SPECIAL ARTICLE

Ketamine Analgo-sedation for Mechanically Ventilated Critically Ill Adults: A Rapid Practice Guideline from the Saudi Critical Care Society and the Scandinavian Society of Anesthesiology and Intensive Care Medicine

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Background: This Rapid Practice Guideline (RPG) aimed to provide evidence-based recommendations for ketamine analgo-sedation (monotherapy and adjunct) versus non-ketamine sedatives or usual care in adult intensive care unit (ICU) patients on invasive mechanical ventilation (iMV) and to identify knowledge gaps for future research.

Methods: The RPG panel comprised 23 multinational multidisciplinary panelists, including a patient representative. An up-to-date systematic review and meta-analysis constituted the evidence base. The Grading Recommendations, Assessment, Development, and Evaluation approach, and the evidence-to-decision framework were used to assess the certainty of evidence and to move from evidence to decision/recommendation. The panel provided input on the balance of the desirable and undesirable effects, certainty of evidence, patients' values and preferences, costs, resources, equity, feasibility, acceptability, and research priorities.

Results: Data from 17 randomized clinical trials (n=898) and 9 observational studies (n=1934) were included. There was considerable uncertainty about the desirable and undesirable effects of ketamine monotherapy for analgo-sedation. The evidence was very low certainty and downgraded for risk of bias, indirectness, and inconsistency. Uncertainty or variability in values and preferences were identified. Costs, resources, equity, and acceptability were considered varied. Adjunctive ketamine therapy had no effect on mortality (within 28 days) (relative risk [RR] 0.99; 95% confidence interval [CI] 0.76 to 1.27; low certainty), and may slightly reduce iMV duration (days) (mean difference [MD] -0.05 days; 95% CI -0.07 to -0.03; low certainty), and uncertain effect on the cumulative dose of opioids (mcg/kg/h morphine equivalent) (MD -11.6; 95% CI -20.4 to -2.7; very low certainty). Uncertain desirable effects (cumulative dose of sedatives and vasopressors) and undesirable effects (adverse event rate, delirium, arrhythmia, hepatotoxicity, hypersalivation, use of physical restraints) were also identified. A possibility of important uncertainty or variability in patient-important outcomes led to a balanced effect that favored neither the intervention nor the comparison. Cost, resources, and equity were considered varied.

Conclusion: The RPG panel provided two conditional recommendations and suggested (1) against using ketamine as monotherapy analgo-sedation in critically ill adults on iMV when other analgo-sedatives are available; and (2) using ketamine as an adjunct to non-ketamine usual care sedatives (e.g., opioids, propofol, dexmedetomidine) or continuing with non-ketamine usual care sedatives alone. Large-scale trials should provide additional evidence. (Anesth Analg 2024;XXX:00–00)

Keywords: Ketamine, Critical care, Sedation, Mechanical ventilation, Practice Guidelines, GRADE

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INTRODUCTION

An accumulation of evidence on pain, agitation, sedation, and delirium in intensive care units (ICUs) has led to an emphasis on analgo-sedation strategies targeting light sedation and prioritizing effective management of pain. Despite wide usage, sedatives such as propofol and midazolam may cause hypotension and respiratory depression, and possibly increase the duration of invasive mechanical ventilation (iMV).[1–3] Consequently, alternatives such as ketamine, which offers analgo-sedation with fewer hemodynamic side effects and reduces opioid requirements when used with multimodal analgesia, have garnered attention.[4,5] Ketamine primarily acts as an N-methyl-d-aspartate receptor antagonist and opioid receptor agonist (activates μ and κ opioid receptors) to provide dissociative anesthetic effects and analgesia.[4] The Society of Critical Care Medicine (SCCM) 2018 Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption (PADIS 2018) guideline issued a conditional recommendation, based on very low certainty evidence from one randomized controlled trial (RCT), to use low-dose ketamine as an opioid-sparing adjunct to manage acute postoperative pain in adult intensive care unit (ICU) patients.[6] Subsequently, several RCTs have been published in various settings, including medical ICUs, and throughout the COVID-19 pandemic.[4] The emergence of newer studies and the equipoise for ketamine use in the ICU highlight the need for updated evidence-based recommendations.

Therefore, the Saudi Critical Care Society (SCCS) and the Scandinavian Society of Anesthesiology and Intensive Care Medicine (SSAI) convened a multidisciplinary expert panel to develop a rapid practice guideline (RPG) on the use of ketamine analgo-sedation in adult ICU patients on iMV. This RPG aimed to summarize and evaluate the available evidence, provide evidence-based recommendations, and identify knowledge gaps for future research to address remaining uncertainties in this area.

METHODS

Organization

The SCCS and SSAI collaborated on this RPG. The SCCS Guideline Chapter proposed the guideline topic and discussed the relevance and potential application of the RPG for the Scandinavian countries and practitioners via a teleconference with the SSAI. Subsequently, five additional subject matter experts from the National Nordic countries were appointed as panel members by the SSAI (Supplemental Digital Content 1, **Appendix 1: Supplemental Content 1,** http://links.lww.com/AA/E986**).** As the sponsoring organization, the SCCS was responsible for establishing the steering committee, inviting the panelists, conducting the systematic review and meta-analysis, and providing methodological and statistical support. The "Intensive care medicine rapid practice guidelines in Acta Anaesthesiologica Scandinavica," "Guidelines International Network-McMaster Guideline Development Checklist," and "Development of an international glossary for clinical guidelines collaboration" were used as references for the RPG preparation.[7–9] This RPG followed the Appraisal of Guidelines for REsearch and Evaluation (AGREE) II reporting checklist (Supplemental Digital Content 2, **Appendix 2,** http://links.lww.com/AA/E987).[10]

Scope

This RPG focused on adult ICU patients on iMV. The recommendations do not apply to children, non-ICU patients, patients undergoing non-invasive MV, or to ketamine use for anesthesia induction, rapid sequence intubation, or procedural sedation.

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Target users

The target users are intensivists, anesthesiologists, advanced practice providers, clinical pharmacists, nurses, nurse practitioners, physiotherapists, and policymakers.

Guideline panel

The Steering Committee (MA, MHM, and WA) selected 23 panelists including a patient representative, content experts, academic intensivists, nurses, pharmacists, methodologists, and frontline clinicians. The selected panelists represented a balance of expertise and gender.[11] The patient representative (NA) provided valuable insights into outcome selection and prioritization and patient values and preferences via teleconferences with the guideline chair.

Managing conflicts of interest

Each panelist completed an electronic conflict of interest (COI) form before their official appointment.[12,13] The Steering Committee reviewed all disclosures and adjudicated any potential conflicts before initiation of the guideline and panel voting. Three members had academic COIs, which were acknowledged and managed in the panel discussions and during the vote. All reported COIs were adjudicated as secondary and managed by the SCCS and SSAI COI policies.[14,15] (Supplemental Digital Content 1, **Appendix 1: Supplemental Content 2,** http://links.lww.com/AA/E986).

Guideline questions

The panel addressed the following questions:

- Should we recommend using ketamine monotherapy for analgo-sedation versus other sedatives or usual care in critically ill patients undergoing iMV?
- Should we recommend using adjunct ketamine for analgo-sedation versus other sedatives or usual care in critically ill patients undergoing iMV?

