

Clinical Research Article

Pain assessment using the Analgesia Nociception Index in patients undergoing sedation: a systematic review and meta-analysis

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ABSTRACT

Background: This systematic review and meta-analysis analyzed the utility of the Analgesia Nociception Index (ANI) in detecting intraoperative and procedural pain in sedated patients.

Methods: A comprehensive search of the Cochrane Central Register of Controlled Trials, Ovid-MEDLINE, Ovid-Embase, and Google Scholar databases was performed to identify relevant studies. The primary outcome was the diagnostic accuracy of ANI, assessed by pooled sensitivity, specificity, likelihood ratios, and diagnostic odds ratio (DOR). Secondary outcomes were the correlation between ANI and pain assessment scales, the effect of norepinephrine (NE) on ANI, and differences in opioid consumption between the ANI-guided and control groups.

Results: Eleven studies were included in the systematic review, with ten studies incorporated into the meta-analysis. ANI demonstrated moderate sensitivity (0.746, 95% confidence interval [CI] = 0.683–0.803) and specificity (0.776, 95% CI = 0.741–0.808) for detecting intraoperative and procedural pain, with a pooled DOR of 10.491. ANI was lower in the pain state than that in the no-pain state (standardized mean difference [SMD] = –1.140, 95% CI = –1.239 to –1.041, I^2 = 93.63%). ANI-guided analgesia was associated with a significant reduction in opioid consumption (SMD = –0.410, 95% CI = –0.643 to –0.178, I^2 = 0.0%). There were no significant differences in ANI between the NE and control groups. ANI showed a negative correlation with pain scales (r = –0.110 to –0.470).

Conclusions: ANI effectively differentiated between the pain and non-pain states in sedated patients with moderate diagnostic accuracy and helped reduce opioid consumption. However, the high heterogeneity suggests the need for cautious interpretation.

Keywords: Analgesia; Analgesics, Opioid; Conscious Sedation; Meta-Analysis; Monitoring, Physiologic; Nociception; Pain Measurement.

Received March 14, 2025; Revised May 23, 2025; Accepted May 25, 2025

Handling Editor: Hojin Lee

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INTRODUCTION

Sedation encompasses a continuum of states, ranging from minimal sedation, where patients retain some level of consciousness and responsiveness, to deep sedation [1]. Unlike general anesthesia, sedation requires careful titration to prevent complications. Inadequate sedation can cause discomfort and movement, while excessive sedation leads respiratory depression, hemodynamic instability, and delayed recovery [2,3]. Even when appearing adequately sedated, patients may still experience pain or distress, highlighting the complexity of defining “adequate sedation” [4,5]. These challenges are heightened during procedures, where sedation depth varies with nociceptive stimuli. Thus, continuous monitoring is crucial to maintain effective analgesia and ensure patient safety.

In sedated patients, the assessment of nociception, the neural process of encoding and processing noxious stimuli, offers an alternative approach for assessing pain intensity. Various methods have been developed to evaluate nociception, including pupillometry, skin conductance, and heart rate variability. Among these methods, the Analgesia Nociception Index (ANI), derived from heart rate variability, reflects the balance between sympathetic and parasympathetic activity. ANI was originally developed to evaluate pain intensity in patients under general anesthesia [6]; however, it has emerged as a useful tool for awake and sedated patients owing to its noninvasive nature and ease of application [7,8].

Several studies have explored the accuracy and reliability of ANI in various clinical contexts. ANI has demonstrated a good correlation with Numeric Rating Scale (NRS) scores in assessing the severity of postoperative pain, suggesting its validity as a surrogate marker of pain [9,10]. A previous meta-analysis reported that ANI monitoring in patients undergoing surgery with general anesthesia serves as a valuable tool for predicting intra- and postoperative pain, reducing the need for intraoperative opioids and enhancing perioperative pain management [11]. However, debate exists regarding the application of ANI in conscious patients, as previous studies have shown weaker correlations between ANI values and self-reported pain levels in this population. [12,13]

This discrepancy raises critical questions regarding the applicability of ANI in sedated patients who represent a unique population with characteristics that lie between fully anesthetized and fully conscious states. Sedated patients often require pain assessment to optimize analgesic management while minimizing over-sedation and

its associated risks. The current literature lacks a comprehensive synthesis of evidence regarding the utility of ANI in this specific condition.

Furthermore, autonomic tone in sedated patients can be influenced by pharmacologic agents and underlying pathophysiology, potentially confounding ANI interpretation. Norepinephrine (NE), a commonly administered sympathomimetic agent, may suppress parasympathetic activity, leading to decreased ANI values independent of nociceptive input [14-16]. Similarly, altered autonomic function in conditions such as severe sepsis has been associated with paradoxical increases in parasympathetic tone and changes in heart rate variability [14-16]. These factors emphasize the importance of evaluating how such clinical contexts impact ANI measurements in sedated patients.

This comprehensive review and meta-analysis aimed to assess the effectiveness of ANI in evaluating nociception in sedated patients. By synthesizing the available evidence, we sought to clarify the accuracy and clinical utility of ANI in this population.

MATERIALS AND METHODS

1. Methodology and registration

The protocol for this comprehensive review and meta-analysis was developed according to the preferred reporting requirements for systematic reviews and meta-analysis protocols (PRISMA-P) statements [17]. It was drafted and registered with the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42024570820; July 31, 2024) and can be accessed at <https://www.crd.york.ac.uk/PROSPERO/view/CRD42024570820>. This study adhered to the methodological recommendations set forth by the Cochrane Collaboration [18] and followed the reporting standards outlined in the PRISMA statement [19] and the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines [20].

2. Eligibility criteria

The research questions and inclusion and exclusion criteria were established prior to conducting this systematic review and meta-analysis. We included published randomized controlled trials (RCTs), as well as observational studies, including cohort, cross-sectional, and case-control studies and case series that addressed the three study

research questions.

The participants, intervention, comparison, outcomes, and study design (PICO-SD) was used to define the research questions:

Primary outcome Research Question: Is ANI monitoring effective in identifying intraoperative or procedural pain in sedated patients?

- Participants (P): sedated patients undergoing a surgery or procedure
- Intervention (I): ANI monitoring
- Comparison (C): not applicable (NA)
- Outcome measurements (O): diagnostic accuracy of intraoperative or procedural pain assessed by sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR-), diagnostic odds ratio (DOR), and area under the curve (AUC)
- Study design (SD): RCTs, cohort, cross-sectional, case-control studies, and case series

3. Secondary outcomes

Research Question 1: Does the ANI score differ between pain and no-pain states in sedated patients?

- Participants (P): sedated patients undergoing a surgery or procedure
- Intervention (I): pain state
- Comparison (C): no-pain state
- Outcome measurements (O): difference in ANI scores
- Study design (SD): RCTs, cohort, cross-sectional, case-control studies, and case series

Research Question 2: Does NE administration affect ANI monitoring scores in sedated patients?

- Participants (P): patients receiving surgery under sedation
- Intervention (I): administration of NE
- Comparison (C): no administration of NE
- Outcome measurements (O): ANI monitoring score (ANI instantaneous [ANII] and ANI mean [ANIm])
- Study design (SD): RCTs, cohort, cross-sectional, case-control studies, and case series

Research Question 3: Is there a correlation between ANI values recorded during surgery or procedures in sedated patients and other pain assessment scales (NRS, Visual Analogue Scale [VAS], Face, Legs, Activity, Cry, Consolability [FLACC] scale, and Behavioral Pain Scale [BPS])?

