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REVIEW

Systematic review and meta-analysis of the correlation between bispectral index (BIS) and clinical sedation scales: Toward defining the role of BIS in critically ill patients

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Abstract

Introduction: The bispectral index (BIS) is an attractive approach for monitoring level of consciousness in critically ill patients, particularly during paralysis, when commonly used sedation scales cannot be used.

Objectives: As a first step toward establishing the utility of BIS during paralysis, this review examines the strength of correlation between BIS and clinical sedation scales in a broad population of non-paralyzed, critically ill adults.

Methods: We included studies evaluating the strength of correlation between concurrent assessments of BIS and Richmond Agitation Sedation Scale (RASS), Ramsay Sedation Scale (RSS), or Sedation Agitation Scale (SAS) in critically ill adult patients. Studies involving assessment of depth sedation periperative or procedural time periods, and those reporting BIS and sedation scale assessments conducted >5 min apart or while neuromuscular blocking agents (NMBA) were administered, were excluded. Data were abstracted on sedation scale, correlation coefficients, setting, patient characteristics, and BIS assessment characteristics that could impact the quality of the studies.

Results: Twenty-four studies which enrolled 1235 patients met inclusion criteria. The correlation between BIS and RASS, RSS, and SAS overall was 0.68 (95% confidence interval, 0.61–0.74, $T^2 = 0.06$ $I^2 = 71.26\%$). Subgroup analysis by sedation scale indicated that the correlation between BIS and RASS, RSS, and SAS were 0.66 (95% confidence interval 0.58–0.73, $T^2 = 0.01$ $I^2 = 30.20\%$), 0.76 (95% confidence interval 0.69–0.82, $T^2 = 0.04$ $I^2 = 67.15\%$), and 0.53 (95% confidence interval 0.42–0.63, $T^2 = 0.01$ $I^2 = 26.59\%$), respectively. Factors associated with significant heterogeneity included comparator clinical sedation scale, neurologic injury, and the type of intensive care unit (ICU) population.

Conclusions: BIS demonstrated moderate to strong correlation with clinical sedation scales in adult ICU patients, providing preliminary evidence for the validity of BIS as a measure of sedation intensity when clinical scales cannot be used. Future studies should determine whether BIS monitoring is safe and effective in improving outcomes in patients receiving NMBA treatment.

KEYWORDS
bispectral index, intensive care unit, Ramsay Sedation Scale, Richmond Agitation Sedation Scale, Sedation Agitation Scale

1 | INTRODUCTION

Electroencephalographic monitoring with the bispectral index (BIS) is a method for assessing level of consciousness that can be used to titrate the dosage of sedative agents in a variety of settings. BIS monitoring was originally developed for the operating room setting, where it demonstrates a strong correlation with drug-induced loss of consciousness,[1] and randomized trials have shown its use to significantly reduce the incidence of accidental awareness during anesthesia.[2] The role of BIS in the critically ill population has yet to be clearly defined, given the lack of data showing a benefit of BIS compared with commonly used clinical sedation scales.[3] However, clinical sedation scales cannot be used in patients treated with neuromuscular blocking agents (NMBA), because such scales require assessment of a patient's movement in response to stimulus.

NMBA are a common adjuvant therapy for mechanically ventilated patients in the intensive care unit (ICU). An estimated one in five patients with acute respiratory distress syndrome (ARDS) are treated with a NMBA,[4] and the prevalence of use has increased substantially since the advent of the coronavirus disease 2019 (COVID-19) pandemic.[5,6] One of the most challenging aspects of NMBA treatment is the management of sedation. The inability to apply clinical sedation scales during NBMA treatment creates a substantial risk of harm from undersedation (i.e., awareness with paralysis) and oversedation (i.e., sedatives are infused beyond what is needed). Awareness during paralysis is a potentially devastating complication that can lead to post-traumatic stress disorder.[7,8] Further, oversedation may be a mediator of increased mortality in patients treated with NMBA.[9,10] Thus, establishing the utility of BIS as a monitoring tool in paralyzed, critically ill patients is of considerable interest.

An effective approach to establishing the validity of BIS would be to examine agreement between BIS and validated clinical sedation scales. However, doing so directly in NMBA-treated patients is not feasible. Thus, as a first step toward this goal, we conducted a systematic review and meta-analysis to provide a definitive evaluation of the literature supporting the validity of BIS in non-paralyzed, critically ill patients. Our primary aim was to determine the strength of correlation between BIS and the following validated clinical scales: Richmond Agitation Sedation Scale (RASS), Ramsay Sedation Scale (RSS), and Sedation Agitation Scale (SAS).[11–13]

2 | MATERIALS AND METHODS

2.1 | Protocol and registration

This review and associated protocol were registered with the PROSPERO international prospective register of systematic reviews (Registration Number: CRD42020158314). This study did not require ethical approval.

