08 (0.64)	1.10 (0.63)	0.02 (−0.13 to 0.18)	0.765	0.04 (−0.12 to 0.20)	0.607
Sleep latency	0.93 (1.07)	0.89 (1.00)	0.97 (1.12)	0.09 (−0.18 to 0.35)	0.512	0.18 (−0.08 to 0.44)	0.181
Sleep duration	1.15 (1.09)	1.23 (1.06)	1.10 (1.10)	−0.13 (−0.40 to 0.13)	0.329	−0.11 (−0.38 to 0.17)	0.448
Sleep efficiency	0.90 (1.08)	0.90 (1.07)	0.90 (1.10)	0.00 (−0.27 to 0.27)	0.996	0.01 (−0.27 to 0.28)	0.964
Sleep disturbance	0.78 (0.65)	0.85 (0.64)	0.73 (0.66)	−0.12 (−0.28 to 0.04)	0.147	−0.09 (−0.26 to 0.07)	0.263
Sleep medication intake	0.66 (1.22)	0.62 (1.19)	0.69 (1.25)	0.07 (−0.23 to 0.37)	0.651	0.13 (−0.17 to 0.43)	0.398
Daytime dysfunction	0.22 (0.54)	0.27 (0.60)	0.18 (0.48)	−0.09 (−0.22 to 0.04)	0.208	−0.07 (−0.21 to 0.06)	0.282
Epworth Sleepiness Scale	4.96 (3.75)	5.29 (4.07)	4.71 (3.47)	−0.58 (−1.50 to 0.33)	0.223	−0.64 (−1.59 to 0.30)	0.182

Generalized linear models comparing the groups of study.

intradaily variability (**Fig. S1**, http://links.lww.com/CCM/H536), which represents the fragmentation of the circadian rest-activity rhythm. Nevertheless, no differences were detected in both adjusted and unadjusted analyses (**Table 3**).

Evolution of Sleep and Circadian Health Along the 12-Month Follow-Up

The PSQI score presented a slight improvement during the follow-up, which was similar between patients who required IMV and those who did not (**Fig. 2**). Tendencies of improvement without statistical significance were also observed for the parametric measure of the circadian function MESOR (**Fig. S2**, http://links.lww.com/CCM/H536). No changes were detected in relation to the other variables.

The analysis comparing the evolution of circadian health between the groups of study revealed a higher intradaily variability at the 3- and 6-month follow-ups among the patients who received IMV, which was no longer observed 12 months after hospital discharge.

Baseline Predictors for Sleep and Circadian Health in the Long Term

The female sex was associated with an increased score in the PSQI at the 12-month follow-up with an effect size (95% CI) of 0.299 (0.036–0.562), whereas a higher age was related to an increment in the intradaily variability (0.208 [0.025–0.391]) (**Fig. 3**). Adjusted analysis (age and sex) revealed that the duration of hospitalization and the length of ICU stay predicted a higher intradaily variability in the long term with effect sizes of 0.183 (0.004–0.361) and 0.200 (0.024–0.376), respectively. The length of ICU stay was also able to predict the CFI at the 12-month follow-up (–0.213 [–0.393 to –0.033]).

Associations With Relevant Factors for the Recovery of Critical Survivors

Correlation analyses revealed a positive association between the PSQI score and both anxiety (rho = 0.55) and depression (rho = 0.50) HADS scores at the 12-month follow-up, which were similar among males and females (**Fig. S3**, http://links.lww.com/CCM/H536). Also, negative correlations between the PSQI and both physical (rho = –0.4) and mental (rho = –0.48) domains of the SF-12 were observed.

Intradaily variability was negatively associated with the DLco (rho = –0.35) (**Fig. S4**, http://links.lww.com/CCM/H536) while the CFI (rho = 0.24) (**Fig. S5**, http://links.lww.com/CCM/H536) and MESOR (rho = 0.26) (**Fig. S6**, http://links.lww.com/CCM/H536) were positively associated with this variable. Correlations related to the interdaily stability and relative amplitude are present in **Figures S7** and **S8** (http://links.lww.com/CCM/H536), respectively.