- Participants (P): sedated patients undergoing a surgery or procedure
- Intervention (I): intraoperative or procedural ANI value

- Comparison (C): other pain score (NRS, VAS, FLACC scale, and BPS)
- Outcome measurements (O): correlation
- Study design (SD): RCTs, cohort, cross-sectional, case-control studies, and case series

Research Question 4: Does ANI-guided analgesia reduce opioid consumption in sedated patients?

- Participants (P): sedated patients undergoing a surgery or procedure
- Intervention (I): ANI guided analgesia
- Comparison (C): standard analgesia (non-ANI guided)
- Outcome measurements (O): total intraoperative or procedural opioid consumption
- Study design (SD): RCTs, cohort, cross-sectional, case-control studies, and case series

The following studies were excluded from the analysis:

- Review articles, case reports, letters to the editor, and conference abstracts, as well as animal, pre-clinical, and all other non-relevant studies
- Studies with missing outcome measures of interest

No language restrictions were applied in this study.

4. Search process and data acquisition

The search for relevant studies was conducted independently by two investigators using Ovid-MEDLINE, Ovid-Embase, the Cochrane Central Register of Controlled Trials, and Google Scholar from the inception of these databases until July 2024. The search strategy was developed in collaboration with a medical librarian and incorporated a combination of free-text terms, medical subject headings, and EMTREE terms related to "Analgesia Nociception Index," "ANI monitor," and "sedation." To ensure comprehensive coverage, the authors also searched ClinicalTrials.gov (<https://clinicaltrials.gov/>, accessed on July 31, 2024) and the Clinical Research Information Service (<https://cris.nih.go.kr/>, accessed on July 31, 2024) for ongoing or unpublished clinical trials. Furthermore, gray literature was reviewed using OpenSIGLE. The reference lists of all included studies were manually examined to identify any additional relevant publications. All retrieved references were organized using Endnote software (version 9.3.3; Thomson Reuters).

Study selection was independently performed by two investigators, who first screened the titles and abstracts. To avoid duplication, studies with overlapping authors, institutions, or countries were cross-checked and excluded when necessary. If a study appeared eligible, the full text was retrieved for further evaluation. Discrepancies

were resolved through discussion, with a third investigator making the final decision if needed. Kappa statistics were used to assess inter-rater agreement, categorized as follows: < 0 (less than chance agreement), 0.01–0.20 (slight), 0.21–0.40 (fair), 0.41–0.60 (moderate), 0.61–0.80 (substantial), and 0.81–0.99 (almost perfect) [21].

Data extraction was performed using a predefined form that included key study details (e.g., study title, first author, journal name, publication year, country, language, sample size, eligibility criteria, study registration, and primary/secondary outcomes). If data were reported as median [P_{25} – P_{75}], median (range), or mean (standard error), they were converted into mean and standard deviation following established methods [21–23]. In cases where necessary data were unavailable, the authors were contacted for clarification. If unresolved, missing values were estimated from the available information. The extracted data were cross-checked for accuracy, and discrepancies were resolved by a third investigator.

5. Quality evaluation of included studies

Study quality was assessed using tools specific to the study design [24]. RCTs were evaluated using the Revised Cochrane Risk of Bias Tool (RoB 2.0) [25]; non-randomized studies, using the Risk of Bias Assessment Tool (RoBANS) [26]; and diagnostic accuracy studies, using the Quality of Diagnostic Accuracy Studies (QUADAS)-2 tool [27]. Any disagreements were resolved through discussion with a third investigator.

6. Statistical analysis

Ad hoc tables were created to summarize the key characteristics of the included studies and highlight key characteristics and essential questions relevant to this review. If data could be combined, a meta-analysis was conducted; otherwise, a systematic review was performed when synthesis was not possible owing to unsuitable or insufficient data.

To evaluate diagnostic performance, values for true positives, false positives, false negatives, and true negatives were extracted from the studies. When these values were not explicitly reported, they were calculated from the available data whenever possible. Pooled sensitivity, specificity, LR+, LR–, combined AUC value with corresponding 95% confidence intervals (CIs), and pooled DOR were determined using the DerSimonian–Laird random-effect model [28].

LR+ was calculated as sensitivity divided by (1–speci-

ficity), while LR– was determined as (1–sensitivity) divided by specificity. The DOR was computed as the ratio of the odds of a positive test result in diseased individuals to that in non-diseased individuals, with higher values indicating better diagnostic performance. A DOR value of 1 suggests no discrimination between diseased and non-diseased states [29].

Summary receiver operating characteristic curves were plotted using proportional hazards and bivariate models to estimate the AUC of accuracy. An AUC value closer to 1 indicated better diagnostic accuracy [30].

The standardized mean difference (SMD) and 95% CIs were used to compare groups.

Heterogeneity among studies was assessed using I^2 , τ , and the 95% predictive interval. Sensitivity analyses were conducted by sequentially removing individual studies to assess their impact on the overall results.

For studies reporting the correlation between ANI and pain assessment scales, correlation coefficients (r) and corresponding P values were extracted and summarized in a table.

Subgroup analysis was performed based on whether ANI monitoring was conducted in critically ill patients requiring sedation or non-critically ill patients undergoing sedation for needing surgery or procedure.

The meta-analysis was performed using Comprehensive Meta-Analysis software version 2.0 (Biostat Inc.), Meta-DiSc version 1.4 (Unit of Clinical Biostatistics, the Ramón y Cajal Hospital), and meta package (version 0.5.11) in R version 4.4.2 (R Foundation for Statistical Computing).

7. Assessment of evidence quality

Evidence quality was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) systems for intervention [31] or for diagnostic tests and strategies [32]. Two investigators independently conducted this assessment following a structured approach that included evaluating evidence quality, analyzing the risk-benefit balance, and determining the strength of recommendations. Any disagreements were resolved through discussion with a third investigator.

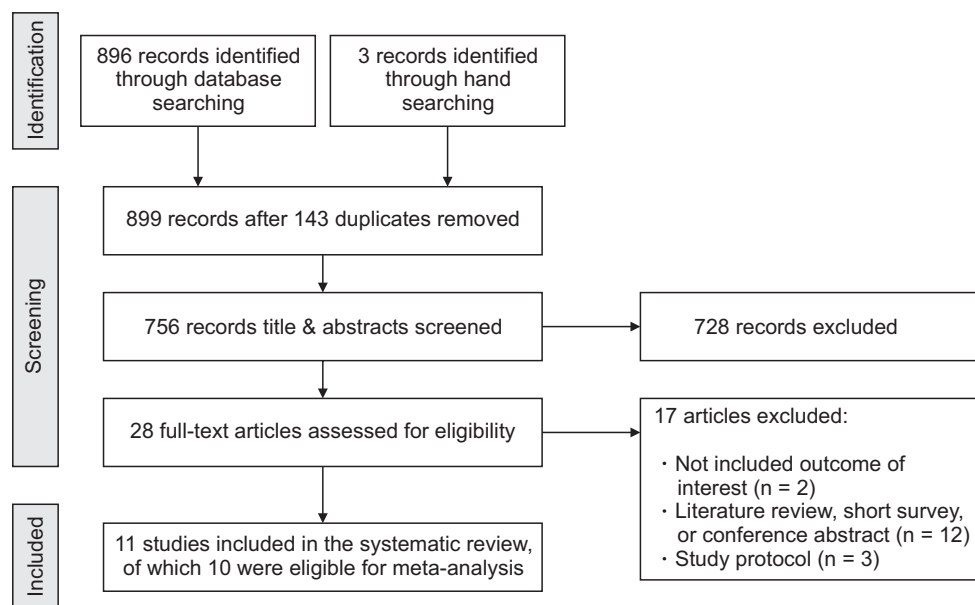


Fig. 1. PRISMA flowchart of included and excluded trials.

