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Authors

Gupta, Prerna

Martin, Jennifer L

Malhotra, Atul

et al.

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SHORT REPORT

Circadian rest-activity misalignment in critically ill medical intensive care unit patients

Prerna Gupta[1] | Jennifer L. Martin[2,3] | Atul Malhotra[4] | Jaclyn Bergstrom[5] | Michael A. Grandner[6] | Biren B. Kamdar[4]

[1]Division of Cardiology, Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA

[2]David Geffen School of Medicine at UCLA, Los Angeles, California, USA

[3]Geriatric Research, Education and Clinical Center, VA Greater Los Angeles Healthcare System, Los Angeles, California, USA

[4]Division of Pulmonary, Critical Care and Sleep Medicine, UC San Diego School of Medicine, La Jolla, California, USA

[5]Division of Epidemiology, Department of Family Medicine and Public Health, University of California San Diego, La Jolla, California, USA

[6]Sleep and Health Research Program, University of Arizona, Tucson, Arizona, USA

Correspondence
Biren B. Kamdar, Division of Pulmonary, Critical Care and Sleep Medicine, University of California, San Diego School of Medicine, 9300 Campus Point Drive #7381, La Jolla, CA 92037, USA.
Email: kamdar@ucsd.edu

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Summary

Circadian alignment of rest–activity rhythms is an essential biological process that may be vulnerable to misalignment in critically ill patients. We evaluated circadian rest–activity rhythms in critically ill patients and their association with baseline (e.g. age) and clinical (e.g. mechanical ventilation status) variables, along with intensive care unit light–dark cycles. Using wrist actigraphy, we collected 48-hr activity and light exposure data from critically ill patients in a tertiary care medical intensive care unit. We evaluated circadian rest–activity rhythms using COSINOR and non-parametric circadian rhythm analysis models, and stratified these data across baseline and clinical variables. We used linear regression to evaluate the association of circadian rest–activity and light–dark exposure rhythms. In COSINOR and non-parametric circadian rhythm analysis analyses, the 34 medical intensive care unit patients completing 48-hr actigraphy recordings exhibited mean MESOR (mean activity levels of a fitted curve) and amplitudes of 0.50 ± 0.32 and 0.20 ± 0.19 movements per 30-s epoch, with high interdaily variability. Patients who were older, mechanically ventilated, sedated, restrained and with higher organ failure scores tended to exhibit greater circadian rest–activity misalignment, with three of 34 (9%) patients exhibiting no circadian rhythmicity. Circadian light–dark exposure misalignment was observed as well and was associated with rest–activity misalignment ($p = 0.03$). Critically ill patients in our MICU experienced profound circadian rest–activity misalignment, with mostly weak or absent rhythms, along with circadian light–dark exposure misalignment. Potentially modifiable factors contributing to rest–activity misalignment (i.e. mechanical ventilation, restraints, low daytime light levels) highlight possible targets for future improvement efforts.

KEYWORDS
actigraphy, circadian rhythms, critical care, light–dark cycle

1 | INTRODUCTION

Many physiological processes follow a 24-hr circadian pattern that can have profound consequences when misaligned (Jobanputra, Scharf, Androulakis, & Sunderram, 2020). In the intensive care unit (ICU) setting, patients are at high risk for circadian misalignment, influenced by numerous factors including older age, mechanical ventilation, sedative medications, critical illness and abnormal light–dark exposure (Oldham, Lee, & Desan, 2016). Prior studies in nursing home, ICU survivor and post-ARDS populations applied COSINOR and non-parametric models to wrist actigraphy rest–activity data to demonstrate high rates of circadian misalignment; however, similar

TABLE 1 Cosinor and NPCRA of rest–activity data, stratified by demographic and ICU variables