2.2 | Study eligibility

We included studies evaluating the strength of correlation between concurrent assessments of BIS and RASS, RSS, or SAS in critically ill adult patients. We excluded studies involving assessment of depth of sedation during perioperative or procedural periods; however, patients admitted to the ICU for postoperative care were included. BIS and clinical sedation scale assessments had to be conducted concurrently and not during a period of neuromuscular blockade. The definition of "concurrent" was met if the methods stated broadly that assessments were done at the same time. If a specific time between assessments was mentioned, it must have been ≤5 min. Studies published in abstract form were included if there was no subsequent manuscript with the same dataset and only if outcomes of interest were reported.

2.3 | Search strategy, sources, and study identification

We performed computerized searches of PubMed, Embase (Elsevier), Cochrane Library (include Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials), Scopus (Elsevier), and OpenGrey with the assistance of an experienced medical librarian (E.F.G.). Searches were conducted on August 18, 2018, and rerun on November 15, 2019, January 15, 2021, and April 14, 2022. Search strategies combined keywords and subject headings for the concepts of consciousness monitors, sedation scales, and ICUs (Appendix S1). No date or language restrictions were applied. Corresponding authors of studies with missing data were contacted one time to obtain data of interest.

2.4 | Study selection and data abstraction

Title and abstract screening for the initial search results was conducted in Excel. Full-text screening for the initial search and all screening for search updates were completed in Covidence.[14] Covidence was also used for data abstraction and quality assessment.

Article selection was independently conducted by two authors (D.D.L. and S.Y.A.Y.) and disagreements were reconciled by a third author (M.S.H.), who reviewed articles independently and determined relevance. If the third author agreed with either of the two authors, that determination was followed. If there was ambiguity

identified by M.S.H., all three authors discussed disagreements for reconciliation. Data of interest were abstracted from full texts by three authors (D.D.L., S.Y.A.Y., and M.S.H.). Two authors independently collected and documented data of interest for each included study. Disagreements in data collected were reconciled by M.S.H., similar to the process defined above for article selection.

Author, publication year, sponsorship source, country of origin, ICU setting, corresponding author information, study design, number of patients, and number of assessments were collected. To gain an understanding of the study population and quality, we also collected data on whether neurologically injured patients were included, goal depth of sedation, if specified, use and timing of NMBA with respect to sedation assessments, monitoring of signal-quality index, monitoring of electromyogram input, number of BIS scores documented at each assessment, number of clinical sedation scores documented at each assessment, percentage of patients receiving mechanical ventilation, sedative and analgesic agents administered, severity of illness, and type of BIS monitor and electrodes used during the study. In addition, data on study quality or risk of bias, and outcomes of interest were collected for each full study included.

2.5 | Assessment of methodologic quality

QUADAS-2 was used to evaluate the risk of bias in included studies. Four key domains of patient selection, index test, reference standard, and flow and timing were evaluated for each study. Three authors (D.D.L., S.Y.A.Y., and M.S.H.) evaluated studies for quality and risk of bias. Two authors independently evaluated and documented assessment for quality and risk of bias for each domain of QUADAS-2. Disagreements were reconciled by M.S.H. using the previously defined approach.

2.6 | Data analysis

Data analysis was conducted by T.A.M. Pooled analyses were based on the Pearson correlation coefficient (*r*). Values from studies reporting other correlation measures (Spearman's Rank correlation, Kendall rank correlation) were converted to r values using published equations.[15] The primary analysis pooled results from all studies. If a study examined the correlation between BIS and more than one clinical scale, the results for only one scale were included in the primary analysis according to the following hierarchy, based on how widely the scales have been reportedly used in practice[16]: RASS is primary, if RASS is not reported, RSS is primary, if RSS not reported, SAS is primary. Estimation of 95% confidence intervals and pooled estimates were obtained after applying the Fischer Z transformation to approximate a normal sampling distribution, with transformation back to the correlation scale for presentation. Pooled estimates were obtained from a random-effects meta-analysis using the method of DerSimonian and Laird.[17] Heterogeneity of correlation estimates between studies was examined by calculating the Q statistics, derived from the chi-square test, and the inconsistency index (I^2). We considered an $I^2 > 50\%$ to indicate important heterogeneity between studies and a *p*-value ≤0.10 as indicating statistically significant heterogeneity.[18]

We specified several subgroup analyses a priori to examine potential sources of heterogeneity: sedation scale (RASS vs. RSS vs. SAS), depth of sedation targeted (deep sedation [RASS < −3, RSS < 4, SAS < 2] vs. higher levels), signal-quality index assessed (yes vs. no), exclusion of patients with prior NMBA use (yes vs. no), ICU population type (mixed vs. medical vs. surgical), inclusion of patients with neurological injury (yes vs. no), and whether the correlation analysis was the study's primary outcome (yes vs. no). We also performed several post hoc subgroup analyses, including electromyographic assessment (yes vs. no), approach to BIS measurement (single measure vs. average of multiple measurements), BIS monitor type (XP vs. non-XP), APACHE II score (0–10, 11–20, >20),[19] and risk of bias (based on bias and applicability ratings).