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to prioritize the outcomes and incorporated patient perspectives during the prioritization process.[16] The outcomes from the Sedation Consortium on Endpoints and Procedures for Treatment, Education, and Research (SCEPTER) Recommendation were also included.[17] (**Table 1**; Supplemental Digital Content 1, **Appendix 1: Supplemental Content 3,** http://links.lww.com/AA/E986). In structuring our PICO (Population, intervention, comparison, and outcome[s]) framework, we aligned our methodology with that employed by Møller MH, et al., in their guideline for the use of dexmedetomidine in sedation for mechanically ventilated adult ICU patients.[18]

The evidence (search strategy and study inclusion)

Our search identified a total of 8 systematic reviews focusing on ketamine as an adjunctive analgo-sedative and 1 on ketamine as the primary analgo-sedative (monotherapy) (Supplemental Digital Content 1, **Appendix 1: Supplemental Content 4,** http://links.lww.com/AA/E986).[4] We used the AMSTAR II tool to select the most relevant, recent, and highest-quality reviews. We updated the search strategy for Chan et al.'s[19] systematic review and meta-analysis, which concluded on November 19, 2021, to include literature up to October 31, 2023. We systematically searched Ovid MEDLINE, Embase, Cochrane Library, and clinicaltrial.gov databases for systematic reviews, individual RCTs, and observational studies. A single search strategy was conducted for both ketamine as adjunctive and monotherapy for analgo-sedation, with results reported separately. A professional librarian, with input from the panel, performed an online literature search for each defined question using pertinent search terms such as "ketamine," "critical care," "sedation," and "mechanical ventilation" combined with appropriate question-specific keywords (Supplemental Digital Content 1, **Appendix 1: Supplemental Content 5,** http://links.lww.com/AA/E986).[20]

Data abstraction and risk of bias assessment

Relevant data from eligible studies were abstracted using a standardized data abstraction form and items relevant to risk of bias (ROB) assessment were identified. Risk of bias assessments were performed using the Cochrane's Risk-of-Bias (RoB 2) for RCTs or Risk-of-Bias in Non-randomized Studies-of Interventions (ROBINS-I) for observational studies.[21]

Statistical analysis

For each question, we used meta-analysis techniques to generate pooled estimates across relevant studies, when applicable. All analyses were conducted using the RevMan software version 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark).[22] In accordance with the published guidelines and owing to methodological differences, the RCTs and observational studies were pooled separately.[23] The DerSimonian and Laird random-effect model and inverse-variance method were used for analysis. Fixed- and random-effect models were compared for smaller studies (<5), selecting the most conservative estimate to ensure robustness in the review

Table 1. Population, Intervention, Comparator, Outcomes (PICO)

Population	Intervention	Comparator	Outcomes[a,b]
Critically ill adults undergoing iMV	Ketamine as continuous infusion for analgo-sedation in any dose and for any duration	Non-ketamine sedatives or usual care (opioids, propofol, dexmedetomidine, or benzodiazepines) or placebo	Critical outcomes 1- iMV duration 2- ICU LOS 3- All-cause mortality at longest follow-up 4- Days alive and free from coma and delirium 5- Long-term cognitive function (EQ-5D-5L index values, EQ-VAS and PTSD) 6- Proportion of patients achieving the sedation and pain score goals 7- Proportion of time at target sedation and target pain score goals 8- Cumulative dose of opioids and sedatives 9- AEs (delirium, agitation, arrhythmia, and self-extubation).

[a] Panelists were asked to list potentially relevant outcomes. Subsequently, each panelist was asked to rate each listed outcome on a scale of 1 (not important) to 9 (critical) via an e-survey. Outcomes with a median rating ≥7 were considered critical. Prioritization was based on the RPG's potential importance to patients and end users rather than on experts' perspectives or interests.

[b] Additional outcomes rated as important were hospital LOS, days alive without sedation, vasopressor-free days, use of additional analgesics and sedatives, change in PaO2:FiO2 ratio, risk of hypersalivation, hepatotoxicity and cholangiopathy, use of additional anti-psychotics, physical restraints, and increased ICP

Abbreviation: AEs, adverse events; **EQ-5D-5L**, EuroQol, 5 dimensions, 5 levels; **FiO2**, fraction of inspired oxygen; **ICU**, intensive care unit; **ICP**, intra-cranial pressure; **iMV**, invasive mechanical ventilation; **LOS**, length of stay; **PaO2**, partial pressure of oxygen in arterial blood; **PTSD**, post-traumatic stress disorder; **VAS**, visual analog scale.

findings. Pooled estimates were reported as relative risks (RRs) or odds ratios (ORs) with 95% confidence intervals (CIs) and mean difference (MD) with 95% CIs for dichotomous and continuous outcomes, respectively. Data for continuous outcomes reported as medians and interquartile ranges were converted into means and standard deviations using an online calculator.[24] Heterogeneity was assessed using the X^2 test ($p<0.05$ indicating substantial heterogeneity) and the I^2 statistic (>50% indicating substantial heterogeneity) and by visually examining Forest plots. The evidence was narratively summarized for questions with insufficient quantitative data. In instances where outcomes were informed by >10 trials, funnel plots were examined, and Egger's test was performed to assess for potential publication bias. All opioids in the study were standardized to morphine equivalents (MEQS) and sedatives (benzodiazepines) to midazolam equivalents, using a standard average patient weight of 75 kg for dose conversions when necessary. Cumulative opioid doses were adjusted for the time of measurement, providing a dose/kg/h estimate. Owing to varied reporting methods across studies, the longest follow-up (hospital or ICU mortality) was used for mortality data.

Subgroup considerations

Two subgroup analyses were conducted to explore heterogeneity in treatment effects according to the ROB (low ROB vs. some concern/ high ROB, hypothesizing larger effects in high ROB studies), and the ICU setting (medical, neuro, and surgical cardiac/ non-cardiac ICUs, hypothesizing larger effects in surgical patients). The credibility of each subgroup analysis was evaluated using the Instrument for Assessing the Credibility of Effect Modification Analyses (ICEMAN).[25]

Certainty of evidence and grading of recommendations

The GRADE approach was used to assess the certainty of evidence and summarize the confidence in the estimated effect to support a recommendation.[26] The certainty of evidence was rated as high, moderate, low, or very low based on ROB, imprecision, indirectness, inconsistency, and publication bias.[27,28] The Guideline Development Tool online software (Evidence Prime, Hamilton, ON) was used to generate evidence profiles/summaries (Supplemental Digital Content 1, **Appendix 1: Supplemental Content 6,** http://links.lww.com/AA/E986).

Recommendation formulation and voting process

The evidence-to-decision (EtD) framework was used to formulate recommendations. The guideline methodologist drafted the preliminary recommendations considering the balance of desirable and undesirable effects, certainty of evidence, costs and resources, equity, feasibility, and acceptability (Supplemental Digital Content 1, **Appendix 1: Supplemental Content 6,** http://links.lww.com/AA/E986).[29] Panel Voice (Evidence Prime, Hamilton, ON) was used to vote on the strength of the recommendation. During the panel meeting, the panelists voted on each EtD component after reviewing the preliminary decisions and subsequent discussions. In the absence of a consensus, the majority vote was adopted and the voting results were recorded. Panelists who were unable to participate in the teleconferences because of time zone differences were expected to review the recordings and were provided an opportunity for input. Panelists assessed whether the desirable effects of an intervention would outweigh the undesirable effects and the strength of a recommendation reflected the panel's degree of confidence in the balance. Thus, a strong recommendation in favor of an intervention indicated

the panel's opinion that the desirable effects would clearly outweigh the undesirable effects, whereas a conditional recommendation indicated that the desirable effects would likely outweigh the undesirable effects. The phrases "the panel recommends" and "the panel suggests" were used for strong and conditional recommendations, respectively.[30] Additional information for the GRADE approach and implications of different recommendations to key stakeholders are presented in Supplemental Digital Content 1, **Appendix 1: Supplemental Content 7,** http://links.lww.com/AA/E986. Acceptance of a recommendation requires at least 75% of the panel votes. Voters could provide feedback for considering revising statements that did not receive consensus in up to three rounds of voting (Supplemental Digital Content 1, **Appendix 1: Supplemental Content 8,** http://links.lww.com/AA/E986).

RESULTS

We included 17 RCTs (n=898) and 9 observational studies (n=1934).[19,31–33] Trials varied in ketamine dosage and treatment duration. Details are included in **Figure 1 and** Supplemental Digital Content 1, **Appendix 1: Supplemental Content 9-10,** http://links.lww.com/AA/E986. The panel issued two conditional recommendations. **Table 2 and Figure 2** present a summary of the recommendations.

Recommendation 1: For critically ill adults undergoing iMV, the panel ***suggests not*** using ketamine monotherapy for analgo-sedation **(conditional recommendation, very low certainty of evidence).**

Remarks:

- In settings with multiple drug options, the use of well-researched alternatives to ketamine is preferred.
- In settings where ketamine is the only available option, such as in low- and middle-income countries, its use is acceptable.

Rationale and Evidence Summary

Ketamine monotherapy may exert beneficial effects on respiratory and hemodynamic outcomes; however, the existing evidence presents considerable uncertainty. Ketamine has minimal respiratory depressive effects and bronchodilatory properties, and it increases inspiratory flow and reduces work of breathing.[1–3] While the underlying mechanisms remain poorly elucidated, the anti-cholinergic effect of ketamine has been hypothesized to induce bronchodilation.