		Cosinor analysis[b]				NPCRA[c]					
Characteristic	*N*	Acrophase (φ), mean (SD)	MESOR, log-activity counts	Amplitude, log-activity counts	Goodness-of-fit (R^2)	IS	IV	RA	L5 start time (SD, hr:min)	M10 start time (SD, hr:min)	Light (lux) goodness-of-fit (R^2)[a]
Baseline variables											
Age (Tertiles)											
25–50 years old	12	13.8 (6.0)	0.70 (0.51)	0.26 (0.20)	0.07	0.30 (0.13)	1.11 (0.50)	0.38 (0.21)	10:41 (9:24)	15:08 (9:16)	0.22 (0.14)
53–65 years old	11	14.0 (3.3)	0.71 (0.26)	0.19 (0.15)	0.04	0.29 (0.09)	1.14 (0.48)	0.38 (0.20)	10:18 (10:29)	16:00 (8:48)	0.25 (0.15)
66–87 years old	11	10.5 (5.2)	0.57 (0.38)	0.25 (0.16)	0.06	0.27 (0.10)	1.17 (0.39)	0.43 (0.21)	12:48 (8:06)	9:13 (7:53)	0.37 (0.21)
Gender											
Female	17	12.1 (4.4)	0.61 (0.44)	0.25 (0.17)	0.06	0.29 (0.11)	1.12 (0.43)	0.43 (0.23)	12.52 (9:03)	11:00 (8:48)	0.28 (0.15)
Male	17	13.5 (5.7)	0.71 (0.34)	0.22 (0.17)	0.05	0.29 (0.11)	1.16 (0.47)	0.36 (0.17)	9:37 (9:15)	16:00 (8:37)	0.29 (0.20)
Ambulatory prior to ICU											
Not walking	2	10.3 (8.6)	0.46 (0.34)	0.38 (0.19)	0.11	0.31 (0.23)	0.87 (0.28)	0.43 (0.11)	12:43 (1:49)	6:32 (9:11)	0.21 (0.20)
Walking	32	13.0 (5.0)	0.68 (0.40)	0.22 (0.17)	0.05	0.29 (0.10)	1.16 (0.45)	0.39 (0.21)	11:09 (9:07)	13:56 (8:54)	0.29 (0.18)
Weight category											
Underweight (BMI < 18)	3	16.9 (3.5)	1.09 (0.37)	0.38 (0.31)	0.14	0.32 (0.25)	0.75 (0.22)	0.40 (0.37)	14:54 (12:34)	14:02 (8:38)	0.26 (0.03)
Normal (BMI 18–24.9)	13	13 (4)	0.73 (0.42)	0.29 (0.14)	0.08	0.31 (0.08)	1.06 (0.47)	0.38 (0.13)	10:42 (10:08)	15:25 (9:23)	0.37 (0.21)
Overweight (BMI 25–29.9)	9	10 (6)	0.48 (0.36)	0.12 (0.07)	0.01	0.28 (0.12)	1.30 (0.44)	0.45 (0.29)	11:06 (8:19)	10:52 (9:39)	0.22 (0.15)
Obese (BMI ≥ 30)	9	13 (6)	0.62 (0.30)	0.21 (0.18)	0.04	0.25 (0.07)	1.23 (0.42)	0.37 (0.14)	10:56 (8:50)	13:11 (08:31)	0.22 (0.14)
Admission diagnosis category											
Respiratory failure	14	13.4 (4.5)	0.63 (0.38)	0.27 (0.21)	0.08	0.31 (0.13)	1.08 (0.52)	0.43 (0.21)	12.32 (09:19)	12:13 (9:38)	0.26 (0.17)
Gastrointestinal	3	9.4 (7.5)	0.67 (0.55)	0.23 (0.13)	0.04	0.23 (0.05)	1.09 (0.27)	0.39 (0.23)	17:04 (6:10)	12:52 (9:27)	0.53 (0.05)
Sepsis	7	10.8 (7.0)	0.58 (0.46)	0.19 (0.12)	0.02	0.26 (0.10)	1.12 (0.39)	0.42 (0.29)	9:13 (7:35)	12:05 (8:33)	0.19 (0.12)
Cardiovascular	4	12.6 (3.5)	0.93 (0.45)	0.29 (0.14)	0.07	0.24 (0.06)	1.19 (0.53)	0.28 (0.15)	10:11 (10:32)	9:59 (10:07)	0.37 (0.09)
Other[d]	6	15.7 (2.7)	0.66 (0.26)	0.17 (0.13)	0.03	0.29 (0.05)	1.29 (0.49)	0.36 (0.12)	8:22 (11:41)	20:50 (04:31)	0.25 (0.23)
ICU variables											
Average daily SOFA tertile											
0.0–3.3	13	14.5 (5.3)	0.81 (0.33)	0.26 (0.17)	0.06	0.30 (0.11)	1.14 (0.41)	0.38 (0.19)	13:14 (9:41)	16:03 (7:22)	0.33 (0.23)
3.7–7.3	11	13.1 (5.3)	0.73 (0.45)	0.28 (0.20)	0.08	0.28 (0.10)	1.16 (0.48)	0.35 (0.21)	5:53 (7:52)	14:03 (9:45)	0.23 (0.13)
8.0–18.3	10	10.4 (3.9)	0.40 (0.29)	0.15 (0.09)	0.02	0.28 (0.12)	1.11 (0.50)	0.47 (0.22)	14:32 (7:49)	9:33 (9:25)	0.27 (0.12)

