Sleep and Breathing (2019) 23:379–388
https://doi.org/10.1007/s11325-018-1718-3

METHODS • ORIGINAL ARTICLE

Atypical sleep in critically ill patients on mechanical ventilation is associated with increased mortality

Yuliya Boyko[1] · Palle Toft[1] · Helle Ørding[2,3] · Jørgen T Lauridsen[4] · Miki Nikolic[5] · Poul Jennum[5,6]

Received: 29 April 2018 / Revised: 30 August 2018 / Accepted: 5 September 2018 / Published online: 13 September 2018

Abstract

Sleep patterns in critically ill patients' polysomnographic sleep studies (PSG) are severely abnormal.

Purpose

We aimed to investigate the association of atypical sleep patterns, micro-sleep phenomena (sleep spindles and K-complexes) and rapid eye movement (REM) sleep with intensive care unit (ICU), in-hospital and 90-day mortality in conscious critically ill patients on mechanical ventilation.

Method

This was a prospective descriptive study. We analysed 52 PSGs recorded in conscious critically ill patients on mechanical ventilation. PSGs were scored according to standard classification when possible. Otherwise, modified classification proposed for scoring sleep in critically ill patients was used. The association of PSG findings with mortality was studied using logistic regression and Weibull model of survival analysis.

Results

The presence of atypical sleep patterns in accordance with modified sleep scoring classification was associated with higher odds for ICU mortality (odds ratio 11.63; $p = 0.03$). The absence of K-complexes was associated with higher odds for ICU mortality (odds ratio 11.63; $p = 0.03$), while the absence of sleep spindles was associated with higher odds for in-hospital (odds ratio 7.80; $p = 0.02$) and 90-day mortality (odds ratio 5.51; $p = 0.02$). Loss of sleep spindles was associated with higher mortality risk with cutoff point 90 days (hazard ratio 3.87; $p = 0.03$).

Conclusions

The presence of atypical sleep and absence of normal PSG sleep characteristics in conscious critically ill patients on mechanical ventilation indicates involvement of sleep producing brain structures in the pathological process and is associated with poor outcome.

The institutions where the work was performed: Department of Anesthesiology and Intensive Care Medicine, Vejle Hospital, Vejle; Department of Anesthesiology and Intensive Care Medicine, Odense University Hospital, Odense

✉ Yuliya Boyko
yuliya.boyko@rsyd.dk

[1] Department of Anesthesiology and Intensive Care Medicine, Odense University Hospital, & University of Southern Denmark, J.B. Winsløws Vej 4, 5000 Odense C, Denmark

[2] Department of Anesthesiology and Intensive Care Medicine, Vejle Hospital, Vejle, Denmark

[3] Faculty of Health, University of Southern Denmark, Beriderbakken 4, 7100 Vejle, Denmark

[4] Department of Business and Economics, University of Southern Denmark, Campusvej 55, 5230 Odense M, Denmark

[5] Danish Center for Sleep Medicine, Department of Clinical Neurophysiology, Rigshospitalet, Nordre Ringvej 57, 2600 Glostrup, Denmark

[6] Faculty of Health, University of Copenhagen, Nordre Ringvej 57, 2600 Glostrup, Denmark

Keywords Polysomnography · Sleep scoring classification · Atypical sleep · Critically ill patients

Introduction

Intensive care is one of the most expensive treatments to patients with severe illnesses, which often are associated with persisting serious consequences for the performance and quality of life in many patients after being discharged from the intensive care unit (ICU) [1]. Accordingly, there has been much focus on the improvement of intensive care based on new knowledge on treatment of the diseases as well as estimation of the prognosis.

Sleep disturbances in critically ill patients have been among the issues receiving more attention in the field of intensive care medicine during recent years. Disrupted sleep may be associated with development of delirium and consequently prolonged stay in ICU and increased mortality [2]. Disrupted sleep is associated with the impaired function of nervous system including cognition and memory consolidation [3], immune system [4] and metabolism [5]. Accordingly, the negative effect of disrupted sleep on prognosis in case of critical illness can be serious [6].

Sleep investigation in critically ill patients is complicated due to the difficulties of monitoring and analysis. Polysomnography (PSG), the criterion standard method of sleep monitoring, is challenging in ICU mostly due to difficulties of interpretation. PSG comprises registration of several physiological signals with electroencephalography (EEG) as one of the main components. The standard for sleep scoring, American Academy of Sleep Medicine (AASM) sleep scoring classification [7] defines sleep scoring for presence of normal sleep pattern but cannot be used for sleep scoring in many critically ill patients with abnormal EEG patterns [8–10]. A modified classification for sleep scoring in critically ill patients was proposed by Watson et al. [11] Watson's classification suggests extension of AASM classification by two new states: atypical sleep and pathologic wakefulness. Atypical sleep part includes six supplemental atypical sleep stages as defined by abnormal EEG findings. Watson's classification has not yet been validated.