DISCUSSION

The findings of the current study revealed compromised sleep and circadian health among critical survivors 12 months after hospital discharge. While the sleep quality displayed a slight improvement, the overall circadian function demonstrated the same pattern throughout the follow-up. The severity of the disease, as marked by the use of IMV, was associated with an additional impact in relation to the fragmentation of the circadian rest-activity rhythm in the short and mid term, which was no longer significant at the 12-month follow-up. Baseline characteristics such as duration of hospitalization and length of ICU stay predicted a higher fragmentation of the rhythm in the long term. Furthermore, additional analyses identified relevant associations between sleep and circadian health and distinct factors linked to the recovery of critical patients at the 12-month follow-up.

The subjective assessment of sleep revealed that 43.1% of the population presented poor sleep quality 12 months after hospital discharge. Despite failing to reach statistical significance, there was a slight improvement in this regard during the follow-up. Also, such percentage is similar to that observed among healthy individuals of similar age or those evaluated in critical illness-unrelated contexts (**Table S4**, http://links.lww.com/CCM/H536) (32). Furthermore, the female sex was the only baseline feature predicting a decreased sleep quality in the long term and the PSQI score was positively correlated with both anxiety and depression scores at the 12-month follow-up. Taken together, these data collectively suggest that the somewhat persistent poor sleep quality herein observed could be related to factors other than the hospital environment or the critical illness itself such as sex and mental health.

TABLE 3.
Objective Evaluation (Actigraphy) at the 12-Month Follow-Up

Variables	Global, *n* = 102	ICU, *n* = 48	ICU + Invasive Mechanical Ventilation, *n* = 54	Model 1 (Unadjusted Analysis)		Model 2 (Adjusted for Age and Sex)	
	Mean (SD)			Mean Difference (95% CI)	*p*	Mean Difference (95% CI)	*p*
Sleep							
Total sleep time, hr	6.84 (1.22)	6.83 (1.03)	6.86 (1.38)	0.03 (−0.45 to 0.51)	0.901	0.06 (−0.41 to 0.54)	0.791
Time in bed, hr	8.29 (1.12)	8.17 (0.93)	8.40 (1.27)	0.22 (−0.22 to 0.66)	0.323	0.21 (−0.22 to 0.64)	0.344
Sleep efficiency, %	82.7 (8.87)	83.7 (7.03)	81.8 (10.2)	−1.95 (−5.40 to 1.50)	0.27	−1.44 (−4.92 to 2.04)	0.42
Sleep latency, min	15.0 (13.9)	13.5 (10.8)	16.4 (16.2)	2.93 (−2.49 to 8.34)	0.292	2.75 (−2.79 to 8.30)	0.332
Arousals, *n*	23.6 (7.26)	23.0 (6.80)	24.1 (7.67)	1.02 (−1.81 to 3.85)	0.482	0.33 (−2.42 to 3.09)	0.813
Wake after sleep onset, min	53.3 (24.8)	49.5 (20.2)	56.6 (28.0)	7.15 (−2.42 to 16.72)	0.146	5.46 (−4.16 to 15.07)	0.269
Rest-activity rhythm							
Intradaily variability	0.79 (0.23)	0.75 (0.18)	0.82 (0.26)	0.08 (−0.01 to 0.17)	0.082	0.07 (−0.02 to 0.16)	0.138
Interdaily stability	0.57 (0.13)	0.58 (0.13)	0.56 (0.13)	−0.02 (−0.07 to 0.03)	0.52	−0.02 (−0.07 to 0.03)	0.516
Relative amplitude	0.87 (0.11)	0.87 (0.12)	0.86 (0.11)	−0.01 (−0.05 to 0.04)	0.773	0.00 (−0.05 to 0.04)	0.855
The mean activity of the 10 consecutive hr with more activity	271 (110)	285 (90.0)	258 (124)	−27.10 (−69.58 to 15.37)	0.214	−20.11 (−61.81 to 21.59)	0.347
The mean activity of the 5 consecutive hr with less activity	19.3 (19.9)	20.1 (22.7)	18.7 (17.2)	−1.37 (−9.14 to 6.40)	0.731	−1.08 (−9.00 to 6.84)	0.79
Circadian function index	0.56 (0.10)	0.57 (0.09)	0.55 (0.11)	−0.01 (−0.05 to 0.02)	0.456	−0.01 (−0.05 to 0.03)	0.553
Midline Estimating Statistic Of Rhythm	166 (67.2)	173 (52.4)	160 (77.9)	−13.67 (−39.78 to 12.43)	0.307	−9.01 (−34.26 to 16.25)	0.486

Generalized linear models comparing the groups of study.