TABLE 1 (Continued)

Characteristic	*N*	Cosinor analysis[b]				NPCRA[c]					
		Acrophase (φ), mean (SD)	MESOR, log-activity counts	Amplitude, log-activity counts	Goodness-of-fit (R^2)	IS	IV	RA	L5 start time (SD, hr:min)	M10 start time (SD, hr:min)	Light (lux) goodness-of-fit (R^2)[a]
Required mechanical ventilation											
Never	25	13.0 (5.8)	0.78 (0.36)	0.26 (0.18)	0.07	0.28 (0.11)	1.06 (0.40)	0.36 (0.16)	10:26 (9:19)	14:25 (8:44)	0.32 (0.19)
Ever	9	12.4 (2.2)	0.33 (0.30)	0.15 (0.09)	0.02	0.31 (0.11)	1.37 (0.50)	0.51 (0.27)	13:29 (8:50)	10:58 (9:35)	0.21 (0.13)
Received sedative infusion[e]											
Never	27	12.9 (5.6)	0.74 (0.38)	0.26 (0.18)	0.06	0.28 (0.10)	1.11 (0.44)	0.38 (0.19)	10:26 (9:18)	14:25 (8:42)	0.29 (0.19)
Ever	7	12.3 (2.5)	0.38 (0.33)	0.15 (0.10)	0.02	0.31 (0.13)	1.24 (0.49)	0.47 (0.26)	14:23 (8;32)	09:57 (09:41)	0.26 (0.12)
Received wrist restraints											
Never	31	13.0 (5.3)	0.70 (0.39)	0.25 (0.17)	0.06	0.29 (0.10)	1.12 (0.42)	0.40 (0.21)	10:21 (9:07)	14:30 (8:43)	0.29 (0.18)
Ever	3	10.8 (1.5)	0.27 (0.12)	0.06 (0.03)	<0.01	0.26 (0.17)	1.37 (0.77)	0.35 (0.05)	20:26 (0:23)	3:06 (1:22)	0.20 (0.04)
Light–dark exposure goodness-of-fit (R^2) tertiles											
0.349–0.712	11	12.2 (4.4)	0.55 (0.32)	0.28 (0.21)	0.09	0.25 (0.08)	0.95 (0.34)	0.32 (0.18)	12:08 (9:10)	12:40 (10:10)	—
0.22–0.346	11	15.2 (4.4)	0.63 (0.32)	0.24 (0.21)	0.06	0.29 (0.13)	1.13 (0.45)	0.25 (0.19)	7:43 (9:39)	17:15 (8:20)	—
0–0.21	12	12.3 (4.5)	0.34 (0.23)	0.09 (0.04)	0.02	0.31 (0.10)	1.32 (0.48)	0.14 (0.08)	12:38 (8:47)	11:51 (7:50)	—
All subjects	34	13.0 (5.0)	0.50 (0.32)	0.20 (0.19)	0.06	0.29 (0.11)	1.14 (0.45)	0.23 (0.17)	11:14 (9:10)	13:30 (8:57)	0.28 (0.18)
Comparators											
Post ARDS patients (Yang et al., 2020)	14	15.4 (2.0)	0.13 (0.19)	1.40 (0.30)	—	0.14 (0.04)	0.24 (0.08)	0.28 (0.05)	3.44 (2:29)	15:16 (2:38)	—
Community adults (Mitchell et al., 2017)	578	14.6 (1.3)	1.69 (0.22)	3.04 (0.13)	—	0.21 (0.05)	0.37 (0.10)	0.33 (0.05)	2.7 (1:18)	14:12 (1:36)	—