For the depth of sedation subgroup analysis, we classified scales as follows (from deepest to lightest and excluding the agitated states for clinical scales): BIS 0–39 (ultra-deep), 40–59 (deep), 60–79 (moderate), 80–100 (light); RASS −5 to −4 (deep), −3 (moderate), −2 to 0 (light); RSS 6 to 5 (deep), 4 (moderate), 3 to 2 (light); and SAS 1 to 2 (deep), 3 (moderate), 4 (light).[20]

We considered a correlation coefficient between 0.0 and 0.09 to be negligible, 0.10 and 0.39 to be weak, 0.40 and 0.69 to be moderate, 0.70 and 0.89 to be strong, and 0.90 and 1.0 to be a very strong correlation.[21] We examined the risk of publication bias by visual inspection of funnel plots. All analyses were performed with Stata version 17.1 (College Station, TX).

3 | RESULTS

3.1 | Study Identification and Selection

The comprehensive electronic search yielded 2973 citations. Removal of duplicates and screening for inclusion criteria yielded 59 studies. After elimination of 35 studies for exclusion criteria, 24 studies enrolling 1235 patients were included in the final analysis.[22–45] Figure 1 depicts the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) flow diagram.

3.2 | Study characteristics

The 24 studies included in the analyses were published between 2001 and 2015. Eighteen studies enrolled patients in mixed or general ICUs. All studies were prospectively conducted and included only mechanically ventilated patients except one study that did not report this information. Nineteen studies evaluated BIS and clinical

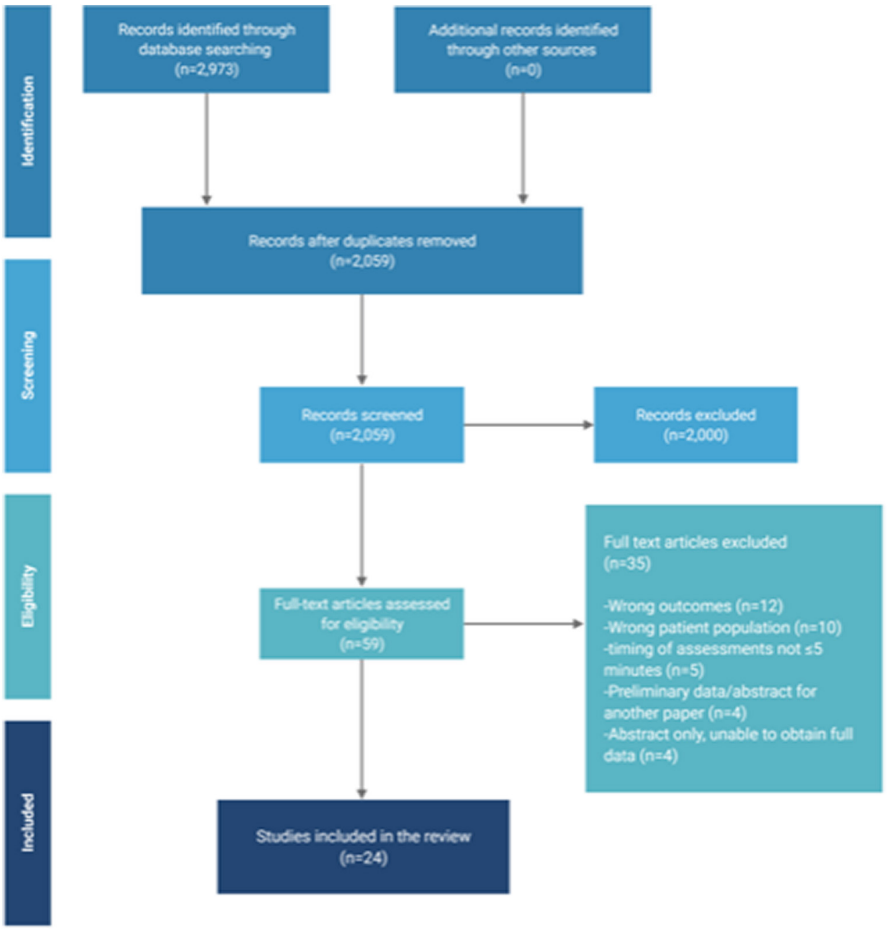

FIGURE 1 Preferred reporting items for systematic review and meta-analyses flow diagram for systematic review phases for correlation between concurrent measurements of bispectral index (BIS) and clinical sedation scale assessments

sedation scale correlation as the primary outcome. Nine studies correlated BIS with RASS, 11 with RSS, and 9 with SAS.