The prognostic value of sleep characteristics in the EEG has been mentioned in a few studies in patients with altered function of central nervous system [12–14].

The absence of sleep characteristics as defined in AASM standard for sleep scoring and the presence of atypical sleep patterns according to Watson's classification [11] were found in many patients in our two previous PSG studies in conscious critically ill patients on mechanical ventilation [15, 16]. The role of the absence of normal sleep characteristics in sleep EEG for the outcome in these critically ill patients is unknown.

The aim of this study was to investigate the association of the presence of atypical sleep patterns as compared to the presence of normal sleep characteristics in sleep EEG with outcome measured by ICU mortality, in-hospital mortality and 90-day mortality in conscious critically ill patients on mechanical ventilation.

Materials and methods

This study was designed as a prospective descriptive study.

Patients

The data used in this study were collected in a general ICU, Vejle Hospital, Vejle (September 2012–November 2013) and Odense University Hospital, Odense (May 2015–March 2016), Denmark. The patients used in this study also participated in one of the following two studies 'Sleep in critically ill patients: the role of environment', registered on ClinicalTrials.gov (NCT01681043) [15], and 'Sleep in critically ill, mechanically ventilated patients with severe sepsis or COPD', registered on ClinicalTrials.gov (NCT02434341) [16]. Both studies were approved by the Regional Ethics Committee of Southern Denmark (S-20120001; S-20140207G) and performed in accordance with principles of the Declaration of Helsinki and rules of Good Clinical Practice.

Conscious critically ill adult patients on mechanical ventilation who were able to understand the project information were considered eligible for participation. The patients were considered conscious if they were clinically awake or waked up on request and were able to communicate. The patients under 18 years old and comatose patients were excluded. The eligible patients were informed about the project by the main investigator. The patients who agreed to participate had to sign the informed consent form or allow personnel of family member to sign on their behalf to fulfil the inclusion procedure. There were always bystanders present during the informing procedure and during the obtaining of informed consent.

Two PSG recordings during two consecutive days were obtained in all but one patients in ICU of Vejle Hospital, while one PSG recording was obtained in all patients included in ICU of Odense University Hospital. First day PSG studies in Vejle patients and all the PSG studies in Odense patients were included in the survival analysis.

The mortality data reported in this manuscript are original and have not been published elsewhere.

Polysomnography

The EEG and Sleep Recorder Trackit (Lifelines LTD, UK) was used for sleep monitoring. The PSG setup was carried out by the main investigator (Boyko Y) according to AASM standard with six EEG channels (left and right frontal, central and occipital), EOG and sub-mental EMG channels included. The sampling rates were 256 Hz. We intended to investigate a total of 24-h recording. PSG was initiated during the day, when the informed consent was obtained. PSG recordings were started at the daytime, between 7 a.m. and 4 p.m. in the majority of cases (94%), and during the evening hours, between 4 p.m. and 11 p.m. in four cases (6%). Depending on the practical issues, such as procedures, PSG recordings were terminated at different time points during the following day.

A dedicated viewer, EEGViewer, was used for scoring PSG [15]. EEGViewer is a software program programmed in Matlab to facilitate features and algorithms not available in our commercial systems. EEGViewer is developed by Nikolic M and has been used for several research projects. For this project, we extended the scoring capabilities of the EEGViewer to support Watson's classification [11]. PSG recordings are imported via the EDF file standard. Standard AASM filters are applied (EEG 0.3–35 Hz and EOG 0.3–35 Hz).

The data files recorded by the EEG and Sleep Recorder Trackit were imported in the EEGViewer. Thirty second epochs were manually scored in the EEGViewer by a professor in Sleep Medicine Jennum P, blinded to patient characteristics. No automatic scoring was performed.

Firstly, PSG was evaluated in accordance with AASM classification for scoring sleep [7]. The AASM scoring refers to normal EEG pattern associated with other polygraphic measures, primarily EOG and EMG activity. We defined the presence of normal sleep characteristics by the presence of normal wakefulness (e.g. beta-alpha activity, reactivity), normal sleep pattern typical for non-rapid eye movement (NREM) sleep stages N1–N3 (e.g. theta activity, K-complexes, sleep spindles, delta-waves) and rapid eye movement (REM) sleep (mixed EEG pattern, sawtooth waves, rapid eye movements). For technical reasons and due to the complexity of manual scoring, the absolute number of sleep spindles and K-complexes was not calculated. The epochs of N2 stage with and without sleep spindles and/or K-complexes were not marked separately, but as N2 in general.

If the mentioned criteria of normal sleep were absent, we used Watson's sleep scoring classification [11]. Polymorphic delta activity with or without alpha, beta or theta activity was scored as atypical sleep (atypical stages 1–3) according to Watson's classification if other characteristics of normal sleep (e.g. sleep spindles, K-complexes) were absent.

The epochs that could not be scored due to artefacts or invalid data were marked as well.