Abbreviations: BMI, body mass index; ICU, intensive care unit; IS, interdaily stability, representing day-to-day activity stability (higher values = higher consistency); IV, interdaily variability, representing day-to-day activity variability (higher values = higher fragmentation); L5 time, time of day (in decimals) for the five least active consecutive hours; M10 time, time of day (in decimals) for the 10 most active consecutive hours; NPCRA, non-parametric circadian rhythm analysis; RA, relative amplitude, calculated by dividing amplitude by the sum of activity values at M10 and L5 (higher values = stronger circadian rhythm); SOFA, sequential organ failure assessments.

[a]R^2 of light–dark curves demonstrated an association with R^2 for rest–activity rhythm by cosinor model ($p = 0.03$).

[b]Calculated by fitting a cosine curve to 24-hr activity data using a least-squares method: φ = acrophase, the time of day (in decimals) of peak activity; MESOR = the mean activity level of the fitted 24-hr curve; Amplitude = the difference between MESOR and peak activity; R^2 = goodness-of-fit of the regression model, representing overall rhythm strength (higher = better).

[c]Calculations involving raw 24-hr activity data.

[d]Includes monitoring for procedures (2 of 34, 6%), renal (1 of 34, 6%), endocrine (1 of 34, 3%) and other (2 of 34, 6%).

[e]Seven of the 34 patients received sedation, accounting for 19 sedative-days total; infusions received included propofol (6 sedative-days), fentanyl (18), dexmedetomidine (2) and midazolam (7). Fentanyl was the most common sedative given as a single infusion (5 sedation-days), while fentanyl plus midazolam was the most common combination sedative infusion administered, accounting for 9 sedation-days.

