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Sleep assessment in critically ill adults: A systematic review and meta-analysis

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ABSTRACT

Purpose: To systematically review sleep evaluation, characterize sleep disruption, and explore effects of sleepdisruption on outcomes in adult ICU patients.
Materials and methods: We systematically searched databases from May 1969 to June 2021 (PROSPERO protocol number: CRD42020175581). Prospective and retrospective studies were included studying sleep in critically ill adults, excluding patients with sleep or psychiatric disorders. Meta-regression methods were applied when feasible.
Results: 132 studies (8797 patients) were included. Fifteen sleep assessment methods were identified, with only two validated. Patients had significant sleep disruption, with low sleep time, and low proportion of restorative rapid eye movement (REM). Sedation was associated with higher sleep efficiency and sleep time. Surgical versus medical patients had lower sleep quality. Patients on ventilation had a higher amount of light sleep. Meta-regression only suggested an association between total sleep time and occurrence of delirium ($p < 0.001$, 15 studies, 519 patients). Scarce data precluded further analyses. Sleep characterized with polysomnography (PSG) correlated well with actigraphy and Richards Campbell Sleep Questionnaire (RCSQ).
Conclusions: Sleep in critically ill patients is severely disturbed, and actigraphy and RCSQ seem reliable alternatives to PSG. Future studies should evaluate impact of sleep disruption on outcomes.

1. Introduction

Patients admitted to the intensive care unit (ICU) are known to be at risk for disrupted sleep. Important causes for sleep disruption are environmental factors, such as noise and light; physiologic factors, such as pain, immobility, discomfort and coughing; care-related factors, such as nursing care and medication, psychologic factors, and most importantly the severity of illness [1-8]. Disturbed sleep in critically ill patients has been associated with cognitive impairment, delirium, prolonged duration of mechanical ventilation, altered immune function, and long-term psychological comorbidities, which may subsequently contribute to increased morbidity and mortality [1-8].

Polysomnography (PSG) is considered the reference standard to assess sleep quality and provides data on sleep architecture [9-11]. However, its use is logistically challenging and costly, especially in the ICU setting [1,7,12,13]. Therefore, many other sleep assessment tools, both objective (e.g. biosignals such as movements) and subjective (e.g. sleep questionnaires), are applied in the ICU setting.

Although previous studies have summarized sleep assessment methods [14] and risk factors for disrupted sleep [15], to our knowledge, no meta- analysis has been published on the characterization of sleep disruption, on sleep disruption in relation to mechanical ventilation and sedation or the impact of sleep disruption on relevant outcomes in critically ill patients. Therefore, we aimed to summarize current sleep assessment methods as a basis to characterize sleep disruption in ICU patients as compared to normal sleep, to assess the impact of

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additional ICU factors (e.g. mechanical ventilation and sedation) on sleep, and to study the associations between sleep characteristics and relevant health outcomes.

2. Materials and methods

2.1. Protocol and registration

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) [16] guidelines (see supplemental material S1) and was registered with PROSPERO database (https://www.crd.york.ac.uk/PROSPERO) as record number CRD42020175581.

2.2. Literature search strategy

A systematic literature search was performed with assistance of a biomedical information specialist, searching articles between May 14th,1969 and June 24th, 2021. Main keywords included 'assessment tool', 'sleep', and 'intensive care unit'. The Embase, Medline Ovid, Cochrane Central, Web of Science and Google Scholar databases were searched. The pediatric and neonatal population was excluded from the search. The full search strategy is described in supplemental material S2.

2.3. Study screening and selection

Title and abstract screening were performed independently by three reviewers (EK/MP/PW) using the methods described by Bramer et al. [17] Prospective and retrospective studies were included if they studied adult patients (≥18 years) admitted to the ICU in whom sleep quality and/or quantity was studied, using objective or subjective sleep assessment tools. These sleep assessment tools included PSG as an objective tool or patient questionnaires as subjective tools, evaluating sleep by healthcare professionals or investigators. Other inclusion criteria were a sample size of at least ten patients, full text availability and manuscript written in the English language. Two reviewers (MP/PW) assessed full texts independently. Studies were found eligible for full-text analysis if 'intensive care unit' or a closely related term such as 'coronary care unit' or 'acute care unit' were among the keywords of the paper, when focus on intensive care setting was not immediately clear from title/abstract screening. After full text screening, studies not performed in the intensive care were excluded. In randomized controlled trials that investigated the effect of an intervention on sleep, only the non-intervention control groups were included for this review, since the intervention may affect sleep outcomes. If randomization was performed in a crossover design, the outcomes of the 'before' study treatment were extracted. All disagreements between reviewers were resolved by discussion.