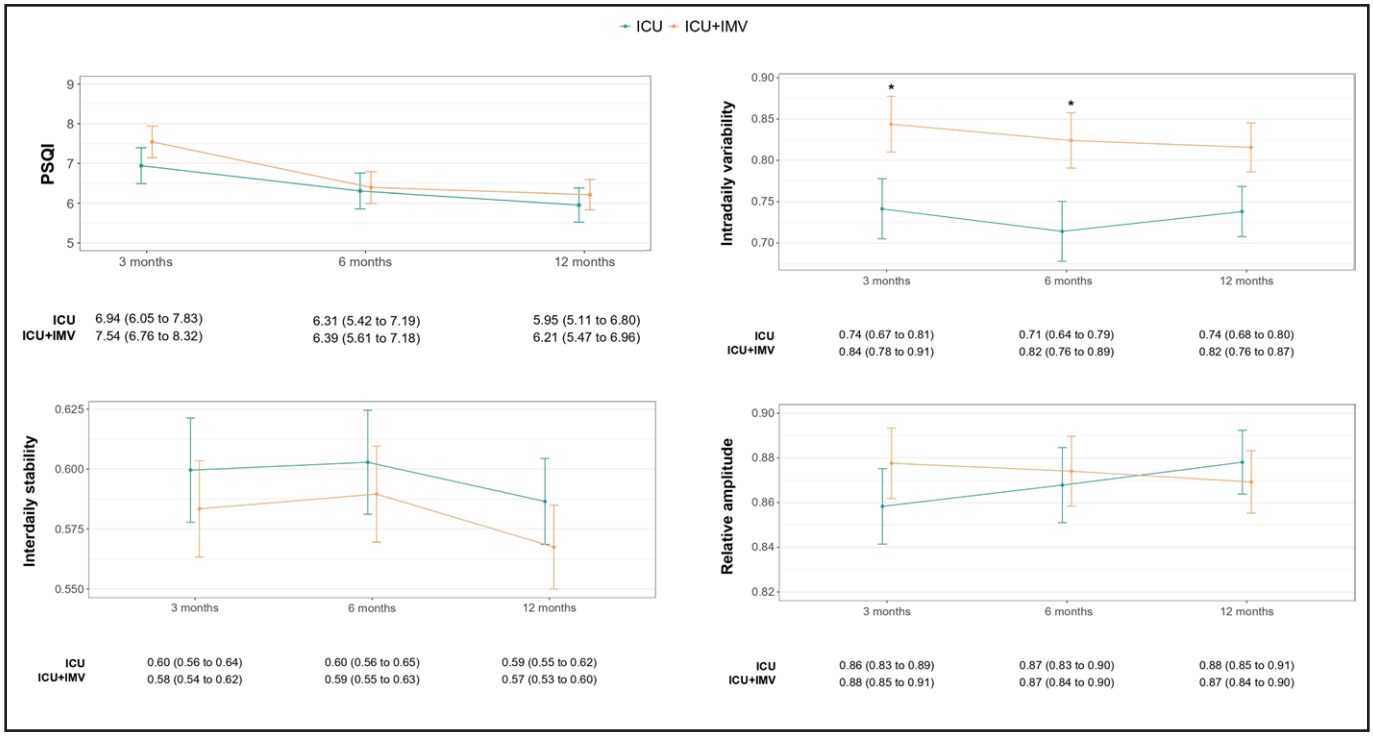

Figure 2. Evolution of sleep and circadian health along the 12-mo follow-up. Data are represented as median (quartile 1–quartile 3). The *p* value threshold defining statistical significance was set at less than 0.05. IMV = invasive mechanical ventilation, PSQI = Pittsburgh Sleep Quality Index.