An overview of the criteria for sleep scoring according to AASM classification and Watson's classification is presented in Table 1.

The data files were exported from the EEGViewer as text files and imported to STATA for the statistical analysis.

Statistical analysis

Multiple logistic regression models with the calculation of odds ratios (OR) were used for the analysis of the association of ICU mortality, in-hospital mortality and 90-day mortality

Table 1 Criteria for scoring sleep according to American Academy of Sleep Medicine (AASM) criteria [7] and criteria for scoring atypical sleep in critically ill patients suggested by Watson [11]

AASM criteria for scoring sleep	Watson's criteria for scoring atypical sleep
N[a]1: predominantly theta, possible vertex sharp waves, possible slow eye movements	At[c]1: alpha and/or theta > 10% of the epoch, no sleep spindles or K-complexes in the preceding 3 min; possible polymorphic delta
N2: Sleep spindles and/or K-complexes not associated with arousal	At2: polymorphic delta with alpha or beta superimposed on delta-waves, no sleep spindles or K-complexes in the preceding 3 min
N3: delta ≥ 20% of the epoch	At3: polymorphic delta, no alpha or beta
REM[b]: low amplitude, mixed frequency EEG pattern, sawtooth waves, rapid eye movements, low sub-mental tone	At4: Burst-suppression < 5 μV for > 0.5 s
Wake: alpha, eye blinks, reading eye movements, rapid eye movements, normal or high sub-mental tone	At5: suppression pattern with EEG amplitude < 20 μV
	At6: isoelectric activity

[a] Non-rapid eye movement sleep (N)

[b] Rapid eye movement (REM)

[c] Atypical sleep (At): atypical sleep scored in accordance with Watson's sleep scoring classification [11]

with sleep pattern (AASM [7] or atypical according to Watson's classification [11]), absence of sleep spindles and K-complexes and absence of REM sleep in sleep EEG. Sleep patterns (AASM or Watson), sleep spindles, K-complexes and REM sleep (present or absent) were included in the analysis as dichotomous variables. The effect of sleep pattern, sleep spindles, K-complexes and REM sleep was tested in four separate parsimonious models with age included as covariate in each model. p values < 0.05 were considered significant.

Weibull models of the survival analysis with the calculation of hazard ratios (HR) and time ratios (TR) were applied for the analysis of association of mortality with cutoff point 90 days with sleep patterns (AASM [7] or Watson [11]), absence of sleep spindles and K-complexes and absence of REM sleep in sleep EEG. Similarly to the multiple logistic regression models, sleep patterns (AASM or Watson), sleep spindles, K-complexes and REM sleep (present or absent) were included in the analysis as dichotomous variables. Separate Weibull models were used for each of the four sleep variables (sleep pattern, sleep spindles, K-complexes, REM sleep) with age included as covariate in each model. p values < 0.05 were considered significant.

The logistic regression models and Weibull models of the survival analysis including sleep pattern, sleep spindles, K-complexes and REM sleep as covariates in the same model and models including supplemental covariates (e.g. severity of critical illness score) were tested as well. The results from these large models were not useful presumably due to a small sample size and collinearity problems. Accordingly, the results of the parsimonious models only are reported.

Results

We included 19 patients from the ICU, Vejle Hospital, and 33 patients from the general ICU, Odense University Hospital. The majority of patients were admitted to the ICU with respiratory failure due to infection. All the patients had Richmond Agitation-Sedation (RASS) score at inclusion from − 1 to + 1. Nine of the patients included at Vejle ICU periodically received small doses of remifentanil analgosedation during the participation period to reduce the irritation from endotracheal tube [15]. The patients included at Odense ICU received no continuous sedation during the period of PSG recording that was used for the survival analysis [16].

We included a total of 52 PSGs for the survival analysis giving approximately 998 h of PSG recording. The median duration of each PSG recording (min; max; interquartile range) was 19.2 h (9.5; 24; 2.3).

Merged patient baseline characteristics, stratified by ICU, in-hospital and 90-day mortality are presented in Table 2.

An overview of the PSG recording time, sleep duration and percentage of the separate sleep stages according to AASM and Watson's classification stratified by ICU, in-hospital and 90-days mortality is presented in Table 3.

The illustration of 90-day survival function depending on the presence or absence of normal sleep characteristics according to AASM classification in these conscious critically ill patients on mechanical ventilation is presented in Fig. 1.

Logistic regression analysis showed significantly higher OR for ICU mortality in case of atypical sleep pattern (classified in accordance with Watson's sleep scoring classification) compared with normal sleep ($p = 0.03$). OR for ICU mortality in case of the absence of K-complexes was significantly higher compared with the presence of K-complexes ($p = 0.03$). Although not significant ($p = 0.10$), OR for sleep spindles, as expected, indicated higher ICU mortality if sleep spindles were absent in sleep EEG. Due to singularity problems caused by the small sample p value for the effect of REM sleep on ICU mortality could not be calculated (Table 4).