2.4. Main outcomes

This review first provides a summary of sleep assessment tools that are used in the critically ill. Furthermore, we assessed sleep characteristics based on these sleep assessment tools and compared them with sleep of healthy subjects. Further, we aimed to study the association of several patient or ICU management related factors on sleep characteristics (these subgroup analyses pertained to mechanical ventilation [MV], sedation, sedation level assessed with a validated scale [Richmond agitation sedation scale (RASS), Ramsay score], reason for ICU admission [e.g. medical versus surgical], severity of disease [acute physiology and chronic health evaluation: APACHE, Simplified Acute Physiology Score: SAPS]. Finally, we assessed associations between sleep characteristics and relevant health outcomes for ICU patients (delirium, length of ICU stay, length of mechanical ventilation, complications during ICU stay, and mortality). Whether tools were validated or not in the ICU population was based on the Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU (PADIS) [1], the American Academy of Sleep Medicine [22], and a more recent study on actigraphy [154].

2.5. Data extraction and quality assessment

Two reviewers independently (MP/PW) extracted study data. The following study and patient characteristics of the included studies were extracted; author name, year of publication, type of study (e.g. retrospective, prospective, cohort, randomized controlled trial), sample size, reason for ICU admission (medical, surgical, or trauma), age, sex, sedation during ICU stay (yes/no), MV during ICU stay (yes/no), RASS, and APACHE scores. For the sleep assessment tools, we extracted type of sleep assessment tool (e.g. PSG, questionnaire, actigraphy, or other), the variables assessed in these tool, and whether the tool was validated in the ICU population. Furthermore, a senior author (MJ) checked at least 10 % of the articles finally included by the junior authors to confirm and establish full consensus on the selection process. Studies were appraised, by two reviewers (MP/EK) during the data extraction phase, based on the method of Boulos et al. [18], in which appraisal was based on whether patients with sleep or psychiatric disorders were explicitly excluded.

2.6. Statistical analysis

Descriptive statistics were expressed in numbers (N) and percentages (%). Pooled means of the sleep variables were separately calculated for each assessment tool. Data were pooled, if >3 studies were available, using the "Metamean" function of R version 4.0.3 and the random effects model. Studies were included in the meta-analysis if mean values and standard deviations (SD) of the main outcomes were reported. If only medians were reported, these were used to calculate an approximation of the mean based on the methods of Hozo et al. [19] Approximations of the SD and interquartile ranges (IQR) were calculated as previously described [19-21]. Additionally, a variable named "slow wave sleep (SWS) merged" was created, in which data of N3 and N4 sleep stages (corresponding to deep sleep) were merged [22]. Heterogeneity was assessed using the I^2 statistics. Comparison between the nocturnal PSG sleep variables assessed in this review and healthy volunteers from the study of Boulos et al. [18] was calculated using the two-sample *t*-test. Nocturnal pooled means and SD's were used for this review and compared with those in healthy volunteers reported by Boulos et al. [18]. Subgroup analysis of the pooled means of the sleep variables was performed, stratified by; MV, sedation, RASS, APACHE score, and reason for ICU admission (surgical, medical, trauma, and mixed [including surgical, medical, and/or trauma patients]) to explore associations of these variables with the sleep characteristics. Results of significant subgroup analysis were reported using the Q-test for heterogeneity (Q). Meta-regression (linear for continuous normally distributed variables and logistic for binary variables) was performed to assess the associations between sleep characteristics and health outcomes, when data were available for the sleep variable and health outcome in ≥10 studies [20]. Statistical significance was inferred at p-value <0.05.

3. Results

The initial search yielded 3421 articles, and after removing duplicates, 2151 were screened on title and abstract. After title and abstract screening, 280 articles were included for full-text assessment. Finally, 132 studies (8797 patients) were included (Fig. 1) [12,23-153].