Detrimental effects of the ICU on circadian health are reported by several studies with evaluations performed either soon after hospital discharge or in the short and mid term (3, 4, 33–36). Potential causative factors include mistimed and excessive artificial light exposure, unusual feeding schedules, nighttime interventions, and noise from alarms and staff conversations. The current study is the first to investigate the existence of circadian alterations among critical survivors in the long term, when one would expect that the effect of such causative factors was no longer present. Nevertheless, we observed that the overall circadian function failed to demonstrate an improvement throughout the 12 months of follow-up. The reasoning behind such outcome is not clear, but some observations could be drawn in this regard. First, given that critical survivors usually suffer from various medical conditions, it is possible that the maintenance of circadian alterations among this population marks unresolved illness. In fact, the patients with a lower DLco, including those identified as the ones who did not recover, presented a higher fragmentation of the rhythm at the 12-month follow-up. The respiratory function and circadian health display a bidirectional relationship, which could further contribute to the maintenance of the observed circadian alterations in the long term (9, 37, 38). A second observation relies on a possible impact of the ICU and its setting at the molecular level, which could lead to a somewhat longer and/or irreversible condition. Previous studies demonstrate that 1 week at the ICU is sufficient to promote an overall impairment of molecular circadian rhythms, including the loss of circadian rhythmicity of several clock genes (39, 40). Nevertheless, information on whether such alterations persist over time when the triggering factors are no longer present remains to be demonstrated.

The current data should be interpreted in light of some aspects. First, it is pertinent to highlight that our cohort was exclusively composed of critical survivors due to SARS-CoV-2 infection. Despite similarities in terms of sleep and circadian-related outcomes among distinct populations of critical patients, subtle differences may exist according to the cause of ICU admission. On the other hand, the evaluation of a well-characterized and highly homogeneous population is beneficial in terms of minimizing the effect of condition-associated confounders. Second, the rationale of the study associated with the unprecedented natural research opportunity provided by the