3.3 | Meta-analysis results

When data from all studies were aggregated, the correlation between BIS and clinical sedation scales was 0.68 (95% confidence interval, 0.61–0.74, $I^2 = 71.26\%$), demonstrating substantial heterogeneity across studies (Figure 2). The correlation with BIS varied significantly by sedation scale (Figure 3), showing the strongest correlation with the RSS scale. The correlation between BIS and clinical scales varied significantly depending on whether patients with neurological injury were included; the correlation was significantly lower in the three studies including patients with neurological injury (Figure 4). When the studies were stratified by depth of sedation, the correlation between BIS and clinical sedation scales was stronger with studies including patients undergoing deep sedation (correlation coefficient 0.76 for deep sedation versus 0.68 for light to moderate sedation). However, heterogeneity was lower across studies with light to moderate sedation (Figure 5). Significant heterogeneity was also observed when analysis was stratified by ICU type (Appendix S2). No significant heterogeneity was observed in the remaining subgroup analyses (Appendix S2).

3.4 | Assessment of methodologic quality

Table 1 summarizes assessments for risk of bias for each study, in each of domain of the QUADAS-2 tool. Ten studies were found to have low risk of bias, four studies with 1 domain considered high or unclear risk of bias, and 10 studies with 2 or more domains considered high or unclear risk of bias. Seventeen studies had low risk in the applicability rating and seven studies with 1 or more domains with high or unclear risk in the applicability rating.

4 | DISCUSSION

In this systematic review and meta-analysis, we observed a moderate-to-strong correlation between BIS and validated clinical sedation scales in a population of critically ill patients who were predominantly receiving light sedation. This finding suggests that BIS monitoring potentially provides clinically relevant information on level of consciousness in critically ill patients receiving sedation. Application of this finding is limited, however, by substantial heterogeneity of the correlation across included studies. We included 24 studies in varied patient populations, using three different clinical sedation scales, and employing numerous differences in methodology. Methodological inconsistencies, such as type of

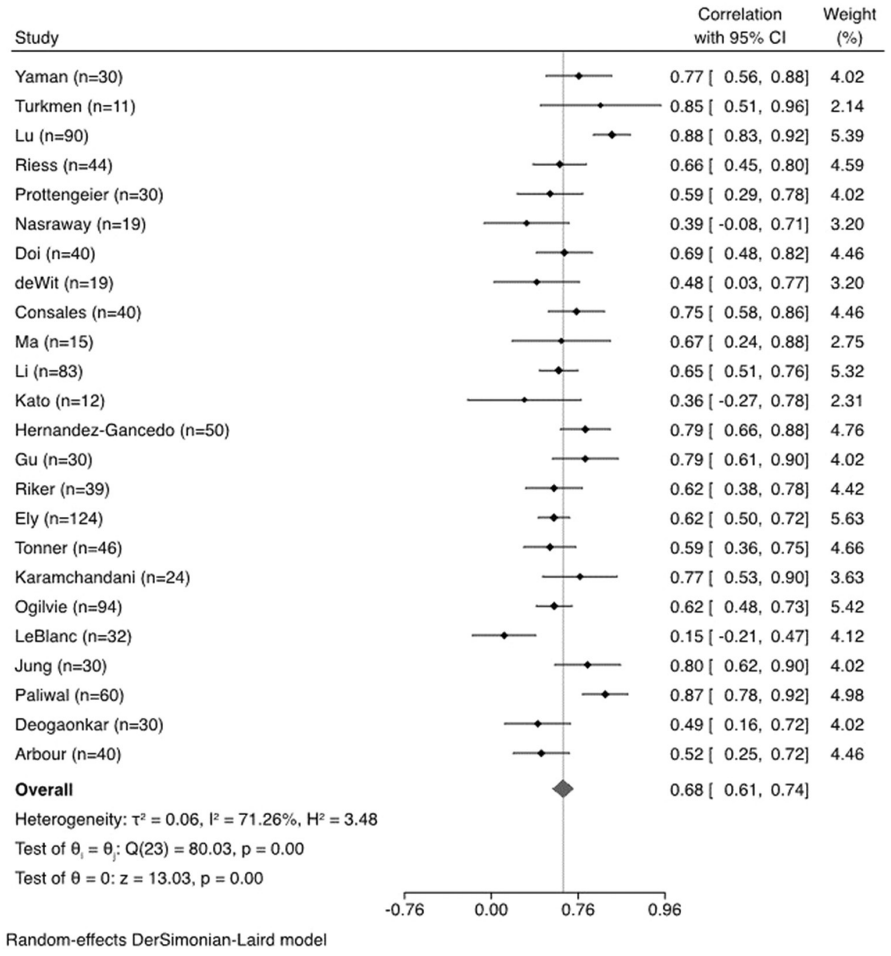

FIGURE 2 Meta-analysis and forest plot of overall correlation between bispectral index (BIS) and clinical sedation scales

BIS monitor or electrodes used, timing of clinical and BIS assessments, and monitoring of electromyogram input or signal-quality index to ensure the appropriateness of the BIS measurements, could explain some of the heterogeneity observed across studies. However, subgroup analyses based on these methodological factors did not explain substantial heterogeneity. Factors that were associated with significant heterogeneity included comparator clinical sedation scale, neurologic injury, and the type of ICU population.