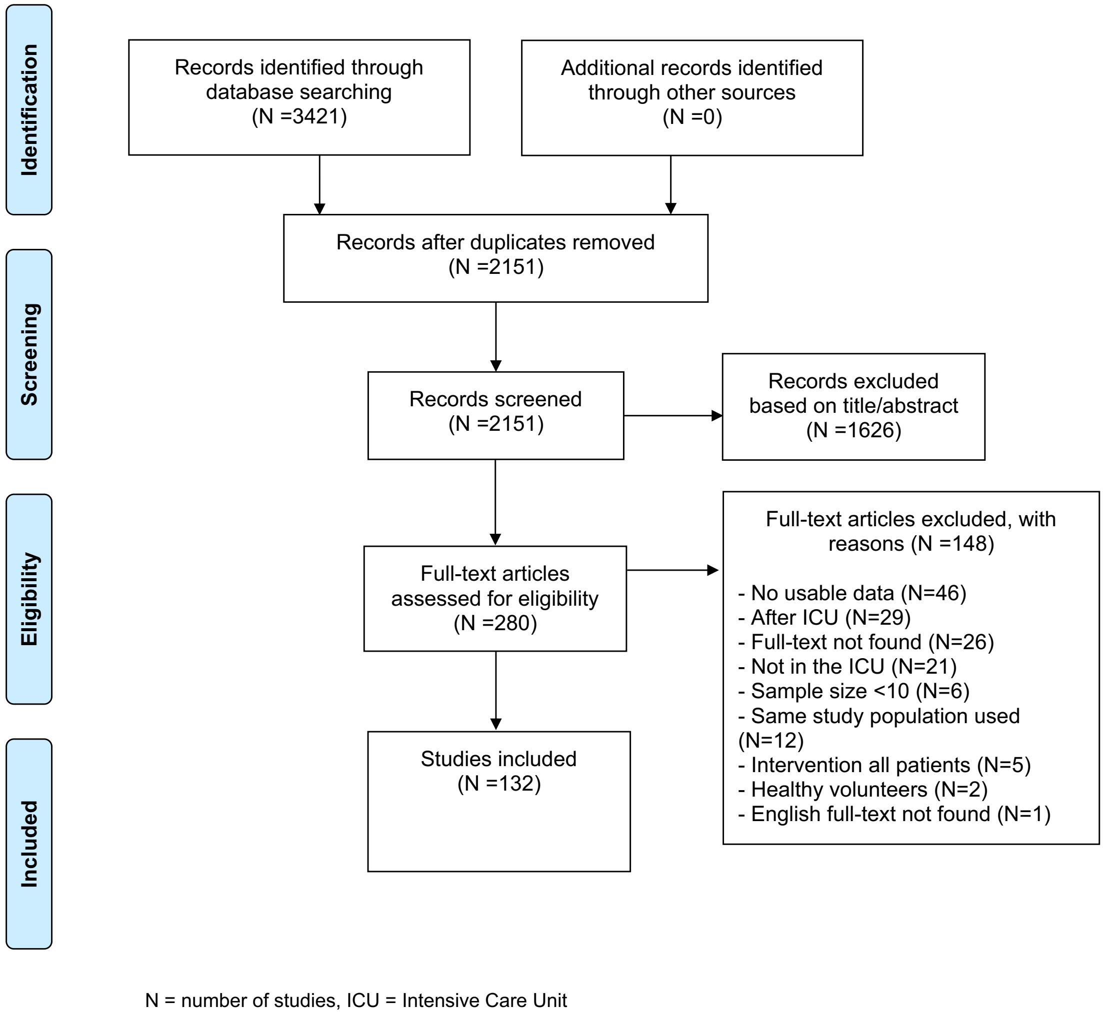

Fig. 1. Flow diagram of article selection.
N = number of studies, ICU = Intensive Care Unit.

3.1. Sleep assessment methods

Results on sleep assessment method and their characteristics are elaborated in detail and tabulated in supplemental material S3-S13. In brief, sixty-four studies used objective measurements (measuring bio-signals), 62 studies used previously validated subjective methods, and 32 studies used non-validated subjective methods.

3.2. Appraisal of studies

Appraisal of the studies can be found in supplemental material S14. Fifty-one studies (38.1%) excluded patients based on sleep disorders and 47 studies (35.1%) excluded patients based on psychiatric disorders. Eighteen of the 48 (37.5%) PSG studies excluded patients based on sleep disorders and 11/48 (22.9%) excluded patients based on psychiatric disorders. For the RCSQ these numbers were respectively 26/49 (53.1%) and 21/49 (42.9%).

3.3. Quantitative analysis

3.3.1. Sleep characteristics

Data on sleep characterization could be pooled for PSG, RCSQ, and actigraphy, since sufficient data for analysis were available. These tools have been previously validated for sleep quality assessment [22,157].