Miller et al.'s systematic review on ketamine monotherapy reported no meaningful effects and primarily focused on surrogate physiological outcomes such as blood pressure and respiratory outcomes. The absence of clear data on several critical and important outcomes necessitated a narrative interpretation of the evidence (**Table 3A**; Supplemental Digital Content 1, **Appendix 1: Supplemental Content 11,12,** http://links.lww.com/AA/E986).[34]

Three RCTs (n=103) reported on respiratory outcomes. In 1 RCT, 53 patients reported a decrease in clinical dyspnea after ketamine administration; however, no significant changes were observed in the forced expiratory volume in 1 second, peak expiratory flow rate, or respiratory rate.[35] A smaller RCT (n=5) reported improvements in decreased airway resistance, increased dynamic compliance, and reduced bronchodilator usage after ketamine administration.[36] However, another RCT reported no significant association of ketamine with reduced inspiratory resistance or improved delta intrinsic Positive End-Expiratory Pressure when compared with fentanyl.[37]

Regarding hemodynamic outcomes, Miller et al.'s systematic review highlighted the hemodynamic stability associated with ketamine infusion, particularly its lack of significant perturbations in blood pressure, heart rate, or vascular resistance compared to non-ketamine sedatives, including opioids, propofol, dexmedetomidine, or benzodiazepines.[34] However, individual RCTs presented a more complex scenario. A smaller RCT (n=5) reported an increase in mean arterial pressure (MAP) with continuous ketamine infusion when compared with fentanyl, while a larger RCT (n=53) reported a decrease in systolic (MD 8.1 mmHg; 95% CI -2.4 to 18) and diastolic (MD 2.4 mmHg; 95% CI -5 to 9.8) blood pressure, which was not significant.[35,36] Furthermore, an observational study (n=234) and a cohort study (n=124) suggested more favorable outcomes in MAP stability and decreased need for vasopressor support in patients receiving ketamine.[38,39] Regarding heart rate, fewer instances of clinically significant bradycardia were observed in patients receiving ketamine (1.3%) compared to those treated with propofol or dexmedetomidine (14.1%).[38]

The pooled estimates for 2 observational studies (n=358) revealed an inconclusive effect and a possible association with increased iMV duration (MD 4.52 days; 95% CI 2.12 to 6.93), ICU length of stay (LOS) (MD 4 days; 95% CI 0.37 to 7.63), delirium (OR 2.81; 95% CI 0.54 to 14.64), and mortality (RR 1.39; 95% CI 0.78 to 2.47), although these findings were imprecise, with very low certainty of evidence.[38,39]

Evidence to recommendation

(Supplemental Digital Content 1, **Appendix 1: Supplemental Content 12, Supplemental Figure 1,** http://links.lww.com/AA/E986)

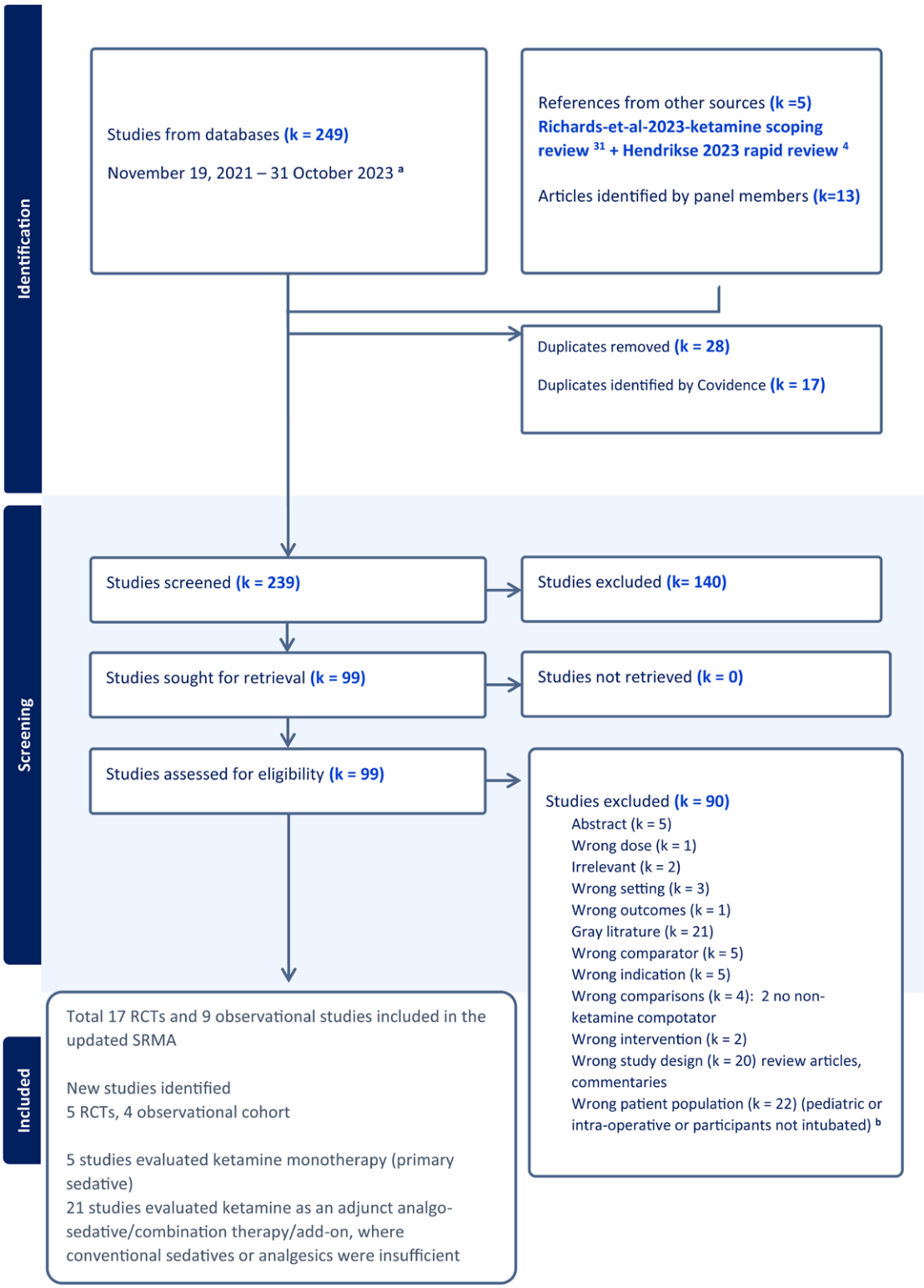

Figure 1: PRISMA diagram. [a] Direct evidence were imported into a reference management software (EndNote version 20; EndNote, Philadelphia, PA), deduplicated, and imported into the Covidence software (Veritas Health Innovation, Melbourne, Australia) to facilitate the systematic review process. [b] One RCT and one observational cohort study from Chan et al. systematic review and meta-analysis were excluded, as they included adolescents and pediatric populations, contrary to our specified age criteria.[32,33] **Abbreviation: RCT**, randomized controlled trial; **k**, number of reported studies; **n**, number of patients.

Desirable and undesirable effects. The panel felt that considerable uncertainty existed, particularly regarding patient-important outcomes. Despite its potential physiologic benefits, such as positive respiratory effects and hemodynamic stability compared with conventional sedatives—albeit

Table 2. Summary of recommendations

Recommendation	Strength and certainty of evidence	Practical considerations	GRADE evidence profile and EtD framework
Should we recommend using ketamine monotherapy for analgo-sedation versus non-ketamine sedatives or usual care for critically ill patients undergoing iMV?			
Recommendation 1: For critically ill adults undergoing iMV, the panel ***suggests not*** using ketamine monotherapy for analgo-sedation	Conditional; very low	In settings with multiple drug options, well-researched alternatives to ketamine are preferrable.[a] In settings where ketamine is the only available option, such as in low- and middle-income countries, its use is acceptable.	**https://guidelines.gradepro.org/profile/GSLUbNQg6sY**
Should we recommend using adjunct ketamine therapy versus non-ketamine sedatives or usual care for analgo-sedation in critically ill patients undergoing iMV?			
Recommendation 2: For critically ill adults undergoing iMV, the panel ***suggests*** using ketamine as an adjunct to non-ketamine usual care sedatives (e.g., opioids, propofol, dexmedetomidine) or continuing with non-ketamine usual care sedatives alone	Conditional; very low	The panel suggests two acceptable approaches based on current evidence. The use of adjunct ketamine may help reduce doses of these agents, facilitate sedation rotation, or serve as an alternative analgo-sedative strategy. Ketamine dosing based on IBW can help minimize AEs, especially in patients with obesity. In practice, a median dosing rate of 0.9 mg/kg/h = 15 µg/kg/min based on IBW, may be considered.[b] The units used require attention as some studies have used mcg/kg/min and others, mg/kg/hr. Ketamine has two enantiomers: S(+) and R(-). The S(+) enantiomer has more potent anesthetic and analgesic activity with a lower probability of AEs than the R(-) enantiomer.[c] Most commercially available ketamine preparations are racemic mixtures, containing equal amounts of both enantiomers, which may influence the incidence and severity of AEs.	https://guidelines.gradepro.org/profile/_U2PaPFXqGc