The ORs for in-hospital mortality and 90-day mortality calculated in logistic regression analysis were found to be insignificantly higher in case of atypical sleep ($p = 0.08$; $p = 0.10$, respectively). Analysis of in-hospital mortality and 90-day mortality revealed a significant effect of the absence of sleep spindles in sleep EEG on mortality: ORs for in-hospital mortality and 90-day mortality were significantly higher in case of the absence of sleep spindles in sleep EEG ($p = 0.02$; $p = 0.02$, respectively). Although not significant ($p = 0.08$; $p = 0.10$), ORs for K-complexes, as expected, indicated higher in-hospital and 90-day mortality if K-complexes were absent in sleep EEG. Similar results were received for the analysis of the effect of REM sleep on in-hospital and 90-day mortality ($p = 0.12$; $p = 0.22$, respectively) (Table 4).

The logistic regression showed higher ORs for ICU mortality, in-hospital mortality and 90-day mortality with increasing age. The effect of age on in-hospital and 90-day mortality was not significant though. The results of logistic regression analysis on ICU, in-hospital and 90-day mortality are presented in Table 4.

Weibull models of the survival analysis showed higher mortality risk in case of the presence of atypical sleep (Watson's classification) in sleep EEG compared with normal sleep (AASM classification), or a reduction of lifetime in case of atypical sleep. This was however not significant ($p = 0.10$ for HR and $p = 0.11$ for TR).

In case of the absence of sleep spindles in sleep EEG, mortality risk was significantly increased ($p = 0.03$ for HR), and lifetime was reduced ($p = 0.04$ for TR).

Table 2 Merged patients' baseline characteristics, stratified by intensive care unit (ICU), in-hospital and 90-day mortality

Patient characteristics ($n = 52$)	Survived at ICU discharge ($n = 42$)	Expired at ICU discharge ($n = 10$)	Survived at hospital discharge ($n = 33$)	Expired at hospital discharge ($n = 19$)	Survived at 90 days ($n = 31$)	Expired at 90 days ($n = 21$)
Admission diagnosis, *n*	Respiratory distress, $n = 35$ Chronic obstructive pulmonary disease exacerbation (20%) Pneumonia (68.5%) Heart failure (3%) Neurologic disease (8.5%) Haemorrhage, $n = 2$ Trauma, $n = 1$ Sepsis, $n = 14$					
Median age, year (min; max)	68 (26; 87)	76 (62; 88)	67 (26; 87)	71 (51; 88)	66 (26; 87)	72 (51; 88)
Sex, male/female (*n*)	Male $n = 28$ Female $n = 14$	Male $n = 5$ Female $n = 5$	Male $n = 21$ Female $n = 12$	Male $n = 12$ Female $n = 7$	Male $n = 20$ Female $n = 11$	Male $n = 13$ Female $n = 8$
Median APACHE IIa (min; max)	24 (11; 35)	23.5 (18; 31)	22.5 (11; 35)	24 (15; 31)	22.5 (11; 25)	24 (15; 35)
Median length of ICU stay before inclusion, days (min; max)	35 (0; 42)	2 (1; 30)	4 (0; 42)	2 (1; 30)	3 (0; 42)	3 (1; 30)

[a] Acute Physiology and Chronic Health Evaluation II-score (APACHE II)

In case of the absence of K-complexes in sleep EEG, mortality risk was increased and lifetime was reduced. This was not significant ($p = 0.10$ for HR and $p = 0.11$ for TR).

In case of the absence of REM sleep in sleep EEG, mortality risk was increased and lifetime was reduced. This was not significant ($p = 0.20$ for HR and $p = 0.21$ for TR).

As expected, survival analysis showed increase in the risk of death with increasing age.

The results of the Weibull models of the survival analysis are shown in Table 5.

Discussion

This is the first study to analyse the association of atypical sleep patterns in accordance with Watson's sleep scoring classification [11] in sleep EEG with ICU, in-hospital and 90-day mortality in conscious critically ill patients on mechanical ventilation.

The main findings of the study were

- Significantly higher OR for ICU mortality was found if atypical sleep patterns were present in sleep EEG. The absence of K-complexes was significantly associated with higher OR for ICU mortality, while the absence of sleep spindles was significantly associated with higher ORs for in-hospital and 90-day mortality.
- The absence of sleep spindles in sleep EEG was significantly associated with higher HR for mortality with cutoff point 90 days.

