BMJ Open

Prospective cohort study on characteristics, associated factors and short-term prognosis of sleep and circadian rhythm in intensive care unit: protocol for the SYNC study

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To cite: Guan T, Li J, Hou J, *et al*. Prospective cohort study on characteristics, associated factors and short-term prognosis of sleep and circadian rhythm in intensive care unit: protocol for the SYNC study. *BMJ Open* 2025;**15**:e091184. doi:10.1136/bmjopen-2024-091184

► Prepublication history for this paper is available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-091184).

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Received 15 July 2024
Accepted 24 January 2025

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ABSTRACT

Introduction Acute sleep and circadian rhythm (SCR) disruption can lead to a range of negative physical and mental consequences, such as depression, delirium, respiratory dysfunction and increased mortality. In the intensive care unit (ICU), the unique environment can exacerbate disruptions in SCR. Few studies have identified the characteristics of SCR in the ICU, and the roles of patient characteristics, illness and medical interventions in ICU SCR remain unclear. A single-centre prospective cohort study, called SYNC study (Sleep and circadian rhYthm in iNtensive Care unit), will be conducted to explore the characteristics and associated factors of SCR and investigate the short-term prognosis among patients in the surgical ICU.

Methods and analysis Patients from a surgical ICU at a tertiary teaching hospital will be enrolled. SCR will be assessed by both objective and subjective indicators, including melatonin secretion rhythm, activity rhythm, sleep pattern and perceived sleep quality. Data on eight potential factors that influence SCR, including light exposure, noise level, pain level, nighttime disturbances, mechanical ventilation, sedative and analgesic use, meal pattern and restraints, will be collected. These data will be gathered in the first 3 days after ICU admission. Short-term prognostic indicators, including anxiety, depression, cognitive function, insomnia, activities of daily living, ICU stay, hospital stay and hospital mortality will be collected during the hospital stay and at 1 month after discharge.

Ethics and dissemination The study has been approved by the Ethics Committee of Zhongshan Hospital, Fudan University (B2024-076R). The results of this study will be published in peer-reviewed journals.

Trial registration number NCT06346613.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Sleep and circadian rhythm (SCR) currently lacks a universal definition; this study describes it by employing the most commonly used indicators including melatonin secretion rhythm, activity rhythm, sleep pattern and perceived sleep quality.
⇒ This study plans to use both objective and subjective indicators rather than a single indicator to reflect the SCR profile of patients admitted to the ICU.
⇒ This study will be conducted in the surgical ICU of a tertiary hospital, which may lower the representativeness of the results.
⇒ This study will assess sleep patterns using polysomnography during nocturnal sleep duration, which may lead to a decrease in the explanatory power of daytime rhythm.

INTRODUCTION

Circadian rhythm refers to 24-hour oscillations in physiology and behaviour that allow organisms to anticipate and adapt to the daily demands associated with the day–night cycle.[1] A range of critical functions in organisms, such as the sleep–wake cycle, cardiovascular function, coagulation, immune function, glucose control and metabolism, exhibit circadian rhythmic fluctuations.[2] Circadian rhythms are the result of the action of internal biological clocks, whose activity must be synchronised every day by external periodic factors called zeitgebers.[3] The most significant natural phenomenon guiding circadian rhythms in the environment is the cycle from light to dark, and retinal light exposure is the most powerful synchroniser of the internal and external biological clocks in humans.[4] Other time cues include waking, activities, meal timing, sleep and temperature, all of which affect the rhythms of social animals, such as humans.[5] Close interactions between different central and peripheral clocks are necessary to maintain physiological and metabolic circadian rhythms, and increasing evidence suggests that the dysregulation of central and peripheral biological clocks and misalignment between the external environment and the central clock can lead to

physiological complications and disease.[5 6] The unique environment in hospital intensive care units (ICUs) can exacerbate circadian rhythm disruption. The lack of normal light–dark cycles, coupled with continuous noise, pain, immobility, mechanical ventilation and feeding, often results in a misalignment or absence of circadian rhythms in critically ill patients.