[a] For a detailed understanding of the alternatives, readers are encouraged to refer to the most recent PADIS guidelines.
[b] Panel advises caution regarding this relatively high dosing approach, especially in surgical patients, where lower doses (e.g., 8–12 mg/h or 0.15 mg/kg/h) may offer benefits while minimizing the risk of psycho-cognitive and cardiovascular AEs.
[c] S-Ketamine is more expensive but frequently utilized in higher-income countries
Abbreviations: AEs, adverse events; **GRADE**, Grading of Recommendations, Assessment, Development, and Evaluations; **IBW**, ideal body weight; EtD, evidence to decision; **iMV**, invasive mechanical ventilation; PADIS, Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption.

underscored by the very low certainty of evidence—the precise impact of ketamine on patient-important outcomes is difficult to discern owing to the paucity and limitations of existing data. Data from adequately sized comparative RCTs that clarify the effect of ketamine monotherapy on overall patient-important outcomes such as pain management, sedation depth, psychomimetic effects, long-term quality of life, and mental health outcomes are lacking. The current body of evidence is insufficient to draw definitive conclusions on these desirable effects. In our analysis, most data on the undesirable effects of ketamine were sourced from observational studies, indicating the dose-dependency of these effects, particularly when using high-dose ketamine as monotherapy. The panel concurred that the adverse events (AEs) of ketamine were moderate. Moreover, the panel noted a gap in reporting specific AEs, such as drooling or hypersalivation, which have been inadequately assessed in the available literature.

Certainty of evidence. The overall certainty of evidence was very low owing to the following reasons: (1) high ROB - no mention of allocation concealment or blinding, and the dropout rate was >10% in some studies (risk for attrition bias); (2) indirectness for outcomes (surrogate outcomes); (3) serious inconsistency; and (4) imprecision with wide CIs and low number of events.

Values and preferences. The patient representative valued the positive respiratory effects of ketamine, notably its minimal respiratory depressant effects, enhanced breathing efficiency, and bronchodilatory properties. Hemodynamically, the perceived benefits of ketamine in cases of hypotension and its capacity to reduce bradycardia incidence and vasopressor use were particularly appreciated, resonating with the patient's perspective that minimizing medication use signifies a step toward recovery. However, the patient representative expressed reservations regarding the potential risk of increased mortality and the moderate undesirable effects. The panel perceived that it was essential to factor in the universally negative perception of outcomes such as mortality and delirium and the specific concerns such as drooling or hypersalivation, which were pertinent for patients undergoing iMV. While the evidence base presented uncertainties, the perceived variability in patients' perception of the desirable effects, particularly those related to pulmonary function, necessitated a nuanced

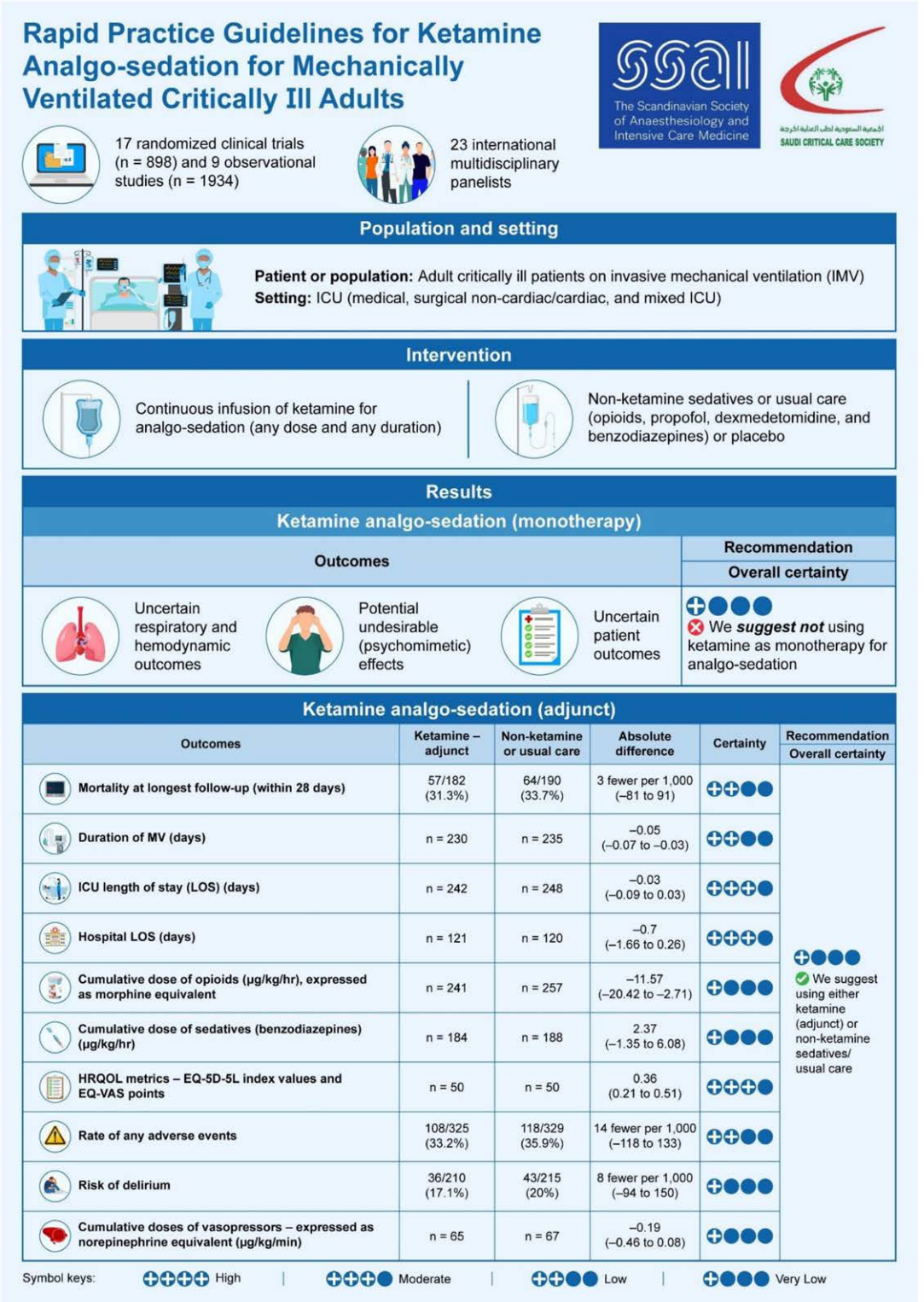

Figure 2: Visual summary. EQ- 5D-5L index value ranges from 1 (perfect health) to values below zero (health states valued worse than death with zero defined as a state equivalent to death). **Abbreviation: EQ-5D-5L,** EuroQol, 5 dimensions, 5 levels**; HRQOL,** Health-related quality of life; **ICU,** intensive care unit; **iMV,** invasive mechanical ventilation; **MV**, mechanical ventilation; **VAS**, visual analog scale.

approach. Overall, the panel felt that important uncertainty or variability existed and that engaging the patient representative in discussions was crucial to discern whether these evaluated effects of ketamine vary among individuals or if merely a potential for variability existed.