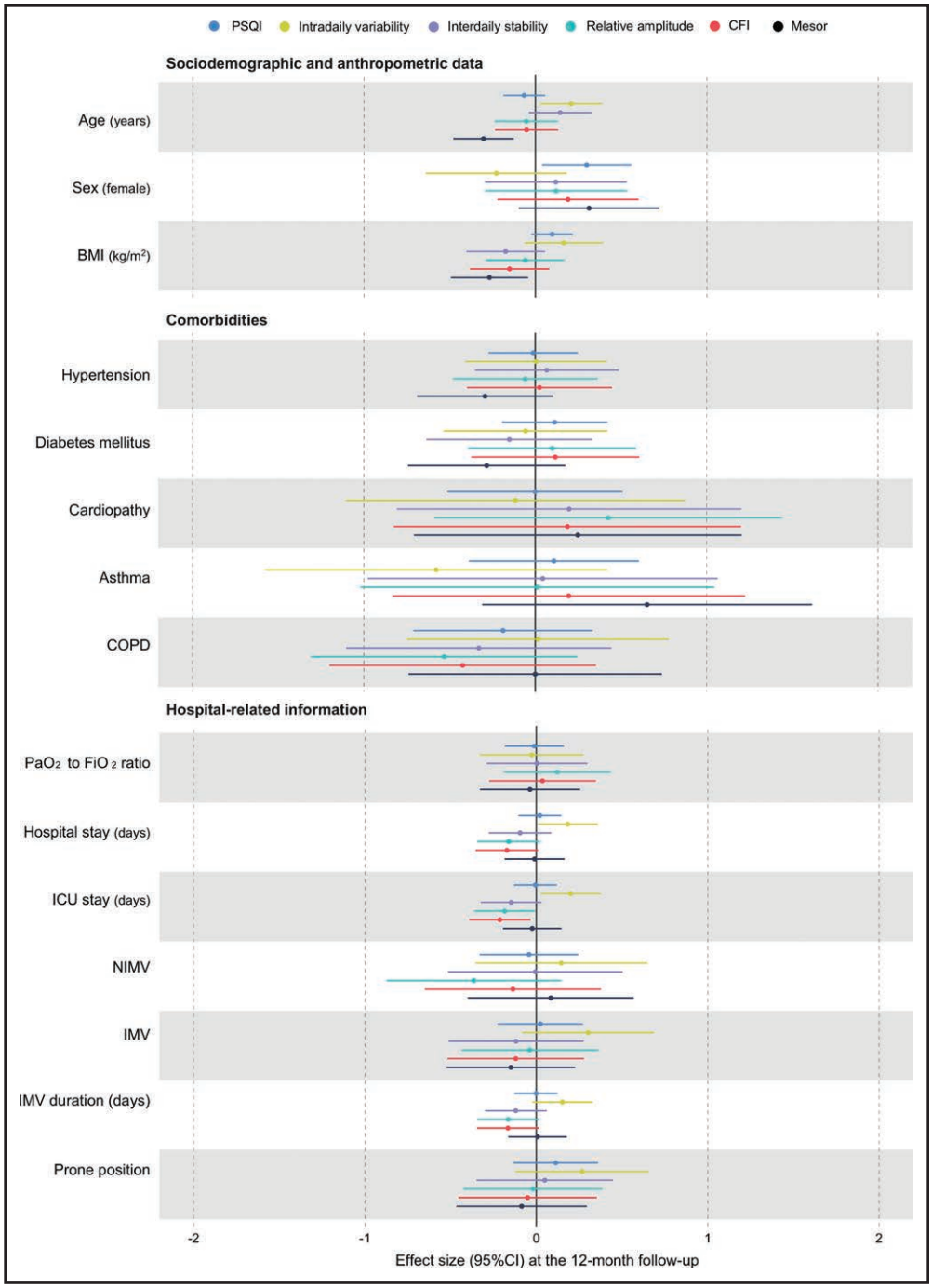

Figure 3. Baseline predictors of the Pittsburgh Sleep Quality Index (PSQI) score and actigraphy-related variables at the 12-mo follow-up. The *forest plot* demonstrates associations between baseline characteristics of the patients (obtained during the ICU stay) and the main outcomes at the 12-mo follow-up, in which *right-sided representations* indicate positive associations and *left-sided representations* indicate negative associations. Significant associations (*p* value threshold defining statistical significance was set at < 0.05) are those in which the *lines* do not cross the *central line* (effect size [95% CI] = 0). The generalized linear models were adjusted for age and sex (except for the sociodemographic and anthropometric data) after the standardization of continuous variables. BMI = body mass index, CFI = circadian function index, COPD = chronic obstructive pulmonary disease, IMV = invasive mechanical ventilation, NIMV = noninvasive mechanical ventilation.

SARS-CoV-2 pandemic led to the recruitment of patients during the ICU stay. Although the presence of previous sleep and circadian alterations were investigated through the available medical records, undiagnosed conditions in this regard might have been overlooked. Third, the dropout and consequent inclusion of additional subjects for the objective evaluations along the follow-up is a potential source of bias. Still, characteristics such as age, sex, BMI, comorbidities, length of hospital and ICU stay, and requirement and duration of IMV were similar among the groups of patients starting the objective assessment at distinct time points. Fourth, given the observational design of the study, relationships of causality between predictive factors and outcomes as well as between the correlated sequelae should be considered with caution. The effects attributed to the ICU stay or the severity of the disease cannot be confirmed with the current data. Nevertheless, this was beyond the objectives of this study. Here, we provide information related to the sleep and circadian health of critical survivors in the long term for the first time, both through the perspective of SARS-CoV-2 patients and critical survivors in general.

CONCLUSIONS

Our findings reveal poor sleep quality and the persistence of circadian alterations among a great percentage of critical survivors 12 months after hospital discharge. Taken together, these results highlight the relevance of considering the sleep and circadian health of this population in the long term. This could potentially improve the overall quality of life, ameliorate the recovery process, and prevent or attenuate conditions associated with sleep and circadian alterations.

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