RESULTS

1. Study selection

A comprehensive search, including manual searches, identified 899 articles (896 from databases and 3 through manual searching) up to July 2024. After excluding 143 duplicates, 756 articles were screened. During the title and abstract review, 728 articles were excluded, with an inter-rater agreement kappa value of 0.895. Subsequently, 28 full-text articles were evaluated for eligibility, and 17 articles were removed for the following reasons: two did not align with the outcome of interest, one was a literature review, one was a brief survey, 10 were conference abstracts, and 3 were study protocols, with the kappa value during this phase reaching 0.922 (**Supplementary Material 1**). Ultimately, 11 studies met the inclusion criteria. Among these, one study was deemed unsuitable for data synthesis [33], resulting in ten studies being included in the meta-analysis (**Fig. 1**) [3,8,14,16,34-39].

2. Study characteristics

Table 1 presents an overview of the characteristics of the 11 included studies. Nine were prospective observational studies [3,8,14,16,34-38], one was a RCT [39] and one [33] was a secondary outcome analysis of an RCT [40].

3. Quality of included studies

Supplementary Tables 1, 2, and 3 show the risk of bias assessment for the studies evaluated using three different tools: QUADAS-2, RoBANS, and RoB 2.0. In QUADAS-2, nine studies showed low risk in patient selection, reference standards, and flow/timing, except in the index test domain. RoBANS indicated variability in participant selection and confounding variable control, with blinding practices being inconsistent, while intervention measurement and reporting were generally low risk. For RoB 2.0, two studies were classified as having concerns. As fewer than 10 studies were included, publication bias was not evaluated.

4. Prediction of intraoperative and procedural pain

Seven studies evaluated the ability of ANI monitoring to accurately reflect pain levels in sedated patients [3,16,34-38], and two studies assessed the accuracy of ANI monitoring in reflecting pain during sedation by analyzing both ANIi and ANIm [36,38]. For predicting painful intraoperative or procedural stimuli, the pooled sensitivity and specificity were 0.746 (95% CI = 0.683–0.803, $I^2 = 46.2\%$, $P_{\text{chi}^2} = 0.062$) and 0.776 (95% CI = 0.741–0.808, $I^2 = 91.2\%$, $P_{\text{chi}^2} < 0.001$), respectively (**Fig. 2**). The pooled LR+ and LR– were 3.349 (95% CI = 2.099–5.345, $I^2 = 81.9\%$, $P_{\text{chi}^2} < 0.001$) and 0.384 (95% CI = 0.277–0.532, $I^2 = 44.0\%$, $P_{\text{chi}^2} = 0.075$), respectively (**Fig. 3**). DOR was 10.491 (95% CI =

Table 1. Characteristics of included studies

Author (year)	Study design	Characteristics of participant (n)	Noxious stimuli	Pain assessment	Study objective
Aragón-Benedí et al. [3] (2022)	Multicenter prospective cohort study	Critically ill patients with COVID-19 (n = 112)	N/A	N/A	Predict severity and 30-day mortality of critically ill patients COVID-19 have greater autonomic nervous system dysregulation by assessing ANI
Avez-Couturier et al. [8] (2016)	Prospective observational study (pilot study)	Children undergoing muscle biopsy conducted under analgesia and light sedation (n = 26)	Muscle biopsy	FLACC	1 st : effectiveness of ANI in detecting pain 2 nd : correlation between ANI and FLACC Feasibility of ANI across age
Brouqsault-Dédrie et al. [14] (2016)	Prospective observational study	Critically ill patients receiving invasive mechanical ventilation and deep sedation (n = 41)	Turning	BPS	1 st : effectiveness of ANI in detecting pain 2 nd : impact of NE on the effectiveness of ANI in detecting pain Correlation between ANI and BPS
Jendoubi et al. [16] (2017)	Prospective observational study	Ventilated and deeply sedated TBI patients (n = 21) 100 measurements	Tracheal suction	BPS	1 st : effectiveness of ANI in detecting pain 2 nd : impact of NE of ANI Correlation between ANI and BPS
Baroni et al. [33] (2023)	Secondary outcome analysis of RCT (Sado-Filho et al. [40], 2021)	Children undergoing minimally invasive dental treatment (n = 31)	Dental procedure	FLACC	Association between children's pain/distress levels and patient characteristics, sedation type, nociception and pain intensity reported by the parents in sedated children undergoing minimally invasive dental treatment
Aragón-Benedí et al. [34] (2021)	A single-center, prospective, observational pilot study	Critically ill patients with COVID-19 (n = 14)	N/A	N/A	Assess predictive value of ANI in terms of severity and mortality in critically ill patients suffering from COVID-19
Boselli et al. [35] (2015)	Prospective observational study	Patients undergoing suspension laryngoscopy using TIVA (n = 50)	Suspension laryngoscopy	Hemodynamic reactivity ^a	Performance of ANI to predict hemodynamic reactivity
Chanques et al. [36] (2017)	Prospective observational study	Critically ill non-comatose and non-communicative patients (n = 110) 969 measurements	Catheter dressing Turning Tracheal suction	BPS	1 st : ANI performance to detect pain define as a BPS ≥ 5 2 nd : variables associated with ANI
Papaioannou et al. [37] (2016)	Prospective observational study	Burnt patients (n = 20)	Dressing changes [†] procedures	NRS	Assess predictive value of real time changes of ANI for pain
Belyakov et al. [38] (2024)	Prospective observational study	Patients with sinus rhythm and elective catheter ablation (n = 188)	Catheter ablation	NRS	Evaluate the effectiveness of ANI for patients with sinus rhythm and short-term induced (< 1 minute) atrial arrhythmia
Soral et al. [39] (2020)	RCT	Patients undergoing colonoscopy with sedo-analgesia (n = 102)	Colonoscopy	NRS	Compare the effects of analgesia management with conventional methods and with ANI monitoring on total opioid consumption, sedation and analgesia levels in patients who underwent colonoscopy using sedo-analgesia

N/A: not assessed, ANI: Analgesia Nociception Index, FLACC: Face, Legs, Activity, Cry, Consolability, BPS: Behavioral Pain Scale, NE: norepinephrine, TBI: traumatic brain injury, RCT: randomized controlled trial, TIVA: total intravenous anesthesia, NRS: Numeric Rating Scale.

^aHemodynamic reactivity was defined as an increase by more than 20% of heart rate and/or systolic blood pressure within 5 minutes.