SCR disruption (SCD) in the ICU is defined as alterations in multiple domains of sleep and circadian function that occur during acute critical illness or ICU admission.[7] SCR in the ICU often manifests as sleep construction, internal and external circadian alignment, circadian amplitude, self-perception of sleep, wakefulness quality and daytime function.[7] Critically ill patients frequently experience SCD, including reduced total sleep time (TST) within 24 hours, a higher proportion of daytime sleep, highly fragmented sleep, decreased rapid eye movement (REM) and non-REM stage 3 (NREM3) sleep.[8 9] In addition, melatonin and other circadian rhythm markers exhibit abnormal amplitudes and phases.[10–13] Emerging data suggest that acute SCDs can lead to negative physical and mental consequences, such as depression,[14] delirium,[12] respiratory dysfunction,[15] metabolic derangements,[16] immune dysfunction[17] and increased ICU mortality.[18] Thus, the normalisation of sleep and circadian processes is important for improving ICU outcomes.

Despite increasing studies on ICU SCR over the past decade, evidence gaps remain. Most studies have relied on subjective sleep quality questionnaires, which undermine the credibility of the reported SCR due to a lack of objective data. Few studies have used both objective and subjective measurements to describe SCR in ICU patients and compared the differences between these two kinds of indicators. Furthermore, two studies have used polysomnography (PSG) to measure SCR over random 24–48-hour periods to characterise sleep–wake patterns during ICU stays, which may lead to bias because of the heterogeneity of the measurement period.[9 19] Consequently, a comprehensive profile of SCR in surgical patients following ICU admission remains unclear. Although previous studies have generally recognised factors, such as light exposure, noise and nocturnal therapy, as important contributors to the alterations of SCR, how these factors affect the rhythms of ICU patients and the extent of their effects have not yet been confirmed. Moreover, in addition to environmental factors, the roles of patient characteristics, illness and medical interventions in ICU SCR remain poorly understood. Furthermore, few studies have focused on the relationship between ICU SCR and short-term prognosis.

Therefore, the study will collect both objective and subjective data on SCR, including melatonin secretion rhythm, activity rhythm, sleep pattern and perceived sleep quality. Data on the factors associated with ICU SCR will be collected, and patients' short-term prognosis will be evaluated. The results of the SYNC study (Sleep and circadian rhYthm in iNtensive Care unit) may provide a deeper understanding of the characteristics of SCR in surgical ICU patients and the development of effective circadian intervention strategies.

METHODS AND ANALYSIS

Aims

The SYNC study aims to investigate the characteristics and identify the associated factors of SCR in the ICU and explore the relationship between ICU SCR and patients' short-term prognosis. The specific objectives are as follows:

- To evaluate ICU SCR by collecting data on both objective and subjective indicators, including melatonin secretion rhythm, activity rhythm, sleep pattern and perceived sleep quality.
- To identify factors associated with ICU SCR by collecting data on light exposure, noise level, nighttime disturbances, meal patterns, pain level, sedative and analgesic use, mechanical ventilation and restraints.
- To explore the relationship between ICU SCR and patients' short-term prognosis during their hospital stays, including anxiety, depression, cognitive function, insomnia, activities of daily living, ICU stays, hospital stays and hospital mortality.

Hypothesis

ICU patients commonly experience alterations in multiple domains of SCR, which are vulnerable to various factors related to the ICU environment, their illness and the treatment they receive. These alterations in SCR may be associated with poorer prognosis.

Study design

This single-centre, prospective cohort study will be conducted at a tertiary teaching hospital in Shanghai, China. Patients who were admitted to the ICU between 1 April 2024 and 1 April 2025, who meet the study criteria will be consecutively included in the study. If several patients admitted on the same day meet the study criteria, researchers will select those expected to have a longer ICU stay based on their diagnosis and prognosis, owing to the limitation of available devices. If the target population is not reached by the anticipated end date, recruitment will be extended until the sample size is met. If the sample size is reached early, data collection will end. This study is registered at the US National Institutes of Health (ClinicalTrials.gov NCT06346613).

Setting

This study will be conducted in a large surgical ICU in Shanghai, China. The comprehensive surgical ICU has 42 beds, and the staff includes 96 nurses and physicians. Approximately 50 postoperative patients are admitted per week for thoracic, general, orthopaedic, urological and vascular surgeries.

Participants

Inclusion criteria

1. Patients aged>18 years.
2. Patients transferred to the ICU between 8:00 and 22:00.

3. ICU stay>12 hours and with at least one overnight sleep.

Exclusion criteria

1. Patients who have been in the ICU for >24 hours before assessment.
2. Acute brain injuries within 30 days, including acute intracranial bleeding, traumatic brain injury, central nervous system infection or chronic brain injuries lasting >30 days, with an inability to live independently.
3. Previously diagnosed with severe cognitive impairment or Alzheimer's disease.
4. Patients with blindness or optic nerve disorder.
5. Patients who are pregnant or breastfeeding.
6. Imminently dying or with a hospice status.