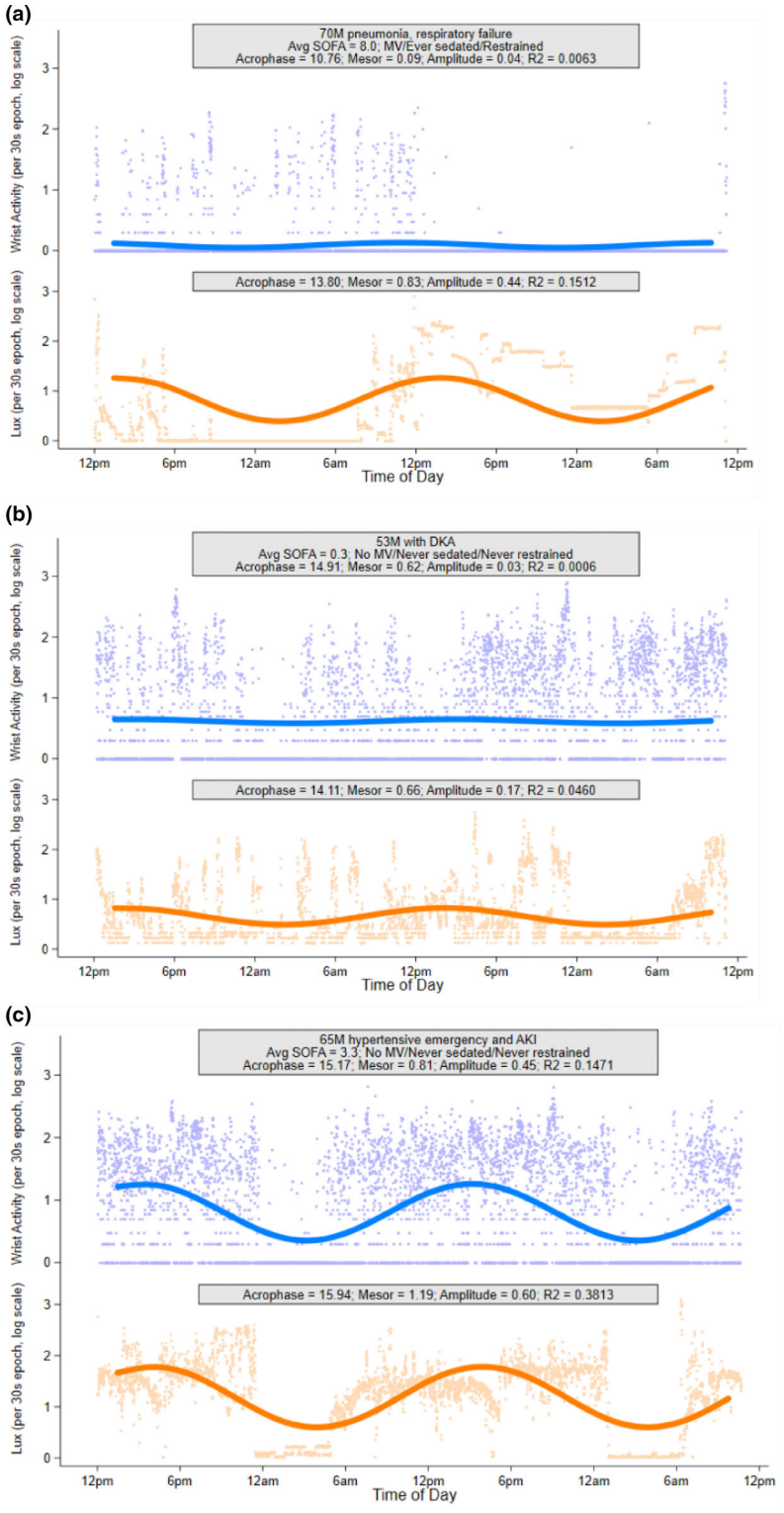

FIGURE 1 Representative rest–activity and light–dark exposure patterns in three medical intensive care unit (MICU) patients. Scatterplots depict log activity (blue) and log light (gold) levels with 48-hr rhythm trendline generated by fitting a cosine curve using the least squares (COSINOR) method. Grey boxes depict subject characteristics and COSINOR parameters. (a) A patient who was mechanically ventilated and sedated, of moderate illness in the 48 hr recorded; (b, c) activity and light exposure curves for patients who were not intubated or sedated during the 48-hr recording period. Notably, the patient in (c) demonstrated a more robust activity distribution, as reflected by a higher amplitude and goodness-of-fit (R^2) values, while the patient in (b) had no circadian rest–activity rhythmicity (p >0.05 for COSINOR regression) and a corresponding lack of rhythmicity in light–dark exposure. All three patients experienced some level of light–dark exposure rhythmicity (p <0.001)

methods have not been applied to data from critically ill patients (Schwab, Ronish, et al., 2018; Schwab, To, et al., 2018; Yang et al., 2020). To fill this important knowledge gap, we used wrist actigraphy to examine rest–activity rhythms in the ICU, hypothesizing that older, mechanically ventilated and sicker patients, along with those experiencing abnormal light–dark exposure patterns, would exhibit greater 24-hr misalignment.

2 | METHODS

This analysis was performed as part of a prospective observational study evaluating the feasibility of 48-hr wrist actigraphy in an academic medical ICU (MICU) population. Specifically, this study occurred from November 2014 to January 2015 in a closed 24-bed MICU with a nurse-to-patient ratio of 1:2. Each private room faced the nurse

workstation and featured a sliding glass door, floor-to-ceiling windows with retractable blinds, television and dimmable overhead lighting. At the time of this study, strategies to optimize sleep–wake patterns (i.e. minimization of unnecessary lights and sounds, daily sedation interruption) were being considered on the unit level but had not yet been embedded into daily practice.