Table 3A. Evidence profile for PICO 1

Ketamine analgo-sedation (monotherapy) versus non-ketamine sedatives or usual care[a]						
		Anticipated absolute effects (95% CI)				
Outcome No. of participants (n) (studies)	**Relative effect (95% CI)**	**Without ketamine**	**With ketamine for analgo-sedation (mono)**	**Difference**	**Certainty**	**Comment and interpretation**
MV duration - observational study *n*=358 (2 non-RCTs)	-	246	112	MD **4.52 higher** (2.12 higher to 6.93 higher)	⊕◯◯◯ Very low	Uncertain effect on MV duration
Hospital LOS assessed by days; *n*=358 (2 non-RCTs)	-	246	112	MD **3.77 higher** (0.41 lower to 7.96 higher)	⊕◯◯◯ Very low	Uncertain effect on hospital LOS
ICU LOS assessed by days; *n*=234 (1 non-RCT)	-	156	78	MD **4 higher** (0.37 higher to 7.63 higher)	⊕◯◯◯ Very low	Uncertain effect on ICU LOS
Mortality assessed by mortality within 12 h of stopping sedation; *n*=358 (2 non-RCTs)	**RR 1.39** (0.78–2.47)	30.5%	**42.4%** (23.8–75.3)	**11.9% more** (6.7 fewer to 44.8 more)	⊕◯◯◯ Very low	Uncertain effect on mortality
Delirium *n*=124 (1 non-RCT)	**OR 2.81** (0.54–14.64)	3.3%	**8.8%** (1.8–33.5)	**5.5% more** (1.5 fewer to 30.2 more)	⊕◯◯◯ Very low	Uncertain effect on delirium

Balance between desirable and undesirable effects. The panel concluded that, when considering the balance of effects, the outcomes probably favored the use of non-ketamine sedatives or usual care options including opioids, propofol, dexmedetomidine, or benzodiazepines over ketamine monotherapy. This conclusion was primarily driven by the existing uncertainties regarding the safety profile of ketamine when compared directly with these alternatives.

Equity. The panel recognized that the impact on health equity regarding the use of ketamine in ICUs might vary significantly depending on the regional and economic settings. In high-income regions, ketamine availability may not significantly alter health equity, as a range of sedation options and critical care resources are typically available. Conversely, in low- and middle-income countries, ketamine availability could influence health equity. In such settings, healthcare resources, including critical care manpower and individualized nursing, are often strained; hence, ketamine may be a viable, cost-effective alternative and in some cases the only option. The panel highlighted the potential detriment to health equity in low- and middle-income countries if ketamine was not considered, given its relative accessibility and affordability compared with other sedatives. However, this perspective was tempered by prevailing uncertainties regarding its costs across different regions, and the practicality of managing its adverse effects in resource-limited settings.

Resources and costs. Relevant cost data were collected using two sources: the Saudi Food Drug Authority (SFDA)[40] and the National Unified Procurement Company (NUPCO) for the private and governmental sectors, respectively.[41] The panel acknowledged the complexity of assessing the cost-effectiveness of sedatives in ICUs, particularly given the regional variability of drug prices and the absence of a comprehensive cost-effectiveness analysis. Supplemental Digital Content 1, **Appendix 1, Supplemental Content 12,** http://links.lww.com/AA/E986 included direct medication costs for a 70 kg adult requiring 3 days of analgo-sedation in the ICU. Nevertheless, it is crucial to comprehend that these figures were solely based on direct medication costs and did not factor in other potential aspects of resource use or indirect costs, which could be substantial and challenging to quantify.

Feasibility and acceptability. The panel acknowledged variability in acceptability for ketamine among key stakeholders. A survey conducted in 2019 of SCCM members revealed the infrequent use of ketamine in acute and critically ill patients.[42] Reported barriers to ketamine use include general unfamiliarity with its routine use among several practitioners and restrictive hospital policies. Regarding feasibility, the panel recognized the successful implementation of ketamine administration in the ICU is contingent upon overcoming the identified barriers.

Interpretation and implementation of the recommendation. There is considerable uncertainty about the desirable and undesirable effects of ketamine. The estimates of the undesirable effects are largely derived from observational studies.

Additionally, the costs and required resources, equity, and acceptability vary. In certain settings, particularly in low- and middle-income countries, where ketamine is the only sedative available, its use may be a necessary and acceptable choice. Some panelists felt that ketamine may be a viable monotherapy sedative in patients with reactive airway disease exacerbations, refractory seizures, or intolerance to propofol or dexmedetomidine. However, AEs need to be carefully managed in these patient groups. Notably, psychomimetic hallucinations could contribute to post-traumatic stress disorder (PTSD) or other stress-related issues post-discharge from ICU care.[3–6] Therefore, despite its benefits in certain scenarios, ketamine monotherapy for analgo-sedation is probably better avoided. The implications and interpretation of the proposed recommendation for patients, clinicians, and policymakers are presented in **Table 4**.

Recommendation 2: For critically ill adults undergoing iMV, the panel ***suggests*** using ketamine as an adjunct to non-ketamine usual care sedatives (e.g., opioids, propofol, dexmedetomidine) or continuing with non-ketamine usual care sedatives alone (**conditional recommendation; very low certainty of evidence**).

Remark: For ICU adults requiring analgo-sedation during iMV, the panel suggests two acceptable approaches based on current evidence: using ketamine as an adjunct to usual care sedatives (e.g., opioids, propofol, dexmedetomidine) or continuing with non-ketamine sedatives alone. The use of adjunct ketamine may help reduce doses of these agents, facilitate sedation rotation, or serve as an alternative analgo-sedative strategy, which could be beneficial in specific clinical contexts. The panel acknowledges the potential benefits of adjunctive ketamine but also recognizes the very low certainty of evidence and marginal differences in outcomes compared to continuing non-ketamine sedatives alone. Clinicians are advised to weigh the desirable and undesirable effects of using adjunctive ketamine, taking into account the clinical context and patient preferences.

Rationale and Evidence Summary. The literature search yielded 14 RCTs (n=795) and 7 observational studies (n=1576) (**Table 3B**; Supplemental Digital Content 1, **Appendix 1: Supplemental Content 13-15,** http://links.lww.com/AA/E986).[19,43–59] The pooled estimates from 7 RCTs (n=372) revealed no differences in mortality (within 28 days) (RR 0.99; 95% CI 0.76 to 1.27; low certainty.[2,47–52] The pooled estimates from 6 RCTs (n=465) revealed ketamine for adjunctive analgo-sedation may result in a slight reduction in iMV duration, with a mean decrease noted across all RCTs and in studies with low ROB and surgical non-cardiac surgical subgroups (MD -0.05 days; 95% CI -0.07 to -0.03; low certainty).[2,43,44,50,51,53] Additionally, the pooled estimates from 7 RCTs (n=490) revealed ICU LOS was probably decreased in patients receiving ketamine for adjunctive analgo-sedation; however, the 95% CI was imprecise (MD -0.03 days; 95% CI -0.09 to 0.03; moderate certainty).[2,43,44,47,50,51,53] The pooled estimates of 6 RCTs (n=498) revealed uncertain effects of ketamine as an adjunct on cumulative dose of opioids compared with non-ketamine sedatives/usual care (MD - 11.57 mcg/kg/h MEQ; 95% CI -20.42 to -2.71; very low certainty).[2,44,50,51,53,54] Evidence was downgraded for high ROB, serious inconsistency (I^2 =94%), indirectness of the outcome (i.e., not a patient-centered outcome), and imprecision. Similarly, uncertain effects were noted in cumulative dose of benzodiazepines (7 RCTs; MD 2.37 mcg/kg/h; 95% CI -1.35 to 6.08; very low certainty).[2,47,50–52,55,56] The use of ketamine for adjunctive analgo-sedation may result in little to no difference in cumulative dose of propofol (2 RCTs; MD -0.05 mg/kg/h; 95% CI -0.31 to 0.22; low certainty),[2,51] and dexmedetomidine (1 RCT; MD 0.16 mcg/kg/h; 95% CI -0.01 to 0.33; low certainty).[2] The effects on proportion of time at target sedation and target pain score goals were unclear.[2,45,57,58]

Regarding AEs, a meta-analysis of 12 RCTs (n=654) revealed that ketamine as an adjunct had little to no difference in the rate of any AEs compared with non-ketamine sedatives (RR 0.96; 95% CI 0.67 to 1.37; low certainty).[2,43,44,48–52,54,55,59] The pooled estimates of 6 RCTs (n=425) revealed the uncertain effects of ketamine as an adjunct in the risk of delirium (RR 0.96; 95% CI 0.53 to 1.75; very low certainty).[2,43,49–51,54] The evidence was downgraded for serious inconsistency and imprecision owing to the low number of events and wide 95% CI. Similarly, the pooled estimate for 3 RCTs (n=132) revealed uncertain effects in cumulative dose of vasopressors (MD -0.19 µg/kg/min norepinephrine equivalent; 95% CI -0.46 to 0.08; very low certainty); however, the 95% CI was imprecise, and the evidence was downgraded owing to indirectness of outcome and serious inconsistency (I^2=77%).[2,56,59] A meta-analysis of 3 RCTs (n=183) revealed that adjunctive ketamine had little to no difference in heart rate compared to non-ketamine sedatives (MD 0.65 beats/min; 95% CI -5.56 to 6.85; very low certainty).[2,43,44] The evidence was downgraded for serious inconsistency (I^2=65%) and indirectness of outcome, given heart rate's classification as a surrogate outcome.