Table 1
Comparison of nocturnal PSG data between ICU population and healthy adults.

PSG variables	ICU			Healthy adults			P-value
	Mean	SD	N	Mean	SD	N	
TST, minutes	6.2	3.1	971	6.6	0.6	4038	<0.001
SE, %	52.2	18.2	554	85.7	6.8	4217	<0.001
WASO, minutes	122.9	58.8	155	48.2	21.7	2757	<0.001
N1, %	25.0	14.3	656	7.9	3.2	2940	<0.001
N2, %	49.7	12.7	775	51.4	6.2	2940	<0.001
SWS, %	13.0	10.0	893	20.4	7.3	2995	<0.001
REM, %	5.6	4.1	637	19.0	2.9	3012	<0.001
SOL, minutes	26.3	21.1	279	15.4	7.1	3828	<0.001
REML, %	134.9	15.9	44	97.4	16.9	2859	<0.001
AI, number per hour	18.0	9.5	317	12.6	3.9	2847	<0.001
Actigraphy Variables	ICU			Healthy adults			P-value
	Mean	SD	N	Mean	SD	N	
TST, minutes	8.1	6.3	491	7.2	0.8	21	0.006
SE, %	81.1	3.4	91	97.1	2.2	21	<0.001
WASO, minutes	71.8	17.3	100	12.6	9.6	21	<0.001

TST = Total Sleep Time, SE = Sleep Efficiency, WASO = Wake After Sleep Onset, N1 = light sleep stage, N2 = light sleep stage, REM = Rapid-Eye Movement, REML = REM Latency, SOL = Sleep Onset Latency, AI = Arousal Index, SD = standard deviation, N = number of patients.

We compared our pooled data to normal data of the concerned sleep assessment tool in healthy volunteers as the reference (quantitatively for actigraphy (Table 1) and qualitatively for RCSQ (S18A-E)). Supplemental material S15 provides an overview and specification of the items assessed with these sleep assessment methods and supplemental material S16A-C show the results of the pooled analyses of sleep characteristics. Comparison of PSG data of healthy volunteers [18] versus ICU-patients is shown in Table 1. Critically ill patients had a significantly lower sleep quality. Compared to normal actigraphy values [156], we also found that ICU patients had a lower total sleep time, sleep efficiency, and consequently a higher wake after sleep onset (Table 1). The RCSQ consists of six separate variables, as described in supplemental material S15, which can be converted to one score. A score between 0 and 25 is considered as very poor sleep, 26–50 as poor sleep, 51–75 as good sleep, and 76–100 as very good sleep [158]. A score of <50 on the RCSQ was found for the total RCSQ score, sleep depth, awakening, and quality.

3.3.2. Subgroup analysis

Subgroup analysis of sleep characteristics was performed for critically ill patients with or without MV, stratified by sedation administered or not, and ICU admission category. In the supplemental material, we only show statistically significant associations between sleep characteristics and subgroups. When analyzing PSG data, sedation was associated with a longer total sleep time (supplemental material S17A, $p < 0.001$) and a higher sleep efficiency (supplemental material S17B, $p = 0.01$) compared to patients without sedation. Patients with MV had a significantly lower amount of the sleep stage N1 (light sleep) (supplemental material S17C, $p < 0.001$), a higher amount of sleep stage N2 (light sleep, supplemental material S17D, $p = 0.005$) and a lower arousal index (S17E, p < 0.001). Surgical patients had a significant lower sleep efficiency (supplemental material S17F, $p = 0.004$), a higher sleep stage N1 (supplemental material S17G, p < 0.001), and a lower wake after sleep onset (supplemental material S17H, $p = 0.03$) compared with medical patients. Subgroup analysis for the RCSQ resulted in sedated patients scoring significantly higher on all RCSQ variables, except for the total score of the RCSQ (average all the variables) and noise, and thus having a more favorable sleep characteriation (supplemental material S18A-E, p-values ranged from 0.01 to <0.001). No significant results were found in the subgroup analysis of actigraphy.

3.3.3. Associations of sleep variables with health outcomes

Sufficient data was available for PSG variables to perform only two meta-regression analyses, which showed significant associations between the total sleep time and occurrence of delirium (%) and between slow wave sleep (deep sleep) and duration of MV (days). Results of the meta-regression are depicted in Fig. 2. This shows that one hour increase in the total sleep time may be associated with 5.8% increase in risk of delirium ($p < 0.001$, 15 studies, 519 patients) and for each percent increase of slow wave sleep (deep sleep) there is an association with 0.58 days increase of MV duration ($p = 0.01$, 18 studies, 384 patients).