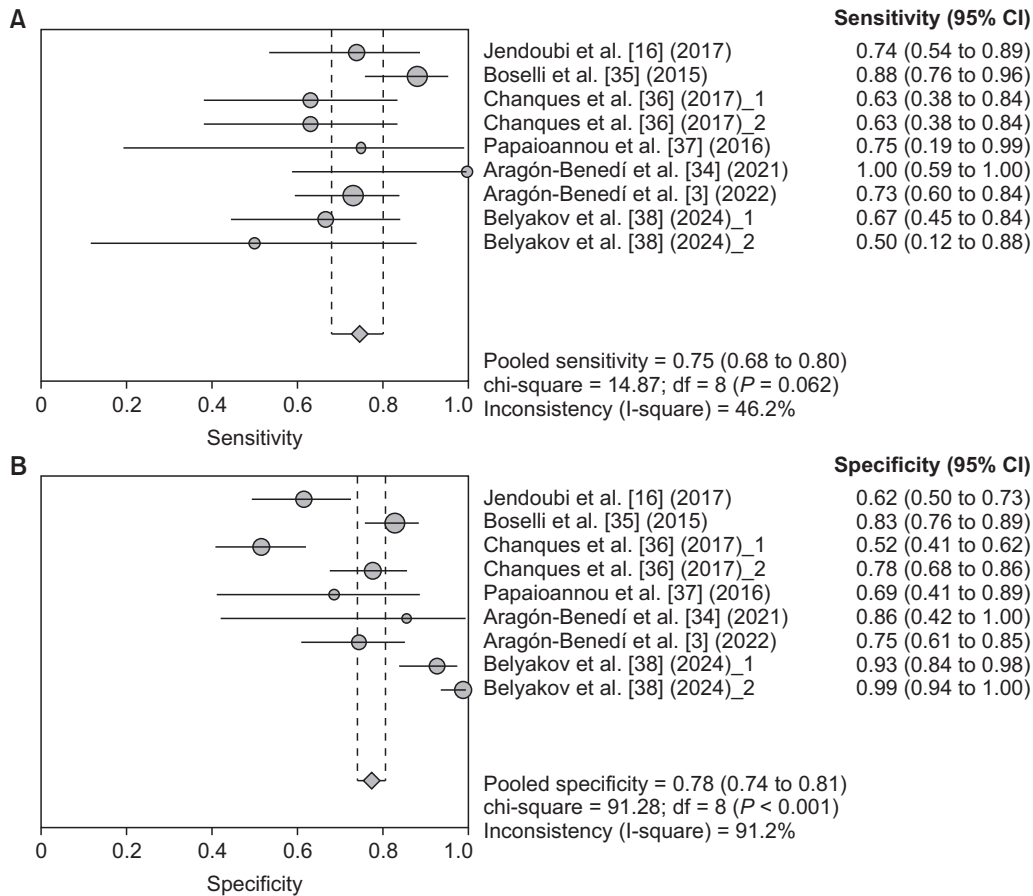


Fig. 2. Forest plot of (A) sensitivity and (B) specificity in predicting intra-operative and procedural pain. Circles represent individual study estimates, with the size of each circle corresponding to the weight of the respective study in the meta-analysis. Horizontal lines denote the 95% confidence intervals (CIs) for each estimate. The pooled estimate is represented as a diamond shape, summarizing the overall sensitivity and specificity.

4.726–23.290, $I^2 = 70.8\%$, $P_{\text{chi}^2} = 0.001$) (**Fig. 4**).

When subgroup analysis was performed, the pooled sensitivity and specificity were 0.788 (95% CI = 0.686–0.869, $I^2 = 59.8\%$, $P_{\text{chi}^2} = 0.059$) and 0.888 (95% CI = 0.849–0.920, $I^2 = 87.8\%$, $P_{\text{chi}^2} < 0.001$) in non-critically ill patients, and 0.719 (95% CI = 0.632–0.795, $I^2 = 34.3\%$, $P_{\text{chi}^2} = 0.192$) and 0.661 (95% CI = 0.606–0.713, $I^2 = 77.5\%$, $P_{\text{chi}^2} = 0.001$) in critically ill patients (**Supplementary Fig. 1**). The pooled LR+ and LR- were 6.101 (95% CI = 2.914–12.772, $I^2 = 64.8\%$, $P_{\text{chi}^2} = 0.036$) and 0.303 (95% CI = 0.161–0.572, $I^2 = 56.0\%$, $P_{\text{chi}^2} = 0.078$) in non-critically ill patients, 2.186 (95% CI = 1.511–3.164, $I^2 = 61.3\%$, $P_{\text{chi}^2} = 0.035$) and 0.448 (95% CI = 0.326–0.618, $I^2 = 16.4\%$, $P_{\text{chi}^2} = 0.310$) in critically ill patients (**Supplementary Fig. 2**). DOR was 30.739 (95% CI = 15.313–61.705, $I^2 = 0.0\%$, $P_{\text{chi}^2} = 0.507$) in non-critically ill patients and 5.074 (95% CI = 2.560–10.058, $I^2 = 45.1\%$, $P_{\text{chi}^2} = 0.121$) in critically ill patients (**Supplementary Fig. 3**).

The AUCs of ANI in predicting painful intraoperative or procedural stimuli when using proportional hazards and bivariate models were 0.855 (95% CI = 0.794–0.926, $P_{\text{chi}^2} = 0.199$) and 0.779 ($I^2 = 17.6\%$), respectively (**Supplementary Fig. 4**).

The results of the sensitivity analysis conducted by sequentially excluding one study at a time are provided in the supplementary materials (**Supplementary Table 4**).

When subgroup analysis was performed, the AUCs of ANI in predicting painful intraoperative or procedural stimuli when using proportional hazards and bivariate models were 0.876 (95% CI = 0.767–1.021, $P_{\text{chi}^2} = 0.199$) and 0.876 ($I^2 = 0.0\%$) in non-critically ill patients, and 0.722 (95% CI = 0.624–0.855, $P_{\text{chi}^2} = 0.117$) and 0.876 ($I^2 = 0.0\%$) in critically ill patients (**Supplementary Fig. 5**).