Regarding the risk of hypersalivation, 1 RCT (n=83) revealed a non-significant difference.[2] Indirect evidence in pre-hospital setting showed that 18–30% of patients in the high-dose intramuscular ketamine group had hypersalivation requiring intubation.[60–62] Whether this AE is clinically relevant when low-dose ketamine is used remains unknown. The risk of

Table 3B. Evidence profile for PICO 2

Ketamine analgo-sedation (adjunct) versus non-ketamine sedatives or usual care[a]

Outcome No. of participants (n) (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	Comment and interpretation
		Without ketamine	With ketamine for analgo-sedation (adjunct)	Difference		
Mortality at longest follow-up (within 28 days)- all RCTs *n*= 372 (7 RCTs)	**RR 0.99** (0.76–1.27)	33.7%	**33.3%** (25.6– 42.8)	**0.3% fewer** (8.1 fewer to 9.1 more)	⊕⊕◯◯ Low	Little to no difference
Duration of MV (days)- all RCTs *n*=465 (6 RCTs)	-	235	230	MD **0.05 lower** (0.07 lower to 0.03 lower)	⊕⊕◯◯ Low	May slightly reduce duration of MV
ICU LOS (days)- all RCTs *n*=490 (7 RCTs)	-	248	242	MD **0.03 lower** (0.09 lower to 0.03 higher)	⊕⊕⊕◯ Moderate	Little to no difference
Hospital LOS (days) *n*=241 (4 RCTs)	-	120	121	MD **0.7 lower** (1.66 lower to 0.26 higher)	⊕⊕⊕◯ Moderate	Little to no difference
Cumulative dose of opioids - (mcg/kg/hr), expressed as morphine equivalent *n*=498 (6 RCTs)	-	257	241	MD **11.57 lower** (20.42 lower to 2.71 lower)	⊕◯◯◯ Very low	Uncertain effect
Cumulative dose of sedatives (benzodiazepines)- (mcg/kg/hr) *n*=372 (7 RCTs)	-	188	184	MD **2.37 higher** (1.35 lower to 6.08 higher)	⊕◯◯◯ Very low	Uncertain effect
Cumulative dose of propofol- (mg/kg/h) *n*=245 (2 RCTs)	-	125	120	MD **0.05 lower** (0.31 lower to 0.22 higher)	⊕⊕◯◯ Low	Little to no difference
Cumulative doses of dexmedetomidine-(mcg/kg/h) *n*=83 (1 RCT)	-	43	40	MD **0.16 higher** (0.01 lower to 0.33 higher)	⊕⊕◯◯ Low	Little to no difference
Proportion of time (%) at target sedation score goal *n*=297 (3 non-RCTs)	-	150	147	MD **5.46 lower** (15.85 lower to 4.92 higher)	⊕◯◯◯ Very low	Uncertain effect
Proportion of time (%) at target pain score goal *n*=297 (3 non-RCTs)	-	150	147	MD **0.39 higher** (7.76 lower to 8.53 higher)	⊕◯◯◯ Very low	Uncertain effect
Rate of any AE *n*=654 (12 RCTs)	**RR 0.96** (0.67–1.37)	35.9%	**34.4%** (24–49.1)	**1.4% fewer** (11.8 fewer to 13.3 more)	⊕⊕◯◯ Low	Little to no difference
Risk of delirium/psychomimetic effect[b] *n*=425 (6 RCTs)	**RR 0.96** (0.53–1.75)	20.0%	**19.2%** (10.6–35)	**0.8% fewer** (9.4 fewer to 15 more)	⊕◯◯◯ Very low	Uncertain effect
Use of additional antipsychotics- observational studies *n*=343 (4 non-RCTs)	**RR 1.28** (1.01–1.64)	36.2%	**46.3%** (36.6–59.4)	**10.1% more** (0.4 more to 23.2 more)	⊕◯◯◯ Very low	Uncertain effect
Use of additional antipsychotics *n*=83 (1 RCT)	**RR 0.81** (0.19–3.38)	9.3%	**7.5%** (1.8–31.4)	**1.8% fewer** (7.5 fewer to 22.1 more)	⊕◯◯◯ Very low	Uncertain effect
Risk of tachyarrhythmia assessed using heart rate *n*=183 (3 RCTs)[c]	-	93	90	MD **0.65 bpm higher** (5.56 lower to 6.85 higher)	⊕◯◯◯ Very low	Uncertain effect
Cumulative doses of vasopressors- expressed as norepinephrine equivalent (μg/kg/min) *n*=132 (3 RCTs)	-	67	65	MD **0.19 lower** (0.46 lower to 0.08 higher)	⊕◯◯◯ Very low	Uncertain effect
HRQOL metrics - EQ-5D-5L index values and EQ-VAS *n*=100 (1 RCT)	-	50	50	MD **0.36 higher** (0.21 higher to 0.51 higher)	⊕⊕⊕◯ Moderate	Probable improvement in HRQOL metrics - EQ-5D-5L index values and EQ-VAS

[a] Usual care (opioids, propofol, dexmedetomidine, and benzodiazepines)

[b] While specific adverse effects such as unpleasant dreams or nightmares were not explicitly mentioned in the reviewed evidence; instead, they were occasionally included within the broader category of psychomimetic effects observed with ketamine use

[c] The following studies described narratively; Bourgoin 2003 RCT: Comparing ketamine and sufentanil (n=25). A higher heart rate was observed on days 3 and 4 in the ketamine group, with no bradycardia observed in both groups. Christ 1997 RCT: Slight, non-significant decrease in heart rate after 24 hours of ketamine/sufentanil (98±22 beats/min) versus sufentanil/midazolam (101±11 beats/min). Jaeger 2020 observational studies: Similar percentages of days with tachycardia between ketamine and non-ketamine sedative groups, (74% vs 50%, P =.10).

Abbreviations: CI, confidence interval; **GRADE,** Grading of Recommendations, Assessment, Development, and Evaluations; **HRQOL,** health-related quality of life; **ICU,** intensive care unit; **LOS,** length of stay; **MD,** mean difference; i**MV,** invasive mechanical ventilation; **OR,** odds ratio; **RCT,** randomized control trial; **RR,** risk ratio

hepatotoxicity and cholangiopathy were described in 1 observational study (n=243). Approximately 100 patients (59%) received long-term ketamine infusion, of which 33 (33%) fulfilled the criteria for severe cholestatic liver injury, adjusted hazard ratio for the incidence of cholestatic liver injury was 3.2 (95% CI 1.3 to 7.8; p=0.01).[46] The evidence was downgraded for ROB because of residual confounding and for the indirectness of the population (COVID-19-associated acute respiratory distress syndrome) and outcome (rising bilirubin level was the primary outcome and longitudinal surrogate for cholestatic liver injury).

Evidence to recommendation

(**Table 3**; Supplemental Digital Content 1, **Appendix 1: Supplemental Content 15, Supplemental Figure 2,** http://links.lww.com/AA/E986)

Desirable and undesirable effects. The panel concurred the desirable effects might be considered trivial, especially when evaluating critical outcomes. While ketamine may result in 1.2 hours less of iMV, 1 hour less in the ICU, and 16 hours less in the hospital, these effects may not be clinically relevant. Adjunct ketamine therapy might improve health-related quality of life (HRQOL) metrics such as the EQ-5D-5L index values and the EQ-VAS, as reported in one RCT.[2] The effect on cumulative dose of opioids and benzodiazepines, the proportion of time at target sedation, and target pain score range were very uncertain. In addition, adjunctive ketamine therapy had little to no effect on mortality (within 28 days) and the cumulative dose of propofol and dexmedetomidine. The panel concurred that the undesirable effects are probably trivial. Ketamine exhibited little to no difference in AEs with an absolute risk difference of 1.4%. The effect on delirium, use of antipsychotics, cumulative dose of vasopressors, tachyarrhythmia, hepatotoxicity, hypersalivation, and the use of physical restraints remains uncertain. While the panel acknowledged the presence of some evidence from 12 RCTs (n=700), these findings were cautiously interpreted owing to the small number of patients and events, leading to considerable uncertainty.