4. Discussion

In this review, we have provided an overview of sleep assessment methods studied in critically ill patients, including objective and subjective tools. Furthermore, based on qualitative analysis of PSG, RCSQ, and actigraphy data, we quantified in more detail the clear presence of significant sleep disruption, referring to significant differences in sleep duration and architecture, in critically ill patients as compared with healthy subjects, which has not been done in previous work. Also, we found that sedation, mechanical ventilation, and ICU admission type (surgical, medical or trauma) had significant effect on sleep characteristics as assessed with PSG, RCSQ, and actigraphy. Finally, increase in the total sleep time might be associated with increase in occurrence of delirium, but scarce data precluded further analyses on relevant sleep-outcome associations and further research is warranted on these preliminary associations, given that these are likely influenced by other factors as well, and therefore unlikely to be uni-directional, or uni-factorial (e.g. associations between delirium and sleep are likely to be affected and confounded by sedation, disease severity, pain and its management, among others).

PSG is considered the reference standard in assessment of sleep quality, but unfortunately it is costly and labour intensive [1,7,9-13]. Recently, actigraphy has been found to be a reliable alternative to the PSG in the ICU population [154]. Based on the PSG and actigraphy analyses in this study, it seems that admission to the ICU causes difficulty in staying asleep and when asleep a reduction of deeper sleep stages occurs, which leads to loss of the restorative and resting function of sleep [6,66,159]. Actigraphy may be a more feasible tool to measure sleep quality at the ICU than PSG, although we found similar detection of sleep disruption based on sleep efficiency and awake after sleep onset-time, but a higher total sleep time as measured with actigraphy versus PSG (Table 1 and S16A-C). Regarding the RCSQ, we found that characteristics indicating sleep disruption seemed to correlate well with PSG, based on the results (S18A-E) of the RCSQ, which show the same disturbances in the equivalent sleep variables of PSG. RCSQ was previously validated against PSG [154,157,160]. Since the patient-nurse interrater reliability for the RCSQ is moderate, the RCSQ assessment is more reliable when assessed by the patient themselves [161].

Compared to PSG data of healthy volunteers [18], ICU patients' sleep is of lower quality. In the PADIS guidelines (2018) it is stated that total sleep time and sleep efficiency are normal in critically ill patients and that the percentage of light sleep is higher than deep sleep [1]. This review confirms the statement regarding the total sleep time and higher proportion of light sleep stages, but shows that sleep efficiency is reduced during critically illness. Interpretation of the total sleep time should be done with caution, since it constitutes an incomplete parameter to characterize the sleep quality and was also slightly different in critically ill versus healthy subjects hampering clinical relevance of this difference (although statistically significant). Also, in the studies that reported a TST the total recording time rages from 7 to 24 h, which impacts on the total sleeping time. This study shows that ICU patients spend three times more time in the N1 sleep stage (light sleep) than healthy people, the same amount of time in the N2 sleep stage. Also, ICU patients spend 1.6 times and 3.4 times less time in the deeper sleep stage and REM, which are important for memory respectively emotion regulation, and may be relevant for recovery from illness [162,163]. Recent reviews have studied sleep assessment tools and risk factors for sleep disruption, but did not focus on sleep characterization in detail nor attempted meta-regression [14,15]. Therefore, the findings of these previous studies are complementary to this review. It should be noted that data from patients in the included studies who received an intervention of some kind which may influence the sleep quality were excluded from the analysis, however this concerned only a small minority of the total patients included for analysis.