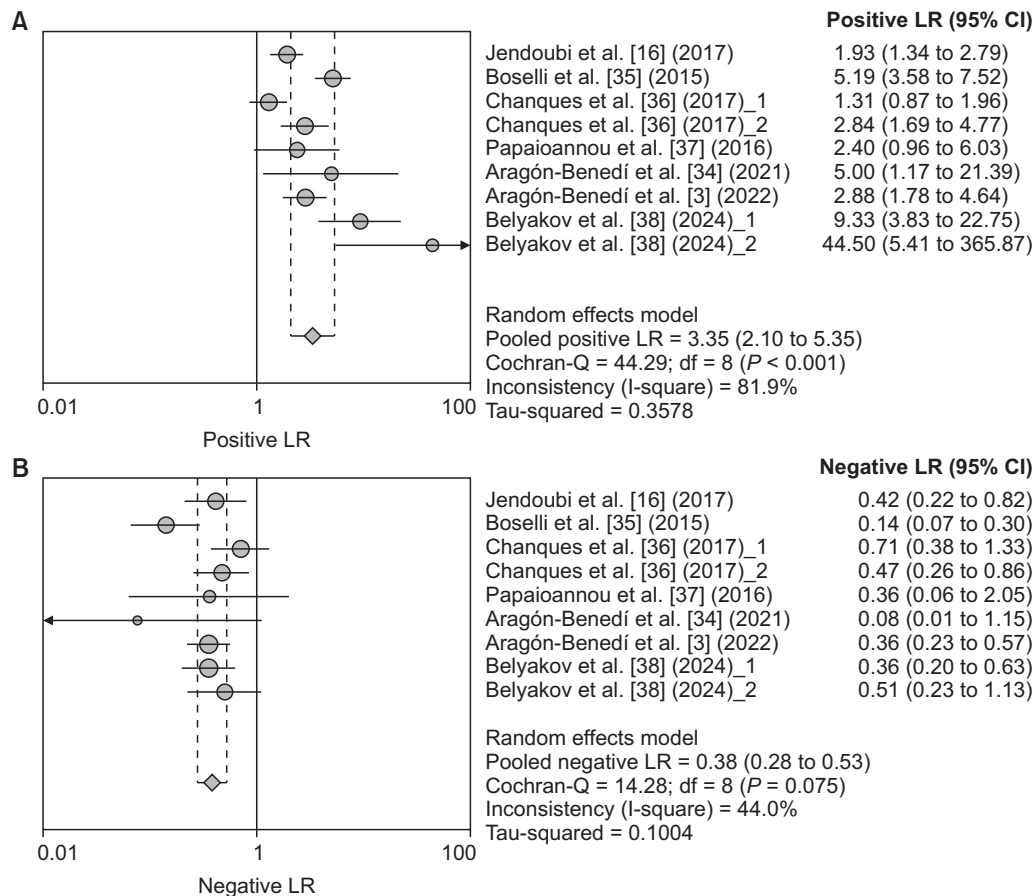


Fig. 3. Forest plot of (A) positive LR and (B) negative LR in predicting intra-operative and procedural pain. Circles represent individual study estimates, with the size of each circle corresponding to the weight of the respective study in the meta-analysis. Horizontal lines denote the 95% confidence intervals (CIs) for each estimate. The pooled estimate is represented as a diamond shape, summarizing the overall positive LR and negative LR. LR: likelihood ratio.

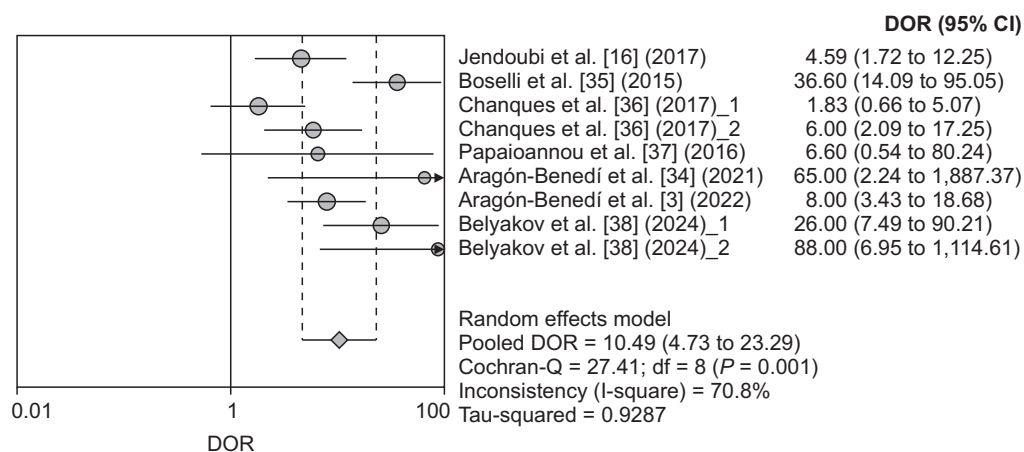


Fig. 4. Forest plot of DOR in predicting intra-operative and procedural pain. Circles represent individual study estimates, with the size of each circle corresponding to the weight of the respective study in the meta-analysis. Horizontal lines denote the 95% confidence intervals (CIs) for each estimate. The pooled estimate is represented as a diamond shape, summarizing the overall DOR. DOR: diagnostic odds ratio.

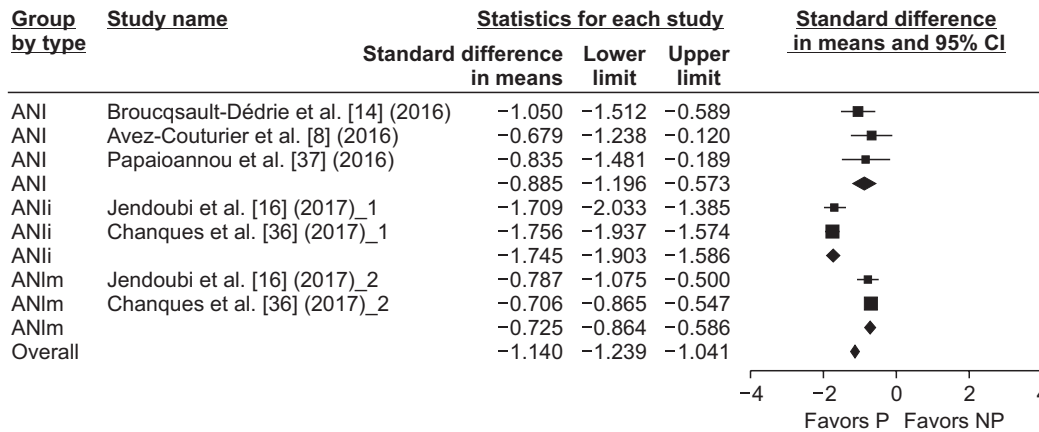


Fig. 5. Forest plot of ANI score compared between P and NP. Squares represent individual study estimates, with the size of each square corresponding to the weight of the respective study in the meta-analysis. Horizontal lines denote the 95% confidence intervals (CIs) for each estimate. The pooled estimate is represented as a diamond shape, summarizing the overall ANI scores. ANI: Analgesia Nociception Index, ANli: ANI instantaneous, ANlm: ANI mean, P: pain state, NP: no pain state.

5. ANI score compared between the pain and no-pain states

Five studies (349 patients and 1,866 measurements) compared the ANI scores between the pain and no-pain states [8,14,16,36,37]. The ANI score was significantly lower in the pain state than that in the no-pain state (SMD = -1.140, 95% CI = -1.239 to -1.041, $I^2 = 93.63\%$, $P_{\text{chi}^2} < 0.001$, $\tau = 0.554$) (**Fig. 5**).

Subgroup analysis based on measured ANI methods also showed that the ANI score was significantly lower in the pain state than that in the no-pain state when measured using ANI (SMD = -0.885, 95% CI = -1.196 to -0.573, $I^2 = 0.0\%$, $P_{\text{chi}^2} = 0.595$, $\tau = 0.0$), ANli (SMD = -1.745, 95% CI = -1.903 to -1.586, $I^2 = 0.0\%$, $P_{\text{chi}^2} = 0.805$, $\tau = 0.0$), and ANlm (SMD = -0.725, 95% CI = -0.864 to -0.586, $I^2 = 0.0\%$, $P_{\text{chi}^2} = 0.625$, $\tau = 0.0$) (**Fig. 5**).

Subgroup analysis based on critically ill or non-critically ill patients also showed that the ANI score was significantly higher in the no-pain state than that in the pain state (SMD = -0.746, 95% CI = -1.168 to -0.323, $I^2 = 0.0\%$, $P_{\text{chi}^2} = 0.721$, $\tau = 0.0$) in non-critically ill patients, and (SMD = -1.202, 95% CI = -1.725 to -0.680, $I^2 = 95.58\%$, $P_{\text{chi}^2} < 0.001$, $\tau = 0.578$) in critically ill patients (**Supplementary Fig. 6**).