Subgroup analysis across clinical scales showed the highest correlation between RSS and BIS (0.76), with lower values between BIS and SAS or BIS and RASS (0.53 and 0.66, respectively). This finding may be due in part to "ceiling effects" at higher levels of consciousness. BIS reaches a maximum value in patients who are awake.[10] Similarly, the RSS scale assigns the same score to all levels of consciousness above "alert and calm." Thus, both BIS and RSS have a ceiling at higher levels of consciousness (e.g., agitation), whereas RASS and SAS continue to differentiate increasing levels of agitation. Similarly, "floor effects" would be expected on the other end of the spectrum; in patients who are deeply sedated, clinical scales reach a minimum value at "unarousable." In contrast, BIS values can, at least theoretically, continue to differentiate lower levels of consciousness.[10] Although this potential non-linear association between BIS and clinical scales is plausible based on mechanistic grounds, subgroup analysis across "targeted depth of sedation" categories did not explain significant heterogeneity. This analysis is limited by the fact that most studies did not report on targeted level of sedation, and further, the targeted level might not reflect the achieved level of sedation at the time of BIS measurement. Although our analysis is not designed to show this, we postulate that a lack of correlation between BIS and clinical sedation scales may represent a potential advantage of BIS in the setting of lower levels of consciousness, which is particularly relevant for patients receiving NMBA. We propose this as an important area for future prospective evaluation, in a critically ill patient population receiving NMBA.

We also observed that the correlation between BIS and sedation scores was significantly lower in brain injury studies. Although the mechanism of this finding is unknown, it might suggest that the relationship between BIS and level of consciousness is altered by brain injury. Alternatively, lower correlation may reflect the difficulty of clinical assessment in patients with significant brain injury. Regardless of the mechanism, our data suggest caution with using BIS in the brain-injured population.

We undertook this evaluation to determine whether BIS could be an appropriate sedation assessment tool in critically ill adult patients treated with NMBA, when clinical sedation scales are impractical. The current standard in this group is to target deep sedation prior to the initiation of NMBA.[46] However, given the inability