Sample size

ICU SCR can be measured using multiple indicators. Most studies have shown that ICU patients experience poor subjective sleep quality,[20 21] and some have reported that the rhythm of melatonin secretion is misaligned or nonexistent.[22] However, the occurrence of SCD is not clearly defined and is difficult to quantify.[7] Our centre previously reported a 72.31% incidence of SCD in the ICU based on whether the melatonin secretion level could generate a cosine curve.[23] We determine the sample size required for the path analysis phase based on the events per variable (EPV) principle for calculating the sample size, which specifies at least five outcome events per variable. This study preliminarily identified eight influencing factors in the path analysis model through a review of prior literature, resulting in the need for at least 40 events. Given the reported positivity rate of SCD in our previous study, the final sample size is at least 56 patients.

Data collection and procedures

After admission, patients who meet the inclusion criteria will be enrolled. The research team has developed a specialised clinical case report form (CRF) that was approved by the hospital's clinical research unit and ethics committee. The CRF includes demographic and illness characteristics, associated factors, SCR assessment indicators and short-term prognosis indicators. Data will be collected by two trained researchers during hospital stay and for 1 month after discharge. The study framework describes the cohort, including the timeframes and data collection (figure 1).

SCR assessment

SCR will be assessed based on the melatonin secretion rhythm, activity rhythm, sleep pattern and perceived sleep quality.

Melatonin secretion rhythm

The melatonin level will be measured by testing the secretion level in the blood serum. Blood samples will be collected starting at 3:00 am on the first night following ICU admission, and four samples will be collected daily at 6-hour intervals (3:00, 9:00, 15:00 and 21:00) for 3 consecutive days. The samples will be immediately centrifuged and stored at −80°C for later analysis.

Activity rhythm

Patient activity will be monitored using Actiwatch (Actiware Spectrum Pro, Philips Respironics), starting at 22:00 on the first day after ICU admission and continuing for 3 days. The actiwatch will be worn on the patient's wrist. Activity rhythm metrics will be obtained by nonparametric analysis of actigraphy data, including interdaily stability (IS), intradaily variability (IV), least 5 (L5), L5 start hour, most 10 (M10), M10 start hour and relative amplitude.[24] The meaning of each activity rhythm metric is explained below:

- IS: quantifies the stability of rest–activity rhythms between days, with 0 indicating a lack of rhythm and 1 indicating a perfectly stable rhythm.

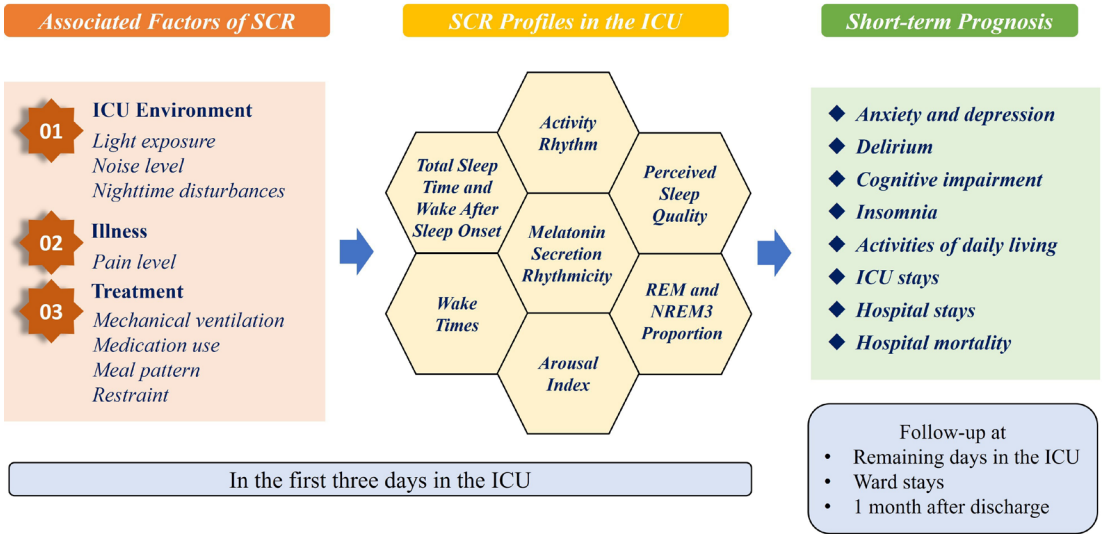

Figure 1 Study framework. ICU, intensive care unit; NREM3, non-rapid eye movement stage 3; REM, rapid eye movement; SCR, sleep and circadian rhythm.