However, it should be noted that in some included studies [36,38,39], ANI values remained within the optimal analgesic range (50–70) during painful conditions or exceeded 70 during the no-pain state. This observation reflects potential variability in ANI responses depending on sedation depth, autonomic modulation, and clinical setting.

6. ANI score in the norepinephrine and control groups

Two studies (83 patients and 241 measurements) compared ANI scores between the NE and control groups [14,16]. There was no evidence of differences between the NE and control groups when pain was applied (SMD = -0.290, 95% CI = -0.933 to 0.353, $I^2 = 81.47\%$, $P_{\text{chi}^2} = 0.005$, $\tau = 0.509$) and when pain was not applied (SMD = -0.154, 95% CI = -1.013 to 0.705, $I^2 = 89.42\%$, $P_{\text{chi}^2} < 0.001$, $\tau = 0.714$) (**Fig. 6**). All studies involved in this analysis were performed on critically ill patients, thus subgroup analysis based on critically ill or non-critically ill patients was not performed.

7. Correlation

The correlation between ANI and pain assessment scales is shown in **Table 2**. Due to heterogeneity in outcome measures and insufficient data for meta-analysis, pooled estimates were not calculated. Five studies demonstrated a negative correlation ($r = -0.110$ to -0.470) between ANI and pain scores [8,14,36,38,39]. However, one study showed a correlation that was not statistically significant ($P = 0.165$) [14].

8. Opioid consumption

Two studies compared opioid consumption between ANI guided and non- ANI guided groups [38,39]. The total amount of opioid used was significantly lower in the ANI guided group than that in the non-ANI guided group

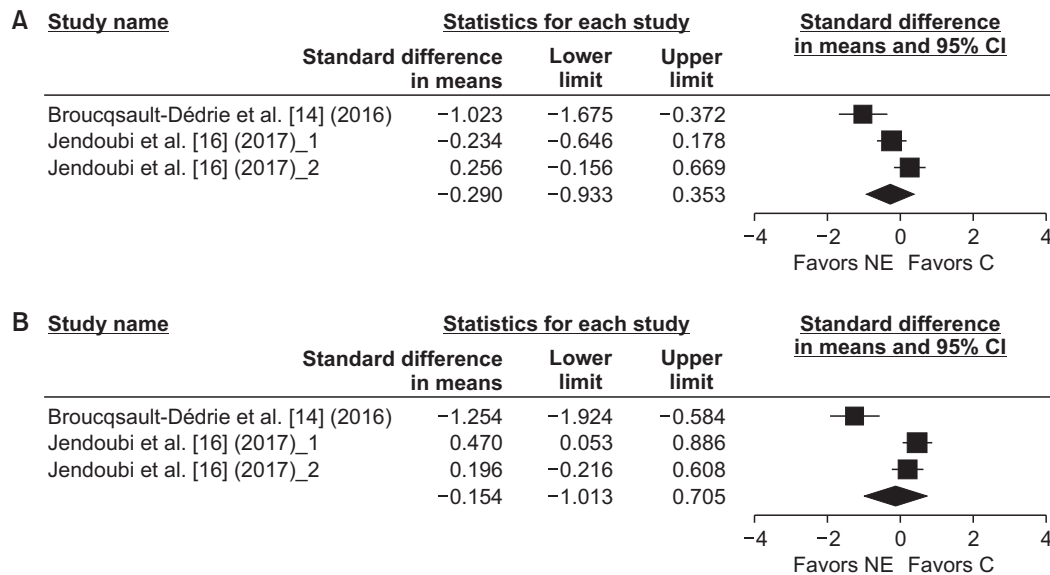


Fig. 6. Forest plot of ANI score compared between NE and C group. Squares represent individual study estimates, with the size of each square corresponding to the weight of the respective study in the meta-analysis. Horizontal lines denote the 95% confidence intervals (CIs) for each estimate. The pooled estimate is represented as a diamond shape, summarizing the overall ANI scores. (A) ANI scores when pain stimulus was applied. (B) ANI scores in the absence of pain stimulus. ANI: Analgesia Nociception Index, NE: norepinephrine, C: control.

Table 2. Correlation between the ANI and pain assessment variables

Author (year)	ANI variable	Variable	Correlation estimate	P value
Broucsault-Dédrie et al. [14] (2016)	ANI	BPS	-0.470	0.165
Avez-Couturier et al. [8] (2016)	ANI	FLACC	-0.450	0.022
Chanques et al. [36] (2017)	ANIm	BPS	-0.110	< 0.001
	ANli	BPS	-0.300	< 0.001
Soral et al. [39] (2020)	ANI	NRS	-0.402	0.003
Belyakov et al. [38] (2024)	ANli	NRS	-0.440	< 0.001
	ANIm	NRS	-0.390	< 0.001

ANI: Analgesia Nociception Index, BPS: Behavioral Pain Scale, FLACC: Face, Legs, Activity, Cry, Consolability, ANIm: ANI mean, ANli: ANI instantaneous, NRS: Numeric Rating Scale.

(SMD = -0.410, 95% CI = -0.643 to -0.178, $I^2 = 0.0\%$, $P_{\text{chi}^2} = 0.836$, $\tau = 0.0$). All studies involved in this analysis were performed in non-critically ill patients, thus subgroup analysis based on critically ill or non-critically ill patients was not performed.

9. Quality of the evidence

The main results and key information on the certainty of evidence assessed using the GRADE systems are summarized in **Supplementary Table 5**. The current evidence level was categorized as either “moderate” or “low.”

DISCUSSION

Our study demonstrated that ANI monitoring showed moderate pooled sensitivity (0.746) and specificity (0.776) for detecting intraoperative or procedural pain in sedated patients, as indicated by a DOR of 10.491. Additionally, ANI scores were significantly higher in the no-pain state than those in the pain state, highlighting its potential utility in distinguishing between pain states. ANI monitoring also contributed to reduced opioid consumption, suggesting its role in optimizing analgesia. However, no definitive evidence was found regarding the effect of NE use on ANI scores. These findings underscore the potential of ANI as a noninvasive tool for intraoperative and pro-

cedural pain assessment in sedated patients. However, there is a need for careful interpretation within specific clinical contexts.

In sedated patients with preserved ability to self-report pain, ANI has shown a negative correlation with pain rating scales ($r = -0.110$ to -0.470), supporting its role as an objective nociceptive monitoring tool [8,14,36,38,39]. Our findings also confirm that ANI effectively differentiated between pain and non-pain states and contributed to opioid reduction when used for analgesia guidance. Subgroup analysis in our study revealed that ANIi provided the strongest differentiation (SMD = -1.745), whereas ANI (SMD = -0.885) and ANIm (SMD = -0.725) demonstrated smaller effect sizes. These findings confirm the ability of ANI to track nociceptive fluctuations in real-time, which aligns with its role in opioid-sparing analgesic strategies. Additionally, subgroup analysis based on patient condition revealed that ANI showed better diagnostic performance in non-critically ill patients compared to critically ill patients, as reflected by higher sensitivity, specificity, and DOR. This suggests that ANI may be more reliable in relatively stable populations, whereas its interpretation in critically ill patients requires greater caution due to autonomic dysregulation.