Within the PSG studies a significant higher total sleep time (14.4 h. vs. 5.3 h.) and sleep efficiency (88.7% vs. 46.4%) in sedated patients compared to non-sedated ICU patients was found. This finding is interesting since sedatives have been considered as disrupting, rather than improving sleep quality [1]. Nevertheless, the clinical importance of these findings is unclear, since total sleep time and sleep efficiency are regarded as less important variables when it comes to the restorative function of sleep. Based on our results, it can be concluded that independent of sedative administration, all ICU patients have an impaired nocturnal sleep. Based on the RCSQ in this review, in which all items of the RCSQ were scored as “good” to “very good” in the sedated group compared to as “poor” in the non-sedated group, it seems that non-sedated patients experience more sleep

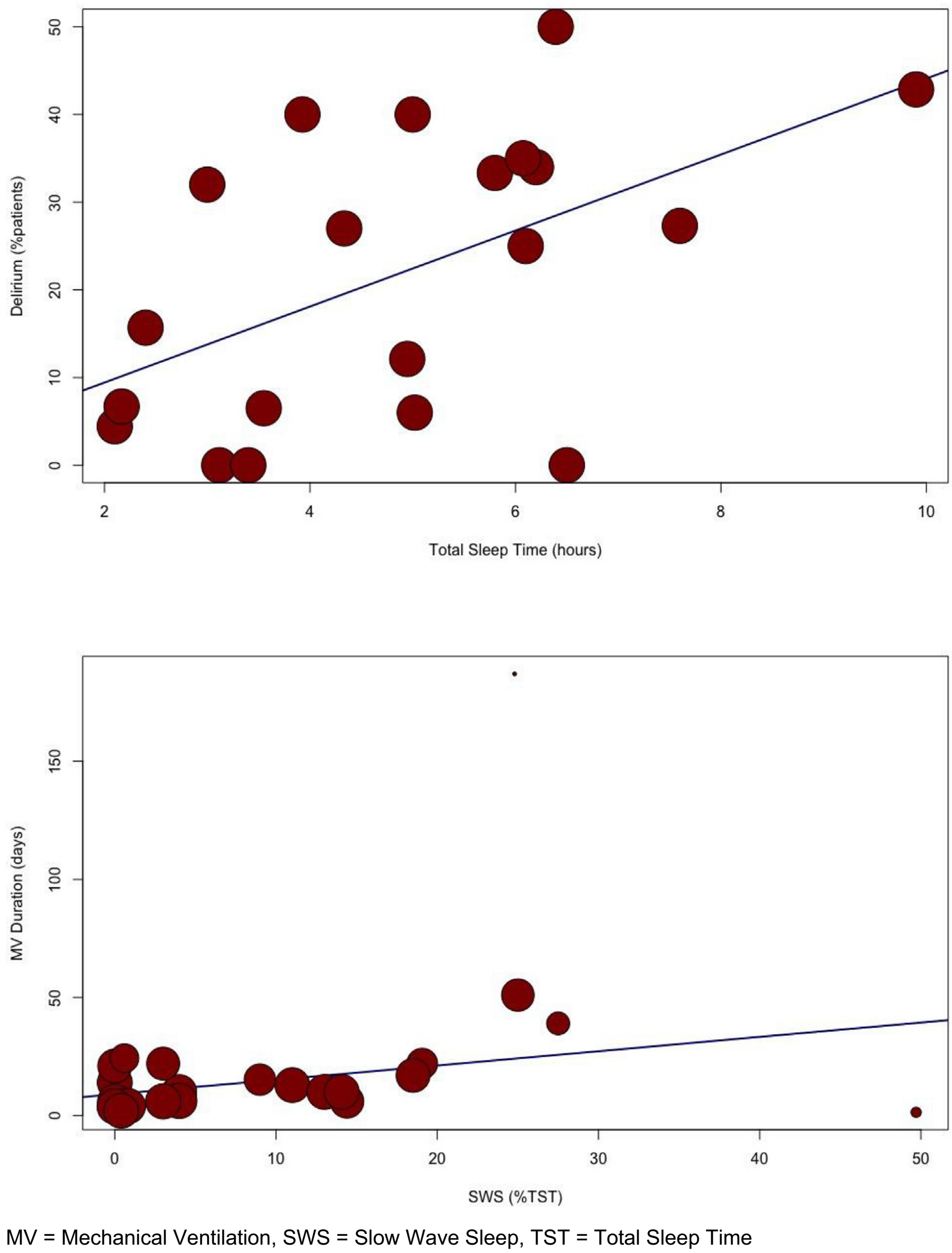

Fig. 2. Bubble plot of the meta-regression.
MV = Mechanical Ventilation, SWS = Slow Wave Sleep, TST = Total Sleep Time.

distruption than sedated patients. In this study it also appears that mechanically ventilated patients seem to spend less time in lighter sleep stage (N1) compared to non-ventilated patients (22.2% vs. 51.2% (normal = 7.9% (SD = 3.2))) and have less arousals during sleep based on PSG data (13.5 vs. 50.0). The level of sedation may importantly influence these associations, but it was not possible to analyze this due to limited granularity of the pertinent data.