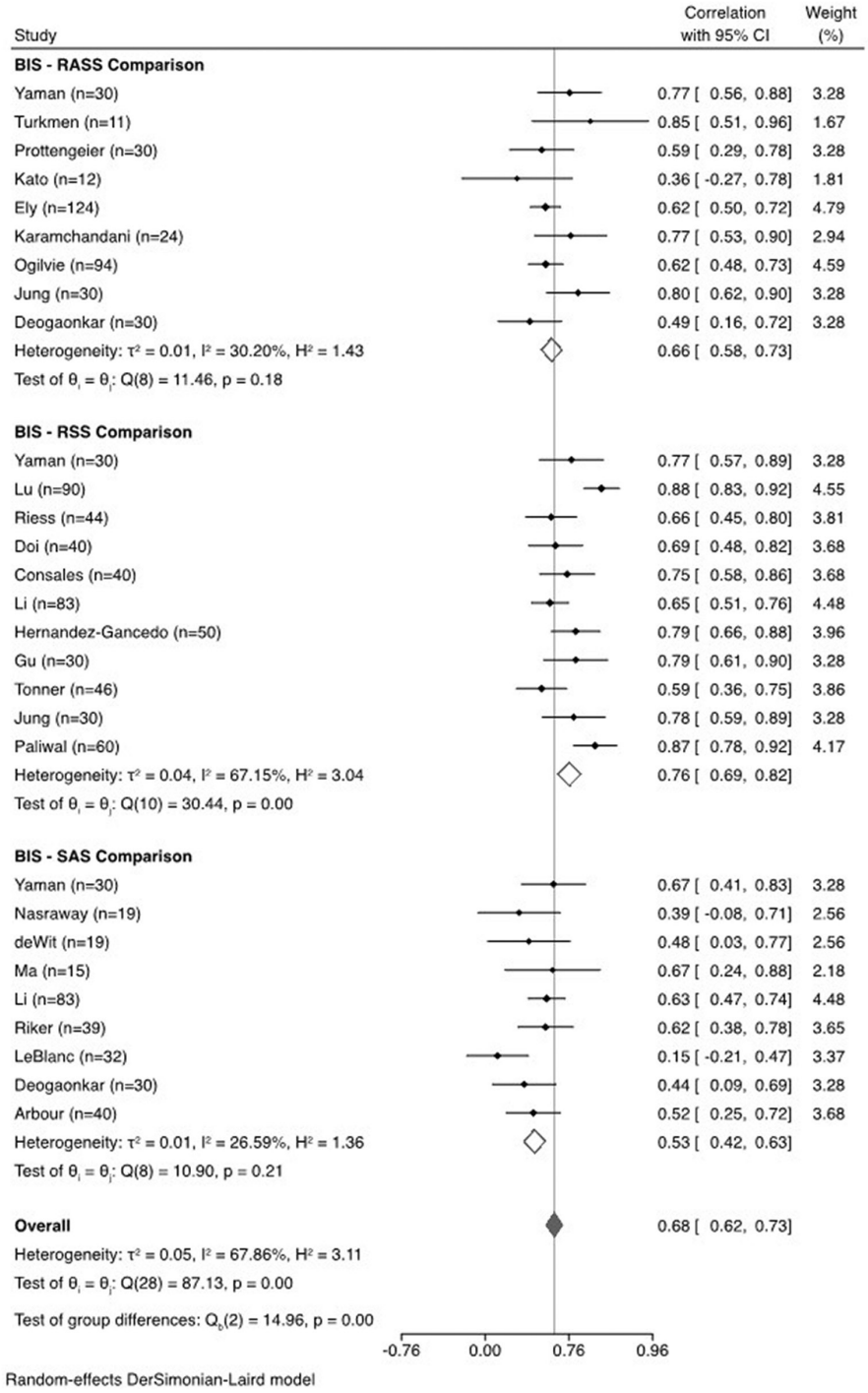

FIGURE 3 Subgroup meta-analysis and forest plot of correlation between bispectral index (BIS) and Richmond Agitation Sedation Scale (RASS), Ramsay Sedation Scale (RSS), or Sedation Agitation Scale (SAS)

to continually assess depth of sedation over time, this strategy creates an important risk of oversedation, which has been associated with worse outcomes. An evaluation of sedation strategies during neuromuscular blockade in ARDS found that a higher proportion of deep sedation mediated the harmful effects of NMBA infusions on mortality and ventilator- and ICU-free days.[9] A subsequent analysis of sedation strategies in mechanically ventilated patients with COVID-19 demonstrated that patients with COVID-19 have been more deeply sedated, with higher sedative doses, and for longer durations of time as compared with non-COVID-19 mechanically ventilated patients with ARDS. Mediation analysis in this study also showed a strong relationship between deep sedation and increased in-hospital mortality.[10] The inability to assess sedation depth also creates an important risk of undersedation. Although awareness with chemical paralysis has been reported with a rate of 0.1% in the operating room, this incidence may be as high as 3.4% in the emergency department or ICU.[47] Taken together, these data suggest that strategies for more accurate sedation titration could improve outcomes during paralysis. Based on the moderate correlation observed between BIS and clinical sedation scales in non-paralyzed patients, we hypothesize that BIS monitoring may provide meaningful information about level of consciousness that could improve sedation titration in patients receiving continuous NMBA.