Sleep is generated in several interconnected brain structures including brainstem, hypothalamus, thalamus and forebrain. The association of preserved sleep elements in the EEG with favourable outcomes was observed in patients with posttraumatic coma in the study by Bergamasco et al. [12] Claasen et al. reported, the absence of sleep architecture was associated with poor outcome in patients with subarachnoid haemorrhage [13]. Sutter et al. studied the association of sleep characteristics in EEG with outcome in critically ill patients with altered levels of consciousness diagnosed with acute encephalopathy. The authors found K-complexes were significantly associated with good outcome measured by Glasgow Outcome Score at discharge [14]. In contrast to the mentioned studies, the patients in our study were conscious and able to cooperate at inclusion. Similarly to the mentioned studies, we found the absence of sleep characteristics as defined in standard for sleep scoring (AASM) was associated with unfavourable outcome.

ICU, in-hospital and 90-day mortality were chosen as outcome variables in this study. Only some of the associations between sleep parameters and the outcome variables were found statistically significant. Nevertheless, we observed a clear tendency towards unfavourable outcomes if normal

Table 3 Overview of polysomnography recording time (hours), total sleep time (hours) and sleep stage distribution according to American Academy of Sleep Medicine (AASM) classification [7] (hours and % of total sleep time, AASM), wake (hours), total atypical sleep time (hours) and atypical sleep stage distribution according to Watson's classification [11] (hours and % of total sleep time, Watson), stratified by intensive care unit (ICU), in-hospital and 90-day mortality

	Survived at ICU discharge	Expired at ICU discharge	Survived at hospital discharge	Expired at hospital discharge	Survived at 90 days	Expired at 90 days
Recording time (h)	798.0	198.9	636.8	360.0	596.4	400.5
Total sleep time, AASM (h)	160.2	5.0	128.8	36.3	124.6	40.7
AASM stages (hours+%Total sleep time, AASM)	N[a]1 20.4 = 12.7%	N1 1.1 = 22.0%	N1 13.4 = 10.4%	N1 8.1 = 22.3%	N1 12.6 = 10.0%	N1 8.9 = 22.0%
	N2 84.9 = 53.0%	N2 2.9 = 58.0%	N2 64.6 = 50.2%	N2 23.1 = 63.6%	N2 62.1 = 50.0%	N2 25.7 = 63.0%
	N3 46.3 = 29.0%	N3 0.9 = 18.0%	N3 44.0 = 34.1%	N3 3.2 = 8.8%	N3 43.4 = 34.8%	N3 3.8 = 9.3%
	REM[b] 8.6 = 5.3%	REM 0.1 = 2%	REM 6.8 = 5.3%	REM 1.9 = 5.2%	REM 6.5 = 5.2%	REM 2.3 = 5.7%
Wake (h)	251.5	23.0	207.0	67.5	191.5	83.0
Total atypical sleep time, Watson (h)	348.2	145.7	263.5	230.3	254.5	239.3
Watson stages (hours+%Total atypical sleep time, Watson)	At[c]1 + At2 345.9 = 99.3%	At1 + At2 145.7 = 100.0%	At1 + At2 261.6 = 99.3%	At1 + At2 230 = 99.9%	At1 + At2 252.6 = 99.3%	At1 + At2 239.0 = 99.9%
	At3 1.2 = 0.3%	At3 0.0 = 0.0%	At3 1.0 = 0.4%	At3 0.2 = 0.1%	At3 1.0 = 0.4%	At3 0.2 = 0.1%
	At4 0.9 = 0.3%	At4 0.0 = 0.0%	At4 0.7 = 0.2%	At4 0.1 = 0.0%	At4 0.7 = 0.3%	At4 0.1 = 0.0%
	At5 0.2 = 0.1%	At5 0.0 = 0.0%	At5 0.2 = 0.1%	At5 0.0 = 0.0%	At5 0.2 = 0.0%	At5 0.0 = 0.0%
Artefact (h)	38.1	25.3	37.5	26.0	25.8	37.6

[a] Non- rapid eye movement sleep (N)

[b] Rapid eye movement (REM)

[c] Atypical sleep (At): atypical sleep scored in accordance with Watson's sleep scoring classification [11]