Furthermore, ANI-guided pain management in sedated patients was associated with significantly lower opioid consumption (SMD = -0.410). Although the absolute reduction may appear modest, it represented approximately 26.6% to 36.1% of the total opioid dose in the included study [39], indicating a potentially meaningful reduction in the context of opioid-sparing strategies. This supports the role of ANI as a complementary tool for optimizing intraoperative and procedural analgesia. By providing continuous, objective monitoring of nociceptive-autonomic balance, ANI facilitates individualized opioid titration and helps minimize unnecessary opioid administration. This, in turn, may contribute to reducing opioid-related adverse effects (e.g., respiratory depression, nausea, and opioid dependence) and aligns with current goals of enhanced recovery protocols and personalized analgesia.

Although ANI monitoring provides valuable real-time insights into nociceptive responses and contributes to opioid-sparing analgesia strategies, its interpretation requires caution. The high heterogeneity observed in the specificity of pain prediction ($I^2 = 91.2\%$) and in the differences between the NE and control groups ($I^2 = 81.47\%$ – 89.42%) suggests that its reliability may vary depending on clinical conditions, sedation protocols, and patient-specific factors. This variability indicates that ANI scores may be influenced by multiple physiological and

pharmacological factors beyond nociception alone [41], necessitating a careful and contextualized approach in its clinical application.

One of the main contributors to this heterogeneity is the type of sedative agent [42,43]. Different sedatives exert distinct effects on nociceptive processing, which may alter ANI readings. Propofol reduces ischemic pain, whereas dexmedetomidine reduces both cold and ischemic pain. In contrast, midazolam has been reported to increase cold, heat, and ischemic pain perception [44]. These findings suggest that ANI responses in sedated patients may not solely reflect nociceptive input, but also the autonomic modulation induced by sedative agents. As ANI is derived from autonomic nervous system activity, particularly the balance between sympathetic and parasympathetic responses, its values may fluctuate independently of actual pain perception. A previous study emphasized the importance of considering patient-specific factors, including sedative administration, when interpreting ANI scores, highlighting that ANI should be used in conjunction with behavioral pain scores and hemodynamic parameters rather than as a standalone measure [45].

Another important factor contributing to ANI variability is the use of vasoactive drugs, such as NE. While our meta-analysis of two studies found no significant differences in ANI scores between the NE and control groups, regardless of pain application, the high heterogeneity ($I^2 > 80\%$) suggests that the effect of NE on ANI is inconsistent across studies. One potential explanation for this inconsistency is the complex interplay between NE's primary action on sympathetic pathways and ANI's reflection of parasympathetic tone. As ANI is derived from heart rate variability, the hemodynamic effects of NE, a potent vasoconstrictor and sympathomimetic agent, might be expected to directly influence ANI values. However, the lack of consistent changes in ANI suggests that this influence may be modulated by other factors, such as baseline autonomic tone, individual patient responses, or specific clinical context. Differences in study populations, with one study including general intensive care unit patients and another focusing on traumatic brain injury patients, may further contribute to the observed variability [14,16]. These findings suggest that NE does not consistently alter ANI values in a predictable manner, emphasizing the need for further standardized research to clarify its impact, including careful consideration of the study population, NE dosage, and baseline autonomic function.

Although the authors' findings support the potential utility of ANI in pain assessment and opioid manage-

ment, some limitations must be considered. First, the observed heterogeneity in the specificity of pain prediction and in the effect of NE on ANI scores highlights the influence of diverse clinical conditions, sedation protocols, and patient-specific factors, which may limit the generalizability of our results. Second, the small number of studies included in certain analyses, particularly the two studies assessing the effect of NE, restricts the power to detect clinically meaningful differences and fully elucidate the relationship. Third, variability in sedation depth and the influence of vasoactive agents can alter autonomic tone, independently affecting ANI values. Unlike general anesthesia, sedation allows fluctuating consciousness, where emotional or cognitive responses may evoke sympathetic activation even with adequate analgesia, or blunt autonomic responses despite insufficient analgesia. Notably, as some included studies reported ANI values remaining within the optimal analgesic range (50–70) during painful stimuli or exceeding 70 in the absence of pain [36,38,39], further research is warranted to investigate the accuracy and reliability of ANI monitoring specifically in sedated patients. Finally, while this study synthesized ANI performance across diverse contexts, further exploration is needed to clarify how factors such as patient age (pediatric versus adult), choice of pain assessment tools (e.g., BPS, FLACC, NRS), and types of nociceptive stimuli (e.g., repositioning, suctioning, procedural pain) may individually impact ANI reliability. Future studies with larger samples and standardized protocols should address these sources of variability to improve the clinical applicability of ANI monitoring.

In conclusion, ANI effectively differentiated between the pain and non-pain states during procedures under sedation, with potential benefits in guiding analgesic administration and reducing opioid consumption. However, its clinical utility should be interpreted in conjunction with other established pain assessment methods and tailored to specific patient populations and procedural contexts.

DATA AVAILABILITY

Data files are available from Harvard Dataverse: <https://doi.org/10.7910/DVN/POQPD1>.

CONFLICT OF INTEREST

Hyun Kang is a section editor of the Korean Journal of

Pain. However, he was not involved in the selection of peer reviewers, the evaluation, or the decision-making process for this article.

FUNDING

No funding to declare.

AUTHOR CONTRIBUTIONS

Min Kyoung Kim: Conceptualization, Investigation, and Writing/manuscript preparation; Oh Haeng Lee: Investigation, Data curation, and Writing/manuscript preparation; Geun Joo Choi: Investigation and Writing/manuscript preparation; Hyun Kang: Conceptualization, Formal analysis, Project administration, and Writing/manuscript preparation.

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SUPPLEMENTARY MATERIALS

Supplementary materials can be found *via* <https://doi.org/10.3344/kjp.25105>.

REFERENCES

1. American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists. Practice guidelines for sedation and analgesia by non-anesthesiologists. *Anesthesiology* 2002; 96: 1004-17.
2. Ramsay MAE. Intensive care: problems of over- and undersedation. *Best Pract Res Clin Anaesthesiol* 2000; 14: 419-32.
3. Aragón-Benedí C, Caballero-Lozada AF, Perez-Catalayud AA, Marulanda-Yanten AM, Oliver-Fornies P, Boselli E, et al. Prospective multicenter study of heart rate variability with ANI monitor as predictor of mortality in critically ill patients with COVID-19.