Certainty of evidence. The overall certainty of evidence was very low owing to the following reasons: (1) high ROB trials with significantly different estimates compared with the subgroup of low ROB trials, suggesting that ROB may be affecting the estimated effects; (2) serious inconsistency in both magnitude and direction; and (3) imprecision with wide 95% CIs, low number of events, and small sample sizes.

Values and preferences. The panel felt patients' values and preferences had a possibility of important uncertainty or variability. The panel recognized gaps in some patient-important outcomes, including ICU-free days, HRQOL with a focus on PTSD, days alive without sedation, vasopressor-free days, and changes in oxygenation. The limited information on long-term functional status further complicated the complete integration of patient values into decision-making, highlighting the need for more data in future research. Based on the patient representative's input, critical outcomes such as health and well-being, iMV duration, ventilator-free days, ICU and hospital LOS, morphine-sparing effect, and risk of delirium, agitation, hepatotoxicity, arrhythmia, and the use of additional anti-psychotics or physical restraints were prioritized. Conversely, less emphasis was placed on outcomes such as hypersalivation and successful extubation. The patient valued decreased morphine and other sedatives use, stressing the importance of remaining pain-free and conscious, and expressed hesitation toward the theoretical risk of hepatotoxicity and preferred to rely on the physician's judgment. Overall, the patient's perspective revealed an equal balance between the desirable and undesirable effects, in which significant

Table 4. Implications of different recommendations for key stakeholders

Category	Strength	For patients	For clinicians	For policymakers
Suggestion against using ketamine monotherapy for analgo-sedation over non-ketamine sedatives or usual care	Conditional	Most patients would avoid ketamine monotherapy for analgo-sedation, although some would not	Different choices might be appropriate for different patients; however, routine use of ketamine monotherapy for analgo-sedation is discouraged	Policymaking will require considerable debate and involvement of several stakeholders
Suggestion for using ketamine as an adjunct to non-ketamine usual care sedatives (e.g., opioids, propofol, dexmedetomidine) or continue with non-ketamine usual care sedatives alone	Conditional	Most patients would use ketamine as an adjunct to non-ketamine usual care sedatives (e.g., opioids, propofol, dexmedetomidine) or continue with non-ketamine usual care sedatives alone	Different choices might be appropriate for different patients; however, use of either ketamine as an adjunct to non-ketamine usual care sedatives (e.g., opioids, propofol, dexmedetomidine) or continuing with non-ketamine usual care sedatives alone should be personalized for every patient	Policymaking will require considerable debate and involvement of several stakeholders

improvements in personal health and recovery were valued over minor differences in AEs.

Balance between desirable and undesirable effects. The panel felt the balance of effects favored neither the intervention nor the comparison driven by the trivial effect in benefits and desirable effects and that in undesirable effects.

Equity. Similar to PICO 1, the panel concurred that the impact of ketamine use on health equity may vary across different settings, influenced by regional healthcare resources, policies, and the socio-economic status of the patient population. In regions with limited healthcare infrastructure and financial resources, ketamine might be a valuable alternative and potentially improve access to quality critical care.[63] Conversely, in regions with well-resourced healthcare systems, ketamine use may not substantially alter the existing health equity dynamics owing to the availability of an array of sedatives.

Resources and costs. The panel recognized the possible variability in the impact of ketamine use on ICU costs and resources, indicating a consensus on its diverse economic implications. The absence of a formal CEA for ketamine as an analgo-sedative for ICU patients was acknowledged. However, existing studies, such as that by Rai et al., clarify the associated potential cost considerations.[38] The benefits of ketamine, owing to its short-acting properties, could contribute to cost savings via earlier tracheal extubation and alleviation of pain, anxiety, and hemodynamic instability. Such outcomes enhance patient care and lead to significant cost savings by reducing the overall burden on healthcare resources. Therefore, the potential role of ketamine in shortening ICU LOS and avoiding costly complications suggests the cost-effectiveness of the intervention. The panel emphasized the importance of conducting comprehensive CEAs, factoring in the broader impacts on the health care system, to clarify the cost-effectiveness of ketamine use.

Feasibility and acceptability. The panel's consensus for the probable feasibility and acceptability of ketamine for adjunctive analgo-sedation in the ICU acknowledged the same barriers identified in PICO 1.[64]

Accordingly, institutions are encouraged to develop specific protocols delineating clear indications for ketamine to enhance the practicability of its use. This involves educating healthcare providers to broaden their understanding of ketamine administration and its potential side effects, enhancing familiarity and confidence via targeted education and protocol development, and conducting rigorous research that evaluates the full effects of ketamine on patient-centered outcomes.

Interpretation and implementation of the recommendation. The desirable and undesirable effects were considered trivial, with a significant level of uncertainty. Patient's valuation of these outcomes indicated a possibility of important uncertainty or variability, leading to a balanced effect that decidedly favored neither the intervention nor the comparison. Moreover, while the cost associated with ketamine use varied, the panel did not foresee any major acceptability or feasibility issues. The panel's conditional recommendation for either the intervention or the comparison prioritized a more selective and judicious application, customized to suit individual patient needs and specific clinical situations. It may be more appropriate to reserve ketamine for select cases where more well-established or thoroughly examined agents have proven ineffective. A suggestion for either the intervention or the comparison implies that most patients in this situation would use ketamine as an adjunct to non-ketamine usual care sedatives (e.g., opioids, propofol, dexmedetomidine) or continue with non-ketamine usual care sedatives alone. The implications and interpretation of the proposed recommendation for patients, clinicians, and policymakers are presented in **Table 4**.

Special Consideration. Both *a priori* subgroups, evaluated for the critical outcomes, were considered to be of low credibility (Supplemental Digital Content 1, **Appendix 1: Supplemental Content 14,** http://links.lww.com/AA/E986). A subgroup difference in AEs was observed in the surgical cardiac ICU patient population. Surgical non-cardiac subgroup analysis exhibited a significant reduction in iMV duration and possible shorter ICU LOS. Reduced opioid use was more pronounced in the surgical population, suggesting ketamine's role as an opioid-sparing analgesic within these subgroups. However, these analyses may be underpowered. Therefore, the panel did not make specific subgroup recommendations based on these analyses.

DISCUSSION

This RPG identified new evidence for evaluating ketamine use for analgo-sedation in a diverse population of critically ill adults, last evaluated in the PADIS guidelines. The evidence comprised of small-scale, single-center RCTs of variable quality, with substantial heterogeneity between the results. Notably, many of these RCTs varied on implementation strategies to adopt the PAD/PADIS guidelines (e.g. the Assessment, prevention, and management of pain; spontaneous awakening and breathing trials; Choice of analgesia and sedation; Delirium assessment; Early mobility and exercise; and Family engagement and

empowerment [ABCDEF] bundle).[5] A recent systematic review and meta-analysis reported that multiple implementation strategies to adopt the PAD/PADIS guideline recommendations may reduce mortality, iMV duration, and ICU LOS.[65]

In the Eastern Association for the Surgery of Trauma and the Chest Wall Injury Society guideline for older adults with multiple rib fractures and dyspnea or refractory pain, ketamine use demonstrated no significant reduction in pain score; however, a trend toward reduced opioid use was found. Due to the lack of data, the committee made no recommendation for or against ketamine vs. usual care (multimodal pain therapy as per institutional protocol).[66]

Recently, a systematic review and meta-analysis involving 252 RCTs with 30,757 patients indicated an association between propofol use in anesthesia and critical care and an increased risk of mortality, with a number needed to harm of 235.[67] On the contrary, a study conducted by Shehabi et al. in 2023 suggested a differential effect of sedation strategies on mortality. In adults < 65 years, sedation with a combination of propofol with dexmedetomidine revealed that the incremental dose of propofol was associated with a decreased mortality, while those with dexmedetomidine had increased mortality at 90 days.[68] Similarly, a study by Schaefer et al. highlighted that an incrementally higher dose of propofol was linked to decreased odds of 1-year mortality in patients without solid cancer (adjusted odds ratio 0.78; 95% CI 0.71–0.85).[69] These debates prompt a broader examination of sedation practices in critical care, emphasizing the importance of further research trajectories to untangle the interactions between sedative choices and patient outcomes.