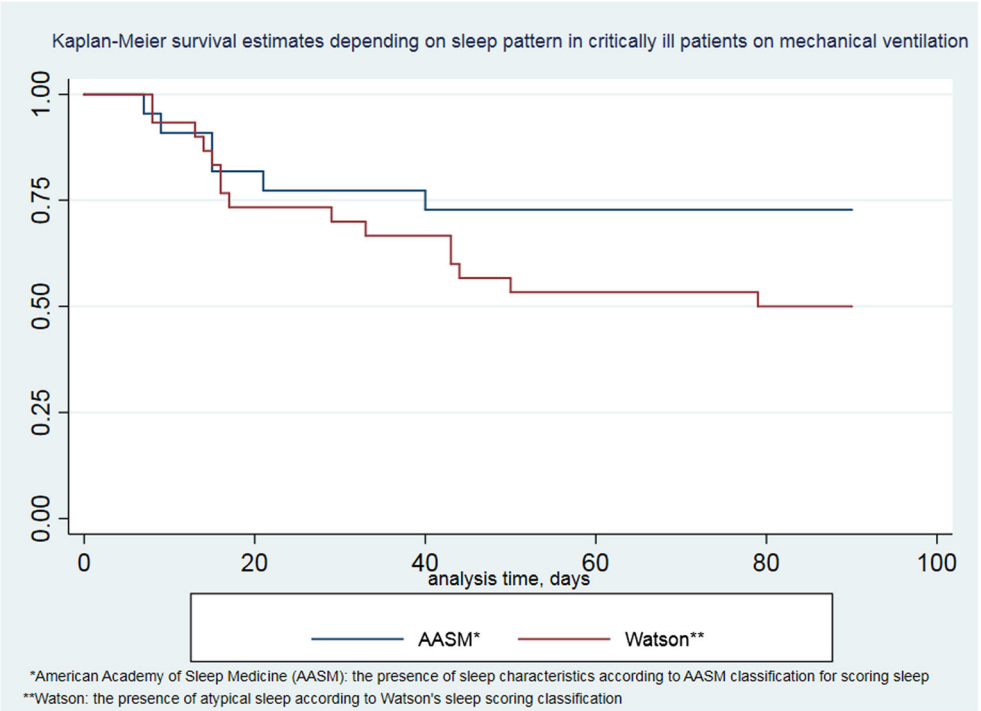

Fig. 1 Kaplan-Meier survival estimates depending on sleep pattern (atypical sleep according to Watson's classification or normal sleep according to standard classification) in conscious critically ill patients on mechanical ventilation. The figure was created using STATA 15

sleep characteristics were absent in sleep EEG in these conscious critically ill patients. The insignificant results can be explained by a small sample size.

Sleep spindles and K-complexes are the signs of stage 2 NREM sleep. Functional MRI study of sleep spindles and K-complexes showed signalling in thalamic structures in

Table 4 Logistic regression analysis of the association of ICU mortality, in-hospital mortality and 90-day mortality with sleep parameters in conscious critically ill patients on mechanical ventilation

	Sleep phenomena	Odds ratio (OR)	*p*	95% CI	Age		
					Odds ratio (OR)	*p*	95% CI
ICU mortality	Atypical sleep[a]	11.63	0.03	1.22–110.66	1.12	0.03	1.01–1.23
	Absence of sleep spindles	6.67	0.10	0.71–62.54	1.11	0.03	1.01–1.21
	Absence of K-complexes	11.63	0.03	1.22–110.66	1.12	0.03	1.01–1.23
	Absence of REM[b]	1*			1.11	0.02	1.01–1.22
In-hospital mortality	Atypical sleep	3.10	0.08	0.87–11.03	1.05	0.13	0.99–1.12
	Absence of sleep spindles	7.80	0.02	1.47–41.41	1.06	0.11	0.99–1.13
	Absence of K-complexes	3.10	0.08	0.87–11.03	1.05	0.13	0.99–1.12
	Absence of REM	3.88	0.12	0.71–21.15	1.05	0.13	0.99–1.12
90-day mortality	Atypical sleep	2.82	0.10	0.82–9.64	1.06	0.08	0.99–1.12
	Absence of sleep spindles	5.51	0.02	1.26–24.21	1.06	0.07	0.99–1.13
	Absence of K-complexes	2.82	0.10	0.82–9.64	1.06	0.08	0.99–1.12
	Absence of REM	2.56	0.22	0.56–11.65	1.06	0.09	1.99–1.12

[a] Atypical sleep: atypical sleep patterns scored in accordance with Watson's sleep scoring classification [11]

[b] Rapid eye movement (REM)

*p value for the effect of absent REM on ICU mortality could not be calculated due to singularity problems caused by the small sample

Table 5 Hazard ratio and time ratio analysis of the association of mortality with cutoff point 90 days with sleep parameters in conscious critically ill patients on mechanical ventilation

Sleep phenomena and age	Hazard ratio (HR) analysis			Time ratio (TR) analysis		
	HR	*p*	95% CI	TR	*p*	95% CI
Atypical sleep[a]	2.20	0.10	0.85–5.69	0.39	0.11	0.12–1.25
Age	1.05	0.04	1.00–1.10	0.94	0.04	0.89–1.00
Absence of sleep spindles	3.87	0.03	1.14–13.19	0.20	0.04	0.04–0.94
Age	1.04	0.04	1.00–1.10	0.95	0.05	0.90–1.00
Absence of K-complexes	2.20	0.10	0.85–5.69	0.39	0.11	0.12–1.25
Age	1.05	0.04	1.00–1.10	0.94	0.04	0.90–1.00
Absence of REM[b]	2.23	0.20	0.65–7.63	0.38	0.21	0.08–1.72
Age	1.05	0.04	1.00–1.10	0.94	0.05	0.89–1.00

[a] Atypical sleep: atypical sleep patterns scored in accordance with Watson's sleep scoring classification [11]

[b] Rapid eye movement (REM)

connection with sensorimotor cortex. Sleep spindles and K-complexes are meant to play an important role in sleep maintenance and the processes of memory consolidation [17]. The absence of these micro-sleep phenomena in critically ill patients' sleep EEG indicates involvement of the brain structures in the pathologic process and adds to the explanation of cognitive impairment after critical illness.