- Sci Rep 2022; 12: 21762.
4. Sanders RD, Tononi G, Laureys S, Sleigh JW. Unresponsiveness $\neq$ unconsciousness. *Anesthesiology* 2012; 116: 946-59.
 5. Deschepper R, Laureys S, Hachimi-Idrissi S, Poelaert J, Distelmans W, Bilsen J. Palliative sedation: why we should be more concerned about the risks that patients experience an uncomfortable death. *Pain* 2013; 154: 1505-8.
 6. Jeanne M, Clément C, De Jonckheere J, Logier R, Tavernier B. Variations of the analgesia nociception index during general anaesthesia for laparoscopic abdominal surgery. *J Clin Monit Comput* 2012; 26: 289-94.
 7. Le Guen M, Jeanne M, Sievert K, Al Moubarik M, Chazot T, Laloë PA, et al. The Analgesia Nociception Index: a pilot study to evaluation of a new pain parameter during labor. *Int J Obstet Anesth* 2012; 21: 146-51.
 8. Avez-Couturier J, De Jonckheere J, Jeanne M, Vallée L, Cuisset JM, Logier R. Assessment of procedural pain in children using Analgesia Nociception Index: a pilot study. *Clin J Pain* 2016; 32: 1100-4.
 9. Boselli E, Daniela-Ionescu M, Bégou G, Bouvet L, Dabouz R, Magnin C, et al. Prospective observational study of the non-invasive assessment of immediate postoperative pain using the analgesia/nociception index (ANI). *Br J Anaesth* 2013; 111: 453-9.
 10. Gall O, Champigneulle B, Schweitzer B, Deram T, Maupain O, Montmayeur Verchere J, et al. Postoperative pain assessment in children: a pilot study of the usefulness of the analgesia nociception index. *Br J Anaesth* 2015; 115: 890-5.
 11. Kim MK, Choi GJ, Oh KS, Lee SP, Kang H. Pain assessment using the Analgesia Nociception Index (ANI) in patients undergoing general anesthesia: a systematic review and meta-analysis. *J Pers Med* 2023; 13: 1461.
 12. Baroni DA, Abreu LG, Paiva SM, Costa LR. Comparison between Analgesia Nociception Index (ANI) and self-reported measures for diagnosing pain in conscious individuals: a systematic review and meta-analysis. *Sci Rep* 2022; 12: 2862.
 13. Yan Q, An HY, Feng Y. Pain assessment in conscious healthy volunteers: a crossover study evaluating the analgesia/nociception index. *Br J Anaesth* 2017; 118: 635-6.
 14. Broucqsaault-Dédrie C, De Jonckheere J, Jeanne M, Nseir S. Measurement of heart rate variability to assess pain in sedated critically ill patients: a prospective observational study. *PLoS One* 2016; 11: e0147720.
 15. Ahmad S, Ramsay T, Huebsch L, Flanagan S, McDiarmid S, Batkin I, et al. Continuous multi-parameter heart rate variability analysis heralds onset of sepsis in adults. *PLoS One* 2009; 4: e6642.
 16. Jendoubi A, Abbes A, Ghedira S, Houissa M. Pain measurement in mechanically ventilated patients with traumatic brain injury: behavioral pain tools versus Analgesia Nociception Index. *Indian J Crit Care Med* 2017; 21: 585-8.
 17. Shamseer L, Moher D, Clarke M, Ghera D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015; 350: g7647.
 18. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. *Cochrane handbook for systematic reviews of interventions*. 2nd ed. Wiley-Blackwell. 2019.
 19. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; 6: e1000097.
 20. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; 283: 2008-12.
 21. Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Stat Methods Med Res* 2018; 27: 1785-805.
 22. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol* 2005; 5: 13.
 23. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014; 14: 135.
 24. Choi GJ, Kang H. Introduction to umbrella reviews as a useful evidence-based practice. *J Lipid Atheroscler* 2023; 12: 3-11.
 25. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; 366: l4898.
 26. Kim SY, Park JE, Lee YJ, Seo HJ, Sheen SS, Hahn, et al. Testing a tool for assessing the risk of bias for nonrandomized studies showed moderate reliability

- and promising validity. *J Clin Epidemiol* 2013; 66: 408-14.
27. Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Methodol* 2003; 3: 25.
 28. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol* 2005; 58: 982-90.
 29. Glas AS, Lijmer JG, Prins MH, Bossel GJ, Bossuyt PM. The diagnostic odds ratio: a single indicator of test performance. *J Clin Epidemiol* 2003; 56: 1129-35.
 30. Moses LE, Shapiro D, Littenberg B. Combining independent studies of a diagnostic test into a summary ROC curve: data-analytic approaches and some additional considerations. *Stat Med* 1993; 12: 1293-316.
 31. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. *BMJ* 2004; 328: 1490.
 32. Schünemann HJ, Oxman AD, Brozek J, Glasziou P, Jaeschke R, Vist GE, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. *BMJ* 2008; 336: 1106-10.
 33. Baroni DA, Corrêa-Faria P, Anabuki AA, Abreu LG, Costa LR. Nociception associated with pain/distress in young children sedated for dental treatment: a clinical study with objective and subjective measures. *Eur Arch Paediatr Dent* 2023; 24: 255-62.
 34. Aragón-Benedí C, Oliver-Forniés P, Galluccio F, Yamak Altinpulluk E, Ergonenc T, El Sayed Allam A, et al. Is the heart rate variability monitoring using the analgesia nociception index a predictor of illness severity and mortality in critically ill patients with COVID-19? A pilot study. *PLoS One* 2021; 16: e0249128.
 35. Boselli E, Bouvet L, Bégou G, Torkmani S, Allaouchiche B. Prediction of hemodynamic reactivity during total intravenous anesthesia for suspension laryngoscopy using Analgesia/Nociception Index (ANI): a prospective observational study. *Minerva Anesthesiol* 2015; 81: 288-97.
 36. Chanques G, Tarri T, Ride A, Prades A, De Jong A, Carr J, et al. Analgesia nociception index for the assessment of pain in critically ill patients: a diagnostic accuracy study. *Br J Anaesth* 2017; 119: 812-20.
 37. Papaioannou V, Chouvarda I, Gaertner E, Benyamina M, Ferry A, Maurel V, et al. Heart rate variability and cardiac baroreflex inhibition-derived index predicts pain perception in burn patients. *Burns* 2016; 42: 1445-54.
 38. Belyakov KS, Ruslyakova IA, Marinin VA, Shamsutdinova EZ. Multimodal monitoring using the Analgesia Nociception Index (ANI) during catheter ablation of the heart in patients with sinus rhythm and short-term induced atrial arrhythmia: prospective observational study. *Вестник интенсивной терапии имени А.И. Салтанова* 2024; 2: 159-71.
 39. Soral M, Altun GT, Dinçer PÇ, Arslantaş MK, Aykaç Z. Effectiveness of the Analgesia Nociception Index monitoring in patients who undergo colonoscopy with sedo-analgesia. *Turk J Anaesthesiol Reanim* 2020; 48: 50-7.
 40. Sado-Filho J, Corrêa-Faria P, Viana KA, Mendes FM, Mason KP, Costa LR, et al. Intranasal dexmedetomidine compared to a combination of intranasal dexmedetomidine with ketamine for sedation of children requiring dental treatment: a randomized clinical trial. *J Clin Med* 2021; 10: 2840.
 41. Tiwari R, Kumar R, Malik S, Raj T, Kumar P. Analysis of heart rate variability and implication of different factors on heart rate variability. *Curr Cardiol Rev* 2021; 17: e160721189770.
 42. Jeanne M, Delecroix M, De Jonckheere J, Keribedj A, Logier R, Tavernier B. Variations of the analgesia nociception index during propofol anesthesia for total knee replacement. *Clin J Pain* 2014; 30: 1084-8.
 43. Kanaya N, Hirata N, Kurosawa S, Nakayama M, Namiki A. Differential effects of propofol and sevoflurane on heart rate variability. *Anesthesiology* 2003; 98: 34-40.
 44. Frölich MA, Zhang K, Ness TJ. Effect of sedation on pain perception. *Anesthesiology* 2013; 118: 611-21.
 45. Boselli E, Jeanne M. Analgesia/nociception index for the assessment of acute postoperative pain. *Br J Anaesth* 2014; 112: 936-7.