Review

Emergency and Critical Care Medicine

OPEN

Ketamine use in adult intensive care unit: a narrative review of emerging applications, efficacy challenges, and safety concerns

Siyao Zeng[a], Zhipeng Yao[b], Chunming Guan[a], Shanpeng Cui[a], Zhen Quan[a], Yue Li[b,*], Junbo Zheng[b,*], Hongliang Wang[b,*]

Abstract

Ketamine, a dissociative anesthetic with distinct sedative and analgesic properties, is receiving renewed attention in critical care owing to its unique pharmacological profile. Although historically limited by concerns over psychoactive side effects, its ability to maintain hemodynamic stability has prompted growing interest in its use in intensive care settings. This narrative review synthesizes emerging evidence on 10 potential applications of ketamine in the intensive care unit (ICU), including opioid-sparing analgesia, sedation during mechanical ventilation, rapid sequence intubation, and management of sepsis, postcardiac surgery states, acute brain injury, super-refractory status epilepticus, acute severe asthma, delirium, and psychiatric disorders. Although ketamine shows promising advantages—such as reduced opioid use and improved cardiovascular stability—the quality of supporting evidence remains low, with limitations including small sample sizes, study heterogeneity, and methodological concerns. Evidence regarding its impact on long-term outcomes, such as mortality, cognitive function, and length of ICU stay remains inconclusive. Some data suggest that ketamine may reduce the incidence of ICU delirium and aid in managing refractory psychiatric conditions; however, concerns about adverse effects—including cardiovascular strain, emergence reactions, and potential neurotoxicity—require cautious application. Despite these challenges, the utility of ketamine in patients with hemodynamic instability, particularly in sepsis and during tracheal intubation, highlights its potential as a versatile agent in critical care pharmacotherapy. Current guidelines recommend restrained, adjunctive use pending further high-quality evidence. This review emphasizes the need for large-scale, multicenter randomized controlled trials to define the role of ketamine, refine dosing strategies, and assess safety across diverse ICU populations. As clinical interest expands, the integration of ketamine into ICU practice must be guided by both innovation and vigilant safety monitoring.

Keywords: Intensive care unit, Ketamine, Mechanical ventilation, Opioid consumption, Rapid sequence intubation, Sepsis

Introduction

Ketamine is a dissociative anesthetic with a unique pharmacological profile that has historically seen limited use in the intensive care unit (ICU). Early hesitation stemmed from concerns about its psychoactive side effects; however, its combined sedative, analgesic, and *N*-methyl-D-aspartate (NMDA) receptor antagonist properties confer distinct advantages for critically ill patients and support its potential use across a range of critical conditions [1]. Well-established clinical applications, such as during orotracheal intubation for its ability to preserve hemodynamic stability, have made ketamine a preferred option in settings where hypotension is a concern [2,3]. In recent years, a growing body of research has expanded its therapeutic roles in critical care, identifying several emerging uses [4–16]. Beyond its traditional role in induction, ketamine is now being explored as an adjunct analgesic to reduce opioid requirements and as an alternative sedative for mechanically ventilated patients [17,18]. Its distinct profile is also under investigation in refractory conditions, such as super-refractory status epilepticus (SRSE) and severe asthma exacerbations (SAEs), and it has shown early promise in preventing ICU delirium [7–11]. This review synthesizes current evidence on 10 emerging ICU applications of ketamine. We critically assess its efficacy, safety, and clinical practicality in each domain, highlighting knowledge gaps and methodological limitations within the literature. By integrating preclinical insights with clinical trial findings, this article aims to support evidence-based practice while identifying priorities for future research. As ketamine evolves from a niche agent into a versatile tool in critical care, balancing its therapeutic potential with rigorous safety evaluation is essential to optimize outcomes for critically ill patients.

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

[a]Harbin Medical University Graduate School, Harbin Medical University, Harbin, Heilongjiang, China, [b]Department of Critical Care Medicine, Second Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang, China.

** Corresponding authors. Address: No. 246 Xuefu Road, Nangang District, Second Affiliated Hospital of Harbin Medical University, Harbin 150086, Heilongjiang, China. E-mail address: icuwanghongliang@163.com (H. Wang); icuzhengjunbo@126.com (J. Zheng); liyuevickey@126.com (Y. Li).*

Emergency and Critical Care Medicine (2025) 5:3

Received: 23 April 2025; Accepted: 23 June 2025

Published online: 29 July 2025

http://dx.doi.org/10.1097/EC9.0000000000000152

Methods

We conducted a focused literature search in PubMed, Scopus and Web of Science from database inception through May 31, 2025, using combinations of the following terms: "ketamine," "ICU," "critically ill patients," "clinical guidelines," "meta-analysis," "systematic review," "randomized controlled trial," "observational study," "retrospective study," and "case report." This narrative review adopted a hierarchical evidence selection framework with the following prioritization: primary sources included recent clinical practice guidelines, systematic reviews, and meta-analyses that offer expert consensus and pooled estimates across multiple studies. When available, we incorporated representative randomized controlled trials (RCTs) and observational studies—whether prospective or retrospective—to contextualize key findings, assess relevance to real-world ICU settings, and identify discrepancies between pooled and individual-study outcomes. In areas with limited high-quality evidence, such as emerging or infrequently studied indications, we included case series and case reports to capture practice variability, novel therapeutic applications, and rare adverse events associated with ketamine use in intensive care. Studies were eligible if they evaluated ketamine use in adult ICU settings, including but not limited to analgesia, sedation, intubation, hemodynamic stabilization, delirium management, or psychiatric complications. We excluded studies unrelated to ICU populations, pediatric-only research, and non-English publications.

Results

Reducing opioid consumption

Analgesia and sedation are essential components of treatment for patients in the ICU. Traditional analgesics, such as opioids, not only carry risks of addiction and tolerance but also cause adverse effects, including respiratory depression, reduced gastrointestinal motility, and immunosuppression. Opioids can also induce opioid-induced hyperalgesia [1]. Ketamine provides analgesia through multiple mechanisms. Although it interacts with μ and κ opioid receptors, contributing to its analgesic properties, its primary mechanism involves inhibition of NMDA receptors. These receptors play a key role in central sensitization and the development of chronic pain. By blocking NMDA receptor activity, ketamine offers effective pain relief without the respiratory depression typically associated with opioids [1].

Furthermore, NMDA receptor blockade by ketamine directly modulates glutamatergic neurotransmission by influencing glutamate release and downstream receptor activity, including α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor signaling. The analgesic profile of ketamine is strengthened through modulation of multiple glutamate-dependent pathways [19]. In addition, ketamine exerts broader pleiotropic effects by enhancing inhibitory γ-aminobutyric acid activity and interacting with monoaminergic, cholinergic, and inflammatory systems. These complex and interconnected mechanisms may explain the broad therapeutic efficacy of ketamine, including its role in treating opioid-resistant pain, hyperalgesia, and psychiatric conditions frequently observed in ICU settings [19].

A clinical practice guideline developed by critical care experts conditionally recommends the use of low-dose ketamine as an adjunct to opioid therapy to reduce postoperative opioid consumption in adult patients in the ICU. However, this recommendation is based primarily on a single-center, double-blind RCT involving only 93 patients following abdominal surgery, which showed a 22-mg reduction in morphine use but no significant difference in patient-reported pain intensity. Although opioid-sparing effects are theorized to reduce adverse events such as respiratory depression and gastrointestinal dysfunction, the guideline panel explicitly notes that reduced opioid consumption is a surrogate outcome, with no demonstrated association with patient-centered outcomes such as mortality or functional recovery. The strength of the recommendation is further limited by a high risk of bias in the trial and limited applicability to nonsurgical or medically complex ICU populations [18].

A recent meta-analysis of 6 RCTs showed that adjunctive ketamine significantly reduced opioid consumption in critically ill patients (mean difference: −13.19 μg/kg/h in morphine equivalents; 95% confidence interval [CI]: −22.10 to −4.28; P = 0.004). However, the certainty of this evidence was rated very low due to substantial heterogeneity among studies. The included trials differed considerably in patient populations (such as postoperative patients in the ICU, mechanically ventilated patients, and patients on extracorporeal membrane oxygenation), ketamine administration protocols, and opioid delivery methods (patient-controlled analgesia vs. continuous infusion) [17]. Among these studies, the trial by Perbet et al. (2018), which enrolled the largest and most representative ICU cohort, reported no significant reduction in opioid use [20]. In contrast, at least 3 other RCTs—Guillou (2003), Minoshima (2015), and Anwar (2019)—consistently reported reduced postoperative opioid requirements with ketamine use [21–23]. The trial by Perbet et al. may have been affected by optimized baseline sedation strategies, including nurse-driven protocols and low-dose remifentanil, which could have masked any opioid-sparing effect of ketamine [20]. The smallest trial, conducted by Dzierba et al. (2016) and involving only 20 patients on extracorporeal membrane oxygenation, also failed to show opioid reduction. This outcome may reflect the absence of a standardized protocol for sedative down-titration [24]. Although the pooled analysis reached statistical significance, small sample sizes, inconsistent trial designs, and limited generalizability led the meta-analysis authors to downgrade the quality of evidence [17].

In addition to these RCTs, 3 retrospective cohort studies—by Reese et al. (2018), Shurtleff et al. (2020), and Jaeger et al. (2021)—consistently reported significant reductions in opioid and sedative requirements with adjunctive ketamine use. A pooled analysis showed a reduction in opioid consumption of −26.53 μg/kg/h in morphine equivalents (95% CI: −50.95 to −2.11; P = 0.03), although the certainty of this evidence remains low given the limitations of nonrandomized designs. Jaeger et al. observed decreased use of continuous fentanyl and intermittent benzodiazepines, whereas Reese et al. reported reductions in fentanyl, lorazepam, midazolam, and dexmedetomidine use among patients with septic shock managed with ketamine as the primary sedative. These findings support the potential opioid-sparing role of ketamine, although confounding factors—such as baseline illness severity, sedation targets, and clinician variability—cannot be ruled out [25–27].

Overall, although the pooled effect from RCTs reached statistical significance, small sample sizes, inconsistent trial designs, and limited generalizability led the meta-analysis authors to downgrade the quality of evidence. Ketamine shows promise as an opioid-sparing agent in critical illness, but routine use should be approached with caution until validated by larger, high-quality trials with harmonized protocols across diverse ICU populations.

Tracheal intubation

In the ICU, rapid sequence intubation (RSI) is often required. Current guidelines from the French Society of Anesthesia and Intensive Care Medicine and the French-speaking Intensive Care Society recommend ketamine, etomidate, and propofol as induction agents. However, the supporting evidence has notable limitations. These guidelines reflect expert consensus but lack a systematic comparison of induction agents and do not adequately address patient-specific management strategies [3].

The 2023 clinical practice guideline from the Society of Critical Care Medicine states that etomidate, ketamine, and propofol show no significant differences in mortality, peri-intubation hypotension, or vasopressor requirements during RSI in critically ill adults. This conditional recommendation, based on moderate-quality evidence, highlights the absence of clear superiority among agents. Although the guideline does not explicitly call for personalized selection, it suggests that the choice of agent should be guided by patient-specific factors such as hemodynamic status and comorbidities, rather than presumed safety differences [28].

Administering induction agents, such as propofol, can cause hypotension, which is especially harmful in patients with hemodynamic instability, such as those in shock [3]. Moreover, prior meta-analyses have shown that etomidate is associated with higher mortality in RSI compared with ketamine, which may be attributed to its common adverse effect of adrenal insufficiency [29]. A recent Bayesian meta-analysis that included 7 RCTs and 1 propensity-matched study compared ketamine and etomidate in critically ill adults requiring endotracheal intubation. The analysis found an 83.2% probability that ketamine reduced mortality, although the relative risk was not statistically significant. Despite the favorable hemodynamic profile of ketamine—through sympathetic stimulation, parasympathetic inhibition, and catecholamine reuptake suppression—the analysis did not show significant differences in secondary outcomes, including Sequential Organ Failure Assessment (SOFA) score, ventilator-free days, vasopressor-free days, or postinduction mean arterial pressure [2].

Two pivotal RCTs contributed substantially to this meta-analysis [30,31]. In the largest trial (Matchett et al., 2022; n = 801), ketamine was linked to significantly higher Day 7 survival compared with etomidate (85.1% vs. 77.3%; $P = 0.005$), although this difference was not sustained at Day 28 (66.8% vs. 64.1%; $P = 0.294$). Despite improving early survival, ketamine was paradoxically associated with more frequent postinduction hypotension requiring vasopressors, raising concerns about its hemodynamic effects in patients with depleted catecholamine reserves [31].

In another multicenter RCT by Jabre et al. (2009; n = 655), ketamine showed a similar trend toward reduced organ dysfunction, with a lower, although not statistically significant, maximum SOFA score over the first 3 ICU days (9.6 vs. 10.3; $P = 0.056$). Notably, adrenal insufficiency occurred significantly more often in the etomidate group (86% vs. 48%; $P < 0.0001$), reinforcing the biological rationale for ketamine as a preferred agent in critically ill patients, particularly those with sepsis [30].

Two RCTs not included in the Bayesian meta-analysis provide additional insights [32,33]. A single-center RCT by Knack et al. (2023; n = 143) compared ketamine and etomidate for RSI in critically ill adults in the emergency department and found no significant difference in the primary outcome of maximum SOFA score over the first 3 days (median 6.5 vs. 7.0; $P = 0.79$). The incidence of postintubation hypotension was also similar (28% vs. 26%), and 30-day mortality did not differ significantly (11% vs. 21%). Although mortality numerically favored ketamine, the difference was not statistically significant, possibly because of limited sample size [32].

Another RCT by Srivilaithon et al. (2023; n = 260) focused on patients with sepsis requiring emergency intubation in the emergency department—a group particularly vulnerable to hemodynamic compromise. In this single-blind, parallel-group trial, patients were randomized to receive either etomidate (0.2–0.3 mg/kg) or ketamine (1–2 mg/kg) for induction during RSI. Although 28-day survival did not differ significantly between groups (80.8% vs. 73.1%; $P = 0.092$), the study revealed a marked difference in early hemodynamic outcomes. A significantly higher proportion of patients in the etomidate group required vasopressor support within 24 hours after intubation (43.9% vs. 17.7%; $P < 0.001$), suggesting greater early circulatory compromise with etomidate despite its traditional reputation for hemodynamic stability [33].

Despite these findings, substantial heterogeneity exists across studies, including differences in patient populations, clinical settings, and intubation protocols. Moreover, all direct comparisons to date involve etomidate, leaving the efficacy of ketamine relative to propofol unexamined [2]. Although emerging evidence suggests that ketamine may offer advantages over etomidate for RSI in critically ill adults—particularly in sepsis—its superiority has not been definitively established. Additional head-to-head trials with other agents and standardized outcome reporting are needed to draw firm conclusions.

Mechanically ventilated patients

Unlike sedatives, such as midazolam and other benzodiazepines, and analgesics, such as morphine and fentanyl, ketamine does not suppress respiratory function [34]. A rapid practice guideline—*Ketamine Analgo-sedation for Mechanically Ventilated Critically Ill Adults*—jointly issued by the Saudi Critical Care Society and the Scandinavian Society of Anesthesiology and Intensive Care Medicine, reports that ketamine-assisted analgesia and sedation do not affect 28-day mortality, may slightly reduce mechanical ventilation duration, and can decrease length of ICU stay [34]. However, these conclusions are based on very low-certainty evidence because of methodological concerns, including high risk of bias, inconsistency, indirectness, and imprecision. Cumulative doses of opioids, sedatives, and vasopressors, along with long-term outcomes, such as cognitive function and posttraumatic stress disorder (PTSD), remain poorly characterized. Adverse effects, such as delirium, hypersalivation, and hepatotoxicity, are inconsistently reported, with observational data suggesting potential risks.

A relatively large RCT conducted by Perbet et al. (2018; n = 162) evaluated low-dose ketamine infusion (2 mg/kg/h) in mechanically ventilated patients in the ICU receiving remifentanil-based sedation. The study found no reduction in opioid use and no improvement in length of ICU stay or mortality [20]. Based on these findings, the guideline conditionally recommends ketamine only as an adjunct to nonketamine sedatives or analgesics, rather than as monotherapy, to optimize analgesia and sedation while limiting potential adverse effects [34]. However, given the lack of high-quality evidence and long-term outcome data, clinicians should exercise caution when incorporating ketamine into sedation protocols for mechanically ventilated patients. Patient-specific factors—including baseline hemodynamic status, vasopressor requirements, risk of delirium or psychiatric effects, hepatic and renal function, cumulative exposure to opioids or benzodiazepines, and potential drug–drug interactions—should be carefully considered when selecting a sedative strategy.

Sepsis and septic shock

Because of its unique pharmacological properties, ketamine may be a suitable option for analgesia and sedation in hemodynamically unstable patients in the ICU [26]. A prospective, open-label study evaluated early ketamine administration in mechanically ventilated patients with septic shock, assessing its impact on hemodynamics and the need for other analgesics and sedatives. The results showed reductions in norepinephrine, vasopressin, benzodiazepine, and opioid use. However, the small sample size (n = 17), nonrandomized design, and reliance on historical controls introduce selection bias and confounding, and the lack of blinding further limits the strength of evidence [26]. Furthermore, a recent RCT compared ketamine with fentanyl in patients with septic shock requiring mechanical ventilation and found that ketamine led to higher cardiac output and stroke volume. Although the design was rigorous, the study had a relatively small sample size (n = 86) and assessed only short-term (15-minute) hemodynamic parameters, without examining clinical end points, such as mortality, organ function, or long-term outcomes [4]. Overall, clinical data suggest that ketamine may offer hemodynamic benefits in septic shock, but current evidence remains limited.

Sedation after cardiac surgery

A network meta-analysis found that, compared with other sedatives, the combination of dexmedetomidine and ketamine was associated with shorter mechanical ventilation duration and reduced length of ICU stay in patients after cardiac surgery. However, conclusions should be interpreted cautiously given the small sample sizes, limited direct comparisons between interventions, and potential methodological biases in the included studies. These findings are supported by an RCT performed by Rai et al. (n = 40), which compared dexmedetomidine alone with a ketamine–dexmedetomidine combination in patients undergoing coronary artery bypass grafting. The combination group required significantly less fentanyl (45.7 ± 8.2 vs. 146.0 ± 14.2 μg; $P < 0.001$), had faster weaning from mechanical ventilation (344.7 ± 43.9 vs. 446.6 ± 73.8 min; $P < 0.001$), and exhibited shorter extubation times (389.9 ± 35.9 vs. 535.3 ± 36.3 min; $P < 0.001$), with no significant differences in length of ICU stay, sedation scores, or hemodynamic measures. These results suggest that ketamine, when added to dexmedetomidine, may improve analgesia and accelerate postoperative recovery after cardiac surgery. Nevertheless, broader validation is needed given the small sample size and single-center design [35]. Although the hemodynamic properties of ketamine—such as sympathetic activation—may theoretically benefit patients with ventricular dysfunction or those receiving mechanical circulatory support, current evidence has not confirmed its safety or efficacy in high-risk subgroups, such as patients with cardiogenic shock or those dependent on ventricular assist devices [5].

Acute brain injury

Cortical spreading depolarization is a key mechanism in the progression of Acute brain injury (ABI) [6]. A systematic review by Telles et al. suggests that ketamine can inhibit spreading depolarization through multiple mechanisms, with neuroprotective effects demonstrated across various types of human ABI. However, most included studies were preclinical or small-scale clinical trials, and clinical evidence remains limited [6]. Concerns also persist regarding the potential of ketamine to elevate intracranial pressure (ICP), contributing to ongoing debate over its use in patients with ABI [36].

Another systematic review by Gregers et al. analyzed 11 studies involving 334 patients with ABI to further assess concerns about ICP. Among the 7 studies that reported ICP outcomes, 2 documented transient elevations—a case during endotracheal suctioning (a known ICP trigger), and another on postinjury days 8 and 10, although values remained within normal clinical limits. In contrast, 2 studies—including 1 in pediatric patients—showed significant ICP reductions after ketamine administration. The remaining studies reported no significant ICP changes and no association between ketamine use and adverse neurological outcomes or mortality. Overall, the evidence suggests that although context-specific ICP elevations may occur, ketamine given under controlled ventilation does not cause clinically meaningful or sustained increases in ICP in patients with ABI [36].

Furthermore, a meta-analysis by Andreasen et al., which included 5 RCTs, found that the effects of ketamine on functional outcomes and severe adverse events in patients with severe ABI remain uncertain because of high risk of bias and small sample sizes. However, no current evidence indicates that ketamine worsens brain injury or increases ICP [37].

In conclusion, ABI is no longer considered an absolute contraindication to ketamine use. Although growing evidence supports its safety regarding ICP stability, the use of ketamine should be individualized and closely monitored, given the limited number of high-quality RCTs and the methodological variability across existing studies.

Super-refractory status epilepticus

SRSE, defined as seizures persisting or recurring despite 24 hours of anesthetic treatment, is associated with high mortality and limited high-quality evidence to guide ICU management. Two systematic reviews, encompassing 19 and 11 studies respectively, suggest that ketamine offers NMDA receptor-mediated neuroprotection and better hemodynamic stability compared with agents that act on the γ-aminobutyric acid system. However, critical limitations weaken these conclusions. Both reviews primarily included retrospective case series and reports without control groups, resulting in low evidence certainty. Heterogeneity in ketamine dosing, timing, and concurrent therapies precluded meta-analysis and obscured dose–response relationships. Outcome reporting was inconsistent, with limited data on adverse effects and functional outcomes. Neither review stratified findings by SRSE etiology or semiology, further limiting clinical applicability [7,8].

Further insights come from 2 large retrospective cohort studies. A multicenter study by Alkhachroum et al. included 68 patients with SRSE treated with continuous ketamine infusion, with 81% achieving seizure termination. Ketamine use was associated with reduced vasopressor requirements compared with other anesthetics, and no significant increases in ICP were reported, supporting its potential for both neuroprotection and hemodynamic stability [38]. Similarly, Sabharwal et al. retrospectively evaluated 67 patients with SRSE treated with ketamine–propofol combination therapy, reporting a 91% seizure resolution rate and a manageable mortality rate of 39%. Early initiation of ketamine (within 24–48 hours) was common, and although vasopressor use was frequent, it was not attributed specifically to ketamine. In this cohort