In the present study, we found a tendency towards poorer outcome if REM sleep was absent in the PSGs. The core of REM sleep involves brain stem structures. Brain stem, hypothalamus and forebrain interact completing REM sleep circuits [18]. Though the functions of REM sleep are not completely understood, experimental studies indicate the role of REM sleep in the processes of memory consolidation [19]. The inability of critically ill patients to produce REM sleep could indicate pathology in the brain stem and result in the disruption of memory processing.

As the AASM standard for scoring sleep is insufficient in many ICU patients, we used Watson's classification, suggested for scoring sleep in this patient population [11]. Watson's classification is based on the EEG criteria of encephalopathy published by Young et al. [20] and Markand [21]. Nevertheless, Watson's criteria for scoring atypical sleep were useful for scoring sleep EEG in these conscious interactive patients. The interpretation and validation of the atypical patterns and the underlying brain pathology represented in Watson's classification are yet not well defined. Encephalopathy states in critically ill patients might be underdiagnosed.

The patients with neurological emergencies (e.g. stroke) were not included in the project. We believe the inclusion criteria (conscious interactive patients) contributed to the mainly seen atypical stages 1 and 2 according to Watson's classification [11]. Atypical stages 3–5 were only scored in a few cases. Atypical stage 6 was not registered in any patients.

The segregation between delta activity related to N3 sleep stage and atypical sleep was one of the challenges of sleep scoring. The epochs containing more the 20% of delta activity were scored as N3 stage provided that the other stages of sleep according to AASM classification were recognized in the recording as well [7]. If no other AASM patterns were detected, the epochs comprising delta activity were scored according to Watson's classification (atypical 1–3). Sleep scoring in the present study was done by an expert in the field of Sleep Medicine. Nevertheless, supplemental sleep scoring by another independent expert with the following interrater reliability test would improve the quality of the results. Unfortunately, the interrater reliability test was not possible due to practical issues.

Medication, inflammation and individual response to critical illness are among possible explanatory factors of the EEG abnormalities in these patients. The subgroup analysis would help understanding the mechanisms of these associations. Though, the validity of such analysis would not be justified due to a small sample size in the present study.

Due to a small sample size, we were able to include only sleep parameters and age as explanatory variables in our statistical models. Future studies with a larger number of participants are needed for the adjustment for other important parameters, such as severity of critical illness scores, delirium and medication.

We intended to investigate the association of sleep characteristics with mortality in a group of conscious critically ill patients on mechanical ventilation. We did not exclude the patients with electrolyte derangement or impaired renal or liver function if they were conscious at clinical examination and could cooperate and fulfil the consent procedure. Though the mentioned conditions can impact the function of the central nervous system and thus bias the results, they are present in a large number of critically ill patients. Accordingly, the included sample well represents the population of conscious

critically ill patients on mechanical ventilation in a general ICU. The length of ICU stay prior to the inclusion can potentially influence sleep patterns in critically ill patients. Nevertheless, the length of ICU stay was not among the inclusion criteria; conscious patients on mechanical ventilation were the target group in this study.

The use of unsupervised PSG and the absence of video recording can be added to the list of limitations of the present study. Supervised PSG with video recording would possibly allow assessing of the behavioural aspects under sleep/wake states.

Conclusion

The absence of normal electrophysiological sleep characteristics in conscious critically ill patients on mechanical ventilation indicates involvement of sleep generating brain areas in the pathological process and is associated with poor outcome. Detection of sleep elements in the EEG could have a place as a supplemental tool in the assessment of prognosis in this patient population.

Acknowledgements Special thanks to the ICU staff, Vejle Hospital and Odense University Hospital, for their great contribution to the project.