When using ketamine for analgo-sedation in the ICU, several factors must be considered to ensure patient safety and optimize therapeutic outcomes (**Table 2, practical considerations**). The very low certainty of evidence necessitates a cautious approach to the clinical use of ketamine. Regarding the monitoring and evaluation of ketamine use in patients with brain injury, existing evidence indicating that ketamine does not significantly increase intracranial pressure may address clinician concerns about its safety.[70–72]

The strengths of this RPG are inclusion of diverse multinational panelists, rigorous adherence to the GRADE methodology which encompasses a thorough assessment of publication bias, comprehensive assessment of the literature, inclusion of a patient representative on the panel, and the use of the EtD framework which enhanced the transparency of the judgments.[73] The panel acknowledged that depending on specific characteristics and clinical circumstances, some patients may require individualized approaches, which warrant deviation from the recommendations; thus, these recommendations cannot completely replace expert bedside clinical judgment.

One notable limitation is the inclusion of a single patient representative as a panel member. Relying on a single individual may not accurately reflect the diversity and patients' values and preferences within the broader cohort of patients. Additionally, the absence of a formal CEA presents another shortcoming. Without a formal CEA, the guidelines may lack a critical evaluation of the economic implications and resource allocation. Together, these weaknesses highlight the need for more diverse representation of patient experiences— including varied diagnoses, geographic locations, and genders—and conducting a rigorous CEA to enhance the guidelines' relevance and effectiveness. Another limitation is the use of a broad range of non-ketamine sedatives or usual care—including opioids, propofol, dexmedetomidine, and benzodiazepines—as comparators. This may introduce heterogeneity due to varying sedative properties, levels of sedation, and delirium risk which we accounted for by downgrading the evidence for inconsistency. Additionally, the under-reporting of specific side effects, such as dreams and nightmares, often grouped under broader categories like CNS or psychomimetic effects, may complicate the accurate assessment of these particular side effects.

Research priorities

High-quality, multicenter clinical trials examining the effects of ketamine use in the ICU on patient-important outcomes are needed. The panel identified several potential research priorities (**Figure 3).** A comprehensive network meta-analysis would likely provide additional insights regarding the efficacy and safety of ketamine against various sedative comparators in different settings to optimize sedation practices.

Plan for guidelines adaptation and updating

The panel agreed that the choice between using ketamine versus non-ketamine sedatives in adult ICU patients should be individualized based on existing frameworks, including the balance between the desirable and undesirable effects, available resources, and clinical context.[74–76] This RPG will be updated if new potentially practice-changing studies are published. Furthermore, the EtD framework may serve as the basis for adaptation of the present recommendations in different contexts by local, regional, or international guidelines.

Additional topics beyond the scope of this guideline

The panel acknowledges the potential consideration of ketamine in cases of status epilepticus requiring general anesthesia. The search strategy and the guidelines developed herein primarily focused on the use

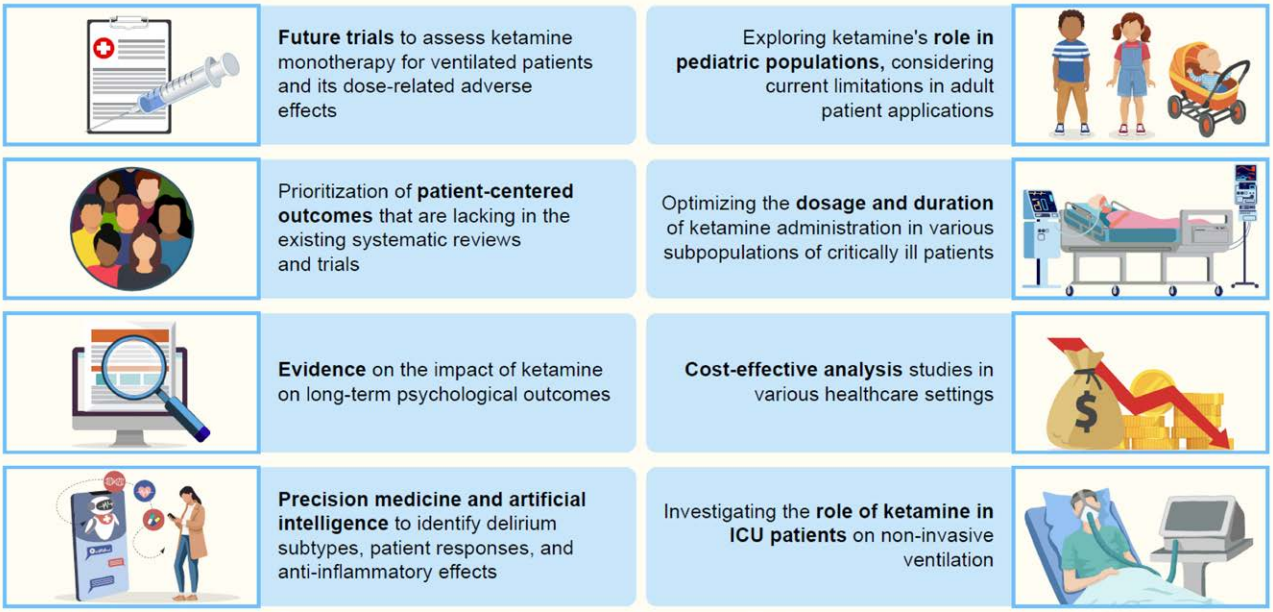

Figure 3: Research priorities. This figure describes the potential research priorities identified by the panel: 1) There are no high-certainty trials evaluating ketamine monotherapy for analgo-sedation. Future trials should compare its favorable cardiorespiratory benefits with its dose-related AEs. 2) Current reports lack comprehensive data on psychomimetic effects including delirium, unpleasant dreams, and nightmares emphasizing the need for their inclusion in future studies for a longer follow-up period to adequately capture and understand the full spectrum of these AEs; 3) Several patient-centered outcomes prioritized by the panel were not reported in any of the systematic reviews and RCTs. Data on outcomes such as long-term mortality (e.g. 90 days or 6 months), ICU-free days, HRQOL, and vasopressor-free days are lacking in existing trials and reviews. Future studies should consider days alive out of hospital, and rates of re-intubation and extubation failure as well; 4) Evidence on the impact of ketamine on long-term psychological outcomes such as cognitive function assessments and PTSD is lacking; 5) Future studies should focus on the integration of precision medicine approaches and artificial intelligence to identify delirium subtypes, specific patient responses, and unique clusters (phenotypes and genotypes) that are most responsive to the anti-inflammatory pleiotropic effects of ketamine, aiming for optimal analgo-sedation; 6) Exploration of the potential role and benefits of ketamine in pediatric populations, acknowledging the current limitations of application to adult patients; 7) Evaluation of the optimal dose and duration of ketamine administration in various subpopulations of critically ill patients; 8) CEA studies are needed in various healthcare settings; 9) Evaluation of the role of ketamine in ICU patients on non-invasive ventilation. **Abbreviation:** AEs, adverse events; CEA, Cost-effectiveness analysis; HRQOL, Health-related quality of life; ICU, intensive care unit; PTSD, post-traumatic stress disorder; RCT, randomized controlled trial.

of ketamine for analgo-sedation in ICU patients. The literature reviewed as part of the guideline development process explicitly excluded the use of ketamine for burst suppression in patients with status epilepticus. Although ketamine may be a valuable therapeutic option for certain patients with seizures, this specific application is outside the purview of this RPG.

CONCLUSION

The panel issued two conditional recommendations: (1) against using ketamine monotherapy for analgo-sedation and (2) using ketamine as an adjunct to non-ketamine usual care sedatives (e.g., opioids, propofol, dexmedetomidine) or continuing with non-ketamine usual care sedatives alone based on an assessment of the balance between desirable and undesirable effects, available resources, and clinical context. Furthermore, the panel identified areas for future research. ■

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AUTHORS' CONTRIBUTIONS

MA was involved in data abstraction, statistical analysis, and methodological aspects of the guideline. Initial collaborative effort was initiated via a teleconference between MA and MHM to discuss the relevance for SSAI. MA, MHM, and WA were members of the steering committee. MA, MHM, KO, MSA, YS, YA, and WA were members of the writing committee and critically revised previous versions of the manuscript. All other authors were panel members and reviewed and approved the final version of the manuscript. NAS was a public panel member who shared patients' perspectives and provided input on patients' values and preferences. All authors read and approved the final manuscript. Details of co-authors' contributions are listed in (Supplemental Digital Content 1, **Appendix 1: Supplemental Content 1,** http://links.lww.com/AA/E986).

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