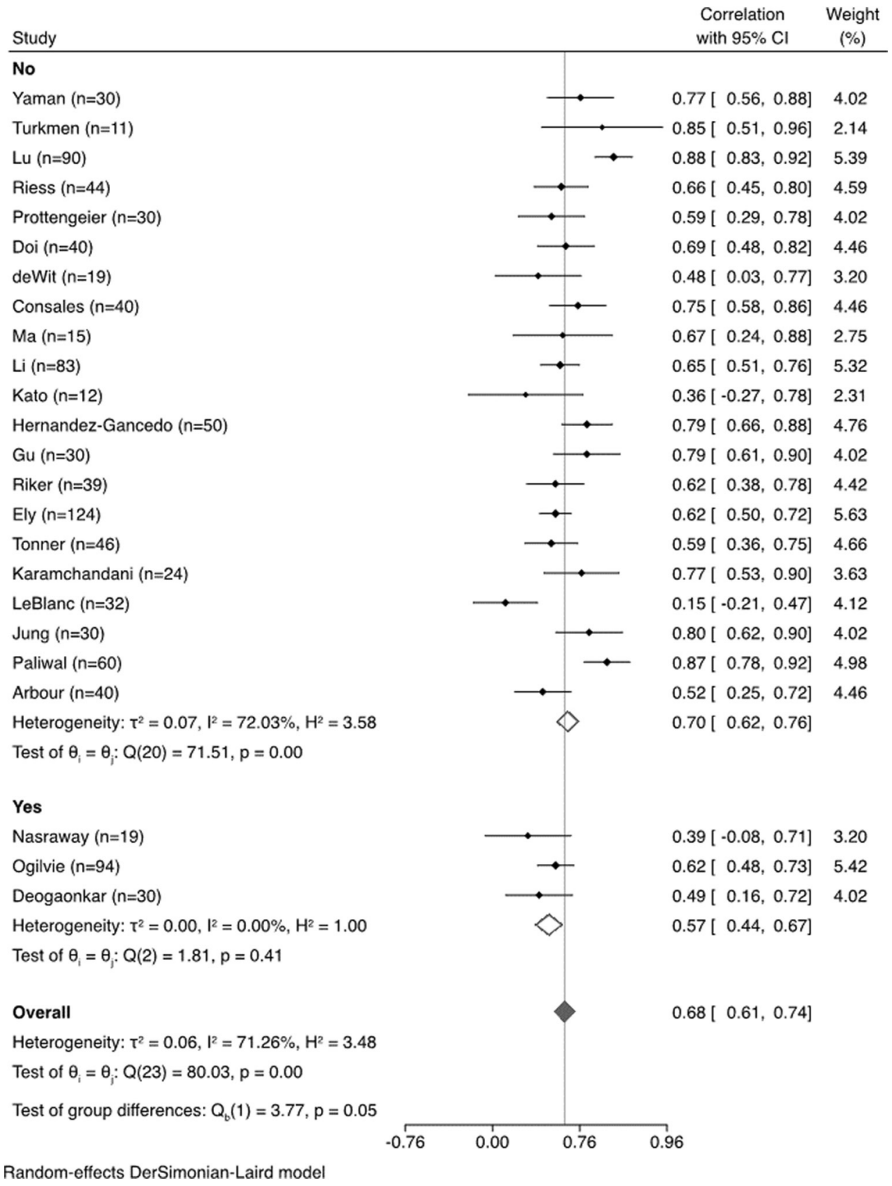

FIGURE 4 Subgroup meta-analysis and forest plot of correlation between bispectral index (BIS) and clinical sedation scales stratified by inclusion of patients with neurologic injury

Although our results provide preliminary evidence for the validity of BIS in the broad ICU population, important questions remain that limit routine use of this technology in paralyzed patients. In particular, the optimal target BIS range during NMBA treatment is unknown. A study in fully awake, healthy volunteers found that BIS values dropped significantly in some awake subjects after the initiation of NMBA. This suggests that NMBA may directly lower BIS measurements, potentially by reducing electromyographic activity.[48] Consequently, target BIS ranges must be developed that account for this direct lowering effect in order to avoid inappropriate down-titration of sedation.[49] Alternatively, sedation algorithms that incorporate BIS monitoring might specify minimum sedative infusion rates below which patients are not titrated during chemical paralysis, even if BIS values are numerically below goal range for deep sedation.

Our analysis was restricted to studies of non-paralyzed patients. Such a restriction was unavoidable, as application of the clinical scales requires assessment of patient movement. Consequently, extrapolation of these results to paralyzed patients should be done with caution, and we consider our findings to be hypothesis-generating. Future studies that directly examine BIS validity during NMBA administration are needed. A possible approach to this would be longitudinal concurrent assessments of BIS and clinical sedation scales during transition periods around NMBA administration. Additionally, studies that directly examine the association between BIS monitoring and clinical outcomes are needed. One study comparing BIS to clinical sedation found no difference in median daily sedation or analgesia exposure in patients receiving NMBA in the ICU; a more robust, prospective evaluation is needed.[50] A systematic review and meta-analysis of BIS monitoring for sedation in critically ill mechanically ventilated adults on clinical outcomes or resource utilization found insufficient evidence on the effects of BIS due to uncertainty of the findings from low- and very low-quality evidence.[51] Lastly, additional research is needed to determine whether a strategy of NMBA holidays and clinical sedation assessment for titration of sedatives versus continuous titration using BIS would have better outcomes, given the considerations we have discussed.