All adult MICU patients were screened; those who were moribund, awaiting transfer out of the MICU, awaiting procedures involving the wrist, with no available wrist (due to lines placed in hand or arm), or unable to consent in English were excluded. The actigraphy feasibility and sleep data, along with actigraphy-based activity data profiles stratified by patient and clinical characteristics have been described previously (Gupta et al., 2020; Kamdar, Kadden, et al., 2017).

In enrolled MICU patients, we used the Actiwatch Spectrum Pro (Philips Respironics) to measure wrist activity and light levels over 30-s epochs across a 48-hr recording period (starting at ~12:00 hours, nighttime defined as 22:00 hours to 06:00 hours). Using STATA 15.1, we applied two statistical methods to activity data, and evaluated the results across various patient, clinical and light exposure variables. First, we fit a cosine curve to log-transformed activity data using a least squares (COSINOR) method, yielding the following parameters: acrophase (Φ; time of day, in decimal hours, of highest activity); mesor (M; mean activity level of the fitted curve); amplitude (A; difference between mesor and peak activity); and goodness-of-fit (R^2) of the regression model, representing overall rhythm strength (Yang et al., 2020). Given the non-normality of activity data, we also performed a non-parametric circadian rhythm analysis (NPCRA), yielding the following parameters: interdaily stability (IS; an estimate of day-to-day activity rhythm consistency); interdaily variability (IV; a measure of daily activity rhythm fragmentation); L5 and M10 (average activity levels and time of onset of the five least and 10 most active consecutive hours, respectively); and relative amplitude (RA; calculated by dividing amplitude by the sum of M10 and L5; Calogiuri, Weydahl, & Carandente, 2013; Yang et al., 2020).

Demographic and ICU variables were extracted from the electronic medical record by clinical research staff. Patients and/or surrogates reported ambulatory status prior to admission. Finally, we applied the COSINOR method to actigraphy-based light measurements, using "goodness-of-fit" (R^2) as a marker of light–dark exposure. Linear regression was used to evaluate the association of rest–activity and light–dark exposure rhythms.

3 | RESULTS

Of 35 enrolled patients, 34 provided 48-hr data for analysis (Gupta et al., 2020). The median (IQR) age of enrolled patients was 60 (44, 69) years old, 50% were female, and 14 of 34 (41%) were admitted with respiratory failure, of which nine (64%) were mechanically ventilated during the study period (Table 1). Of the nine patients who were mechanically ventilated, seven (78%) ever received continuous sedative infusions and three (33%) ever received wrist restraints. Across the 34 patients, we collected 189,595 epochs worth of wrist activity and light data, with a mean ± SD of 5576 ± 275 epochs per person.

In the COSINOR analysis of log-transformed activity data, mean MESOR and amplitudes were 0.50 ± 0.32 and 0.20 ± 0.19 movements per epoch, respectively (Table 1). NPCRA modelling demonstrated high IV of 1.14 ± 0.45 and low RA of 0.23 ± 0.17 compared with post-ARDS and community-dwelling adults (Table 1). Older, sicker (higher daily sequential organ failure assessments or SOFA), mechanically ventilated, sedated and restrained patients demonstrated lower COSINOR MESOR, amplitude and R^2 values and higher NPCRA IV values. Three (9%) patients had no circadian rhythmicity, as demonstrated by R^2 p <0.05 in COSINOR regression (Figure 1).

Regarding light–dark exposure, all actigraphs recorded mean ± SD and median (IQR) light levels of 37 ± 471 and 1.1 (0.2, 16.2) lux, respectively, with 57 ± 597 and 5.7 (0.4, 36.5) during the day and 6 ± 27 and 0.35 (0.1, 1.1) at night. COSINOR goodness-of-fit (R^2) of light–dark exposure demonstrated significant between-patient differences (p <0.001; Table 1). In a linear regression model, circadian rest–activity rhythms were significantly associated with circadian light–dark exposure ($p = 0.03$).