Funding information This study received financial support from the University of Southern Denmark; the Region of Southern Denmark; Department of Anesthesiology and Intensive Care Medicine, Vejle Hospital; The Research Foundation at Vejle Hospital; Department of Anesthesiology and Intensive Care Medicine, Odense University Hospital; Danish Society of Anesthesiology and Intensive Care Medicine; Aage and Viola Holm-Madsens Research Foundation; A.P. Moellers Foundation and Exchange pool Rigshospitalet/Odense University Hospital.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in the study were in accordance with the ethical standards of the national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Hodgson CL, Udy AA, Bailey M, Barrett J, Bellomo R, Bucknall T, Gabbe BJ, Higgins AM, Iwashyna TJ, Hunt-Smith J, Murray LJ, Myles PS, Ponsford J, Pilcher D, Walker C, Young M, Cooper DJ (2017) The impact of disability in survivors of critical illness. Intensive Care Med 43:992–1001. https://doi.org/10.1007/s00134-017-4830-0
2. Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE Jr, Inouye SK, Bernard GR, Dittus RS (2004) Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA 291:1753–1762
3. Stickgold R, Walker MP (2007) Sleep-dependent memory consolidation and reconsolidation. Sleep Med 8:331–343
4. Palmblad J, Petrini B, Wasserman J, Akerstedt T (1979) Lymphocyte and granulocyte reactions during sleep deprivation. Psychosom Med 41:273–278
5. Trivedi MS, Holger D, Bui AT, Craddock TJA, Tartar JL (2017) Short-term sleep deprivation leads to decreased systemic redox metabolites and altered epigenetic status. PLoS One 12:e0181978. https://doi.org/10.1371/journal.pone.0181978
6. Kamdar BB, Needham DM, Collop NA (2012) Sleep deprivation in critical illness: its role in physical and psychological recovery. J Intensive Care Med 27:97–111. https://doi.org/10.1177/0885066610394322
7. Silber MH, Ancoli-Israel S, Bonnet MH, Chokroverty S, Grigg-Damberger MM, Hirshkowitz M, Kapen S, Keenan SA, Kryger MH, Penzel T, Pressman MR, Iber C (2007) The visual scoring of sleep in adults. J Clin Sleep Med 3:121–131
8. Cooper AB, Thornley KS, Young GB, Slutsky AS, Stewart TE, Hanly PJ (2000) Sleep in critically ill patients requiring mechanical ventilation. Chest 117:809–818
9. Foreman B, Westwood AJ, Claassen J, Bazil CW (2015) Sleep in the neurological intensive care unit: feasibility of quantifying sleep after melatonin supplementation with environmental light and noise reduction. J Clin Neurophysiol 32:66–74. https://doi.org/10.1097/WNP.0000000000000110
10. Drouot X, Roche-Campo F, Thille AW, Cabello B, Galia F, Margarit L, d'Ortho MP, Brochard L (2012) A new classification for sleep analysis in critically ill patients. Sleep Med 13:7–14. https://doi.org/10.1016/j.sleep.2011.07.012
11. Watson PL, Pandharipande P, Gehlbach BK, Thompson JL, Shintani AK, Dittus BS, Bernard GR, Malow BA, Ely EW (2013) Atypical sleep in ventilated patients: empirical electroencephalography findings and the path toward revised ICU sleep scoring criteria. Crit Care Med 41:1958–1967. https://doi.org/10.1097/CCM.0b013e31828a3f75
12. Bergamasco B, Bergamini L, Doriguzzi T, Fabiani D (1968) EEG sleep patterns as a prognostic criterion in post-traumatic coma. Electroencephalogr Clin Neurophysiol 24:374–377
13. Claassen J, Hirsch LJ, Frontera JA, Fernandez A, Schmidt M, Kapinos G, Wittman J, Connolly ES, Emerson RG, Mayer SA (2006) Prognostic significance of continuous EEG monitoring in patients with poor-grade subarachnoid hemorrhage. Neurocrit Care 4:103–112
14. Sutter R, Barnes B, Leyva A, Kaplan PW, Geocadin RG (2014) Electroencephalographic sleep elements and outcome in acute encephalopathic patients: a 4-year cohort study. Eur J Neurol 21:1268–1275. https://doi.org/10.1111/ene.12436
15. Boyko Y, Jennum P, Nikolic M, Holst R, Oerding H, Toft P (2016) Sleep in intensive care unit: the role of environment. J Crit Care 37:99–105. https://doi.org/10.1016/j.jcrc.2016.09.005
16. Boyko Y, Jennum P, Oerding H, Lauridsen JT, Nikolic M, Toft P (2018) Sleep in critically ill, mechanically ventilated patients with severe sepsis or COPD. Acta Anaesthesiol Scand 62:1120–1126. https://doi.org/10.1111/aas.13140
17. Caporro M, Haneef Z, Yeh HJ, Lenartowicz A, Buttinelli C, Parvizi J, Stern JM (2012) Functional MRI of sleep spindles and K-

complexes. Clin Neurophysiol 123:303–309. https://doi.org/10.1016/j.clinph.2011.06.018
18. Fraigne JJ, Torontali ZA, Snow MB, Peever JH (2015) REM sleep at its core - circuits, neurotransmitters, and pathophysiology. Front Neurol 6:123. https://doi.org/10.3389/fneur.2015.00123
19. Boyce R, Williams S, Adamantidis A (2017) REM sleep and memory. Curr Opin Neurobiol 44:167–177. https://doi.org/10.1016/j.conb.2017.05.001
20. Young GB, McLachlan RS, Kreeft JH, Demelo JD (1997) An electroencephalographic classification for coma. Can J Neurol Sci 24:320–325
21. Markand ON (2003) Pearls, perils, and pitfalls in the use of the electroencephalogram. Semin Neurol 23:7–46