- IV: quantifies the fragmentation of a rest–activity pattern, ranging from 0 to 2, with higher values indicating more fragmentation.
- L5: provides the average activity level for the daily sequence of 5 hours with the least activity, averaged for all available days.
- L5 start hour: onset of the L5 sequence, indicating the time of most restful hours.
- M10: provides the average activity level for the daily sequence of the most active 10 hours, averaged for all available days.
- M10 start hour: onset of the M10 sequence, indicating the time of most active hours.
- Relative amplitude: obtained by the following calculation: (M10 − L5) / (L5 + M10). The value ranges from 0 to 1, with a higher value indicating a larger amplitude.

Sleep pattern

The sleep pattern will be monitored using a portable PSG device (ALICE PDX, Philips Respironics, Amsterdam, Netherlands) from 22:00 to 6:00 during the first three nights after admission to the ICU. The TST, wake after sleep onset (WASO) duration, wake time (WT), AI, NREM3 proportion and REM proportion will be obtained. EEG (F3/M2, F4/M1), EMG and EOG (right and left) will be recorded. Patients' skin will be prepared according to standard techniques. Gold cup EEG electrodes will be placed at F3/M2 and F4/M1 according to the international 10–20 system.[25] Two EOG electrodes will be used for the right and left eye movements. The EMG electrodes will be placed over the right and left masseter (facial) muscles. Two researchers (TG and JL) trained in the technique will apply the electrodes.

Perceived sleep quality

Perceived sleep quality will be assessed using the Richards–Campbell Sleep Questionnaire (RCSQ) within 12 hours of PSG measurement. The RCSQ was designed for the self-assessment of sleep quality in acutely ill patients. There are five plain 100 mm visual analogue scale (VAS) scores relating to five sleep domains: sleep depth, falling asleep, awakening, falling asleep again and sleep quality.[26]

Associated factors of sleep and circadian rhythm

Light exposure in the ICU will be continuously monitored during the first 3 days using Actiwatch. Noise levels will also be continuously measured for the first 3 days using a decibel meter placed within 2 m of the patient's head. Pain levels will be assessed using either the critical care pain observation tool or the numerical rating scale (NRS) at 9:00 and 19:00 daily. Nighttime disturbances refer to all treatments and nursing activities carried out for patients between 22:00 and 6:00. Information on nighttime disturbances, mechanical ventilation, sedative and analgesic medication use, meal pattern and restraints will be extracted from the Intelligent Critical Care and Anaesthesia System during the first 3 days.

Short-term prognosis

Patients who enrolled in the study will be followed up during the hospital stay and 1 month after hospital discharge. Patients will be asked via telephone about their health status after discharge. Mortality is defined as postoperative all-cause death. Cognitive function will be assessed using the Montreal Cognitive Assessment (MOCA),[27] Confusion Assessment Method for the ICU (CAM-ICU)[28] and the CAM-ICU-7.[29] Anxiety and depression will be evaluated using the Hospital Anxiety and Depression Scale.[30] Insomnia will be evaluated using the American Insomnia Survey.[31] Activities of daily living will be assessed using the Barthel index.[32]

The study variables and their measurement time points are presented in table 1.

Data management

All data will be managed using an electronic data capture database. Two researchers will check each entry together before recording it in the database. Only the researchers have access to the data. The reasons for any data anomalies will be investigated, and the medical records will be reviewed again to ensure data accuracy. In addition to the signed consent form, all study-related documents will refer to participants using their assigned participant numbers rather than their names. During data entry and analysis, all sensitive information will be replaced with the participant numbers to ensure confidentiality.

Proposed analysis

The primary statistical analysis will follow the intention-to-treat principle. All participants recruited into the study, regardless of adherence to the follow-up schedule, will be included in the final analysis. In cases of missing data due to participant withdrawal or loss to follow-up, appropriate methods, such as multiple imputation or last observation carried forward, will be used to handle the missing values.