Regarding the differences in sleep characteristics found between ICU admission types, it seems that surgery also negatively influences sleep efficiency and thus the ability to reach deeper sleep stages, which is also concluded by a large multicentre study [164]. assessing sleep in hospitalized patients. This difference may be caused by the level of pain in the surgical population, since the main reported reasons for sleep problems were noise and pain in that study [164]. Otherwise severity of illness or other variables may be confounding factors.

5. Strengths and limitations

To the best of our knowledge, this is the first meta-analysis that assessed and quantified sleep, using multiple sleep assessment methods, in the critically ill population in detail. However, several limitations should be discussed. First, there is a large heterogeneity in study populations, e.g. differences in diagnosis, medication usage, and ventilation protocols. Second, the sleep disruption-associated health outcomes we aimed to investigate (delirium, ICU LOS, length of MV, complications, and mortality) were scarcely reported. In addition, for MV we did not specify what type of ventilation mode was applied, but this has been investigated recently by Honarmand et al. [15] Third, pooled data for most of the questionnaires evaluating sleep quality could not be assessed. Fourth, although based on a large previous study [18], the quality assessment in our study may have been suboptimal and therefore we want to emphasize the results should be interpreted with caution. Lastly, mere statistical associations cannot be distinguished from causal relations based on our analyses. The associations in our study should therefore be considered hypothesis generating rather than facts and therefore could guide future studies. For example, better sleep quality seems of high importance in general, but possibly the definition of 'better' sleep quality is different for the ICU population vs. healthy subjects.

6. Future studies

Although we provided an overview of sleep disruption in the critically ill and did so in more detail than was done in the PADIS guidelines and summarized sleep assessment methods and their possible yield in clinical practice, further study is needed to determine how assessment of sleep could be used to improve clinical management and outcomes. This review confirms that RCSQ and actigraphy may be reliable, valid, patient-friendly, and feasible alternatives to PSG for assessing sleep quality in the critically ill. It is known that the RCSQ assessment is most reliable when assessed by patients themselves [13]. Still, more studies are needed to define good sleep quality in the ICU population. Our analysis suggests that longer TST, while portending longer and possibly better quality of sleep (indicated by more SWS) in ICU patients, associates with poor outcomes. Although counterintuitive at first sight, this association may indeed signal that wakefulness in critically ill patients, rather than prolonged and even good quality sleep, is preferably maximized.

An important point should be noted regarding the use of PSG to characterize sleep disruption: PSG assesses important parts of the sleep architecture which currently can only be studied by the PSG. Therefore, although other measurement tools (mainly actigraphy and RCSQ) may provide promising results and may have practical advantages, PSG should not be discarded for further studies on sleep quality at the ICU. Therefore, other measurement techniques may provide promising results, but still validation of these new techniques using PSG are needed. A recent review regarding this subject also concludes the above ("ICU patient have atypical brain waves"), indicating that PSG evaluation to assess abnormality of sleep quality may be hampered) [14]. Compared with this previous review, our review characterized and quantified in more detail the clear presence of significant sleep disruption in critically ill patients compared with healthy subjects. Also, in this study associations between sleep and health outcomes were analyzed which has not been done in previous literature using quantified sleep data.

7. Conclusions

This review is the first meta-analysis to provide a detailed overview of sleep characteristics in ICU patients. Sleep in the critically ill is severely disturbed and can be characterized as short, light, and fragmented. Many methods in assessing sleep exist, with only a minority validated or immediately suitable for the ICU setting. Actigraphy and RCSQ seem to be reliable tools in assessing sleep in the critically ill as alternatives to PSG. However their usability and applicability seem to be more dependent on the type of management of the patient (e.g. sedation level) than PSG and therefore comparability is suboptimal. Furthermore, sedation, ventilation, and reason for admission alter sleep characteristics. Future studies investigating consequences of disrupted sleep for clinical outcomes are warranted.

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Author contributions

Conceptualization; MJ, EK Data curation; EK, MP, PW, Formal analysis; EK, MP, PW, Investigation; MJ, ML, AS, EK, MP, PW, Methodology; MJ, ML, AS, Supervision; MJ, ML, AS, Roles/Writing - original draft; EK, MP, Writing - review & editing; MJ, ML, AS, EK, MP, PW.

Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2022.154102.

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