4 | DISCUSSION

We used actigraphy to examine activity and light levels in a MICU setting, demonstrating that most critically ill patients exhibited weak or absent circadian rest–activity and light–dark exposure rhythms. As compared with post-ARDS and community-dwelling adult populations, rest–activity rhythms of our medically complex ICU patients demonstrated low activity levels in general, along with fragmentation and instability (Cespedes Feliciano et al., 2017; Yang et al., 2020). Using a COSINOR model, we found that our ICU patients exhibited rest–activity amplitudes that were approximately 16 and 700 times lower (converted from log scale), respectively, than post-ARDS and community-dwelling populations, despite only nine (26%), seven (21%) and three (9%) of 34 patients ever receiving mechanical ventilation, sedatives and restraints during the 48-hr measurement period. We have previously reported that sedation and restraints did not significantly impact activity level, as well (Gupta et al., 2020). As prior studies defined < 100 movements per 30-s epoch as sedentary, the amplitude (0.20) and MESOR (0.50) of log-activity levels suggest 5 or fewer movements per epoch, highlighting the profound immobility affecting this population (Lee et al., 2018).

Given its potential to entrain circadian rhythms, light–dark exposure has gained attention as a provider-based intervention to improve ICU outcomes (Castro, Angus, & Rosengart, 2011). It is well known that duration and intensity of light serve as signals via the retina to the suprachiasmatic nucleus for sleep–wake cycling via suppression of melatonin release (Castro et al., 2011; Jobanputra et al., 2020). A lack of light–dark exposure alignment to solar time contributes to breakdown of circadian rhythmicity (Durrington et al., 2017). Our data demonstrated substantial light–dark misalignment in the MICU setting, with profoundly low light levels during the day and a near absence of circadian light–dark rhythmicity. While it is postulated that daytime light levels of approximately 300 lux or higher are necessary for circadian entrainment and melatonin suppression, less than 5% of our recorded

light levels exceeded 300 lux, suggesting inadequate light exposure in our population (Aoki et al., 1998; Figueiro et al., 2017). These data align with our observed association between circadian rest–activity and light–dark exposure misalignment. In interventions to improve sleep in the ICU, light-based interventions often focus on reducing nighttime light levels. Our data, however, demonstrate that increasing daytime light exposure could be far more beneficial (Kamdar, Martin, et al., 2017).

While our study is limited by small sample size and single-ICU design, it is the first, to our knowledge, to evaluate circadian rest–activity and light–dark exposure rhythms in a MICU population. Moreover, given rising interest in efforts to optimize rest–activity patterns in critically ill patients (i.e. sleep promotion, early mobility, daily sedation interruption), these findings provide an important foundation to better understand and evaluate the impact of such interventions. As a key limitation, wrist-based light measurements were vulnerable to false readings when obscured by coverings (i.e. blankets) and when not capturing eye-level light levels; future studies involving head-of-bed light measurement can be valuable for validating actigraphy-based light data. Furthermore, we acknowledge that true circadian studies require the use of constant routine or forced dyssynchrony; while the day–night patterns we observe were presumed to be circadian, we acknowledge that further work is needed (e.g. melatonin level measurement) in this area. Regardless, our analysis highlights the profoundly misaligned rest–activity and light–dark rhythms experienced by critically ill MICU patients. The potential association of rest–activity and light–dark exposure rhythms highlights the importance of both the brightness and timing of light and dark when designing and implementing interventions to improve circadian rhythms in critically ill patients.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

PG and BBK had full access to all the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis. PG, JLM, AM, JB, MAG and BBK contributed to the study design, data analysis and interpretation, and the writing of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Prerna Gupta https://orcid.org/0000-0003-1975-5262
Jennifer L. Martin https://orcid.org/0000-0003-0849-3391

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