All data will be analysed using Stata 15 (StataCorp) and R 4.0.4 (the R Foundation for Statistical Computing). All statistical tests will be two-sided, with $p<0.05$ considered significant. Additionally, 95% CIs will be calculated. Continuous data will be expressed as medians (25th to 75th percentiles) or means±SD, and categorical data will be presented as counts (percentages). The intergroup comparison of categorical data will use the χ^2 test, whereas the independent sample t-test and the Mann-Whitney U test will be used for continuous data.

For the analysis of factors associated with melatonin secretion rhythm, GraphPad Prism 9 will be used to plot the cosine of patients' melatonin secretion levels and derived cosine function parameters, including mesor, amplitude and phase. The melatonin secretion rhythm indicators will be categorised into normal and disrupted rhythm groups based on the presence or absence of cosine fluctuations. The factors affecting melatonin secretion rhythm disorder will be analysed using logistic regression. With rhythm disruption as the dependent variable and each influencing factor as an independent variable, a

Table 1 Flowchart depicting the patients' timeline during the study

Events/variables	Day of ICU admission	Follow-up in the ICU		Follow-up in the ward	Follow-up 1 month after discharge
		First 3 days	Remaining ICU stay		
Assess enrolment eligibility	●				
Informed consent	●				
Demographic characteristics	●				
Surgical and illness details	●				
Melatonin secretion levels		●			
Activity counts		●			
Sleep pattern		●			
Perceived sleep quality		●			
Noise level		●			
Light exposure		●			
Mechanical ventilation		●			
Meal pattern		●			
Restraint		●			
Pain level		●			
Sedative and analgesic medication use		●			
Nighttime disturbances		●			
Delirium			●	●	●
Anxiety and depression				●	●
Cognitive impairment				●	●
Insomnia				●	●
Activities of daily living				●	●
ICU stays				●	
Hospital stays				●	
Hospital mortality				●	

ICU, intensive care unit.

one-way logistic regression analysis will first be conducted for each independent variable. Variables with $p<0.1$ will then be included in a multivariate logistic regression analysis to calculate the regression coefficients.

For the analysis of factors associated with activity rhythm, non-parametric analysis will be conducted on Actigraphy data using the nparACT package in the R environment (R V.4.3.0). Key metrics extracted from the analysis included IS, IV, L5, L5 start hour, M10, M10 start hour and relative amplitude.[24] Univariate and multivariate linear regressions will be used to identify factors associated with activity rhythm.

Factors affecting TST, WASO duration, wake times (WT), arousal index (AI), NREM3 proportion, REM proportion and perceived sleep quality will be analysed using both univariate analysis and multivariate regressions. Additionally, the relationship between SCR and short-term prognosis will be examined through univariate and multivariate regression analyses.

Validity and reliability

All SCR indicators of this study will be collected and assessed by designated individuals who have received specialised training in circadian rhythms and sleep assessments to ensure consistency in the assessment results. The validity and reliability of the devices and all questionnaires will be reported in the study. PSG recordings will be scored manually in 30 s epochs by two qualified sleep technologists according to the American Academy of Sleep Medicine standards.[33] If the inter-rater reliability between the two technicians is <60%, the report will be deemed low quality and will not be included in the analysis.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

ETHICS AND DISSEMINATION

Patients or their family members will be fully informed of the entire process and will be asked to provide their consent on the informed consent document. Written consent will be obtained from all participants to indicate their voluntary participation. For patients who are unable to make decisions themselves, written informed consent for research will be obtained from family members. This consent has no direct effect on the patient and may be revoked at any time. In addition, patients and families will be informed that the melatonin, Actiwatch, and PSG tests will be provided free of charge. The study protocol was approved by the ethics committee of the study hospital (B2024-076R). The findings will be disseminated through peer-reviewed journals and scientific conferences. The data obtained will not be shared with anyone outside of this study.

Contributors YZ is the initiator of this study and the guarantor. TG, JL and SC contribute to the development of the core protocol, statistical analysis plan and writing of this study protocol. Critical revision was carried out by YZ, SC, JH, WP and XL. All authors have read and approved the final version of this study protocol manuscript.

Funding This study was supported by the grant from Zhongshan hospital, Fudan University for the Clinical Research (ZSLCYJ202355); National Natural Science Foundation of China (72204052); Shanghai Municipal Hospital Development Center (SHDC22023229).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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