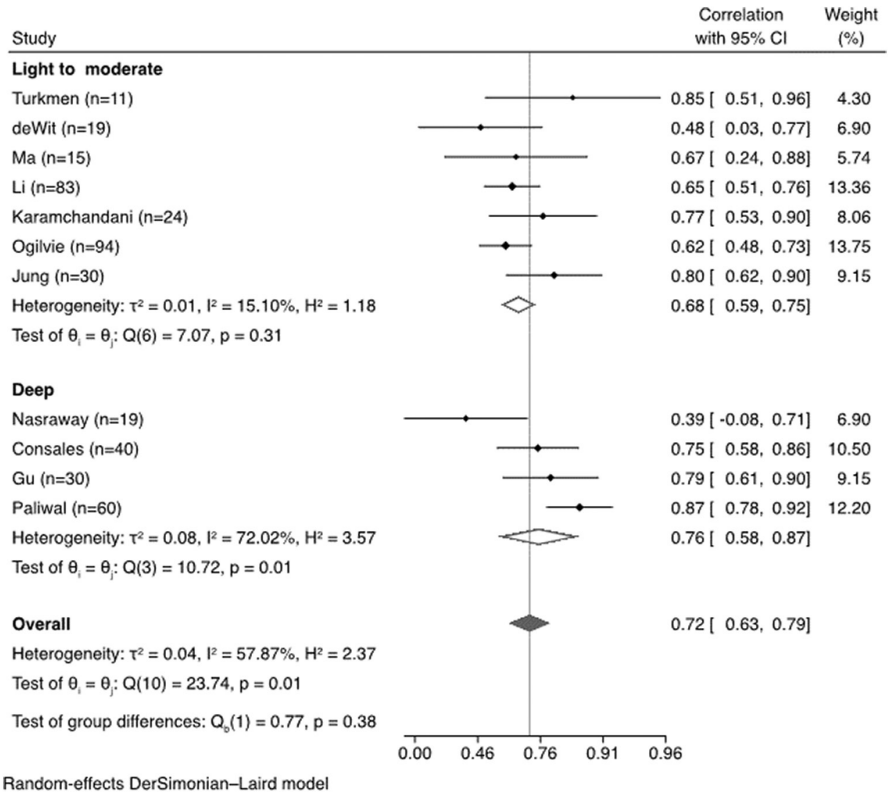

FIGURE 5 Subgroup meta-analysis and forest plot of correlation between bispectral index (BIS) and clinical sedation scales stratified by depth of sedation

TABLE 1 Risk of bias assessment

	Risk of bias				Applicability concerns		
Study	Patient selection	Index tests	Reference standard	Flow and timing	Patient selection	Index tests	Reference standard
Riker, 2001	High	High	Low	Low	Low	Low	Low
Nasraway, 2002	High	Low	Low	Low	Low	Low	Low
Riess, 2002	Low	Low	Low	Low	Low	Low	Low
deWit, 2003	Low	Low	Low	Low	Low	Low	Low
Deogaonkar, 2004	Low	Low	Low	Low	High	Low	Low
Ely, 2004	Low	Low	Low	Low	Low	Low	Low
Doi, 2005	Low	High	Unclear	Low	High	Low	Low
Tonner, 2005	Unclear	High	Low	Low	Low	Low	Low
Consales, 2006	Low	Low	Unclear	Low	Low	Low	Low
Ma, 2006	Low	Unclear	Unclear	Low	Low	Low	Low
Turkmen, 2006	High	Unclear	Unclear	Unclear	Low	High	Low
Gu, 2007	Low	Low	Low	Low	Low	Low	Low
Hernandez-Gancedo, 2007	Low	Low	Low	Low	Low	Low	Low
Lu, 2008	Low	High	Low	Low	Low	High	Low
Arbour, 2009	Unclear	High	Low	Low	Low	Low	Low
Li, 2009	Low	High	Unclear	Low	Low	Low	Low
Karamchandani, 2010	Low	Low	Low	Low	Low	Low	Low
Ogilvie, 2011	Low	High	Low	Low	High	High	Low
Jung, 2012	Low	Low	Low	Low	Low	Low	Low
Kato, 2012	Low	High	High	Low	Low	High	Low
LeBlanc, 2012	Low	Low	Low	Low	Low	Low	Low
Yaman, 2012	Low	High	Low	Unclear	Low	Low	Low
Prottengeier, 2014	Unclear	Low	Low	Unclear	Low	Low	Low
Paliwal, 2015	Low	Low	Low	Low	Low	High	Low

5 | CONCLUSIONS

Our results suggest that BIS has moderate to strong correlations with clinical sedation scales in adult ICU patients, providing preliminary evidence for the validity of BIS as a measure of sedation intensity when clinical scales cannot be used. However, mapping specific BIS values to validated clinical sedation scales is hindered by heterogeneity across studies, and potential ceiling effects at the extremes of consciousness. This makes implementation of BIS at the bedside challenging. Although our findings represent an important step toward defining a role for BIS monitoring during paralysis, additional research is required to use BIS safely during NMBA treatment. Prospective studies that directly examine the association between BIS scores and clinical outcomes are needed to identify optimal BIS ranges that could be applied in routine practice in patients receiving NMBA. Additionally, future research should evaluate the utility of BIS for titration of sedatives versus paralytic holidays and intermittent clinical assessment in patients undergoing neuromuscular blockade.

AUTHOR CONTRIBUTIONS

All authors had full access to study data and contributed substantially to study design, data collection and interpretation, and writing of the manuscript.

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None.

CONFLICT OF INTEREST

D.D.L. is employed by Philips North America but was employed at Manchester University College of Pharmacywhile this work was being conducted. M.S.H., E.F.G., S.Y.A.Y., and T.A.M. have no relevant relationships and activities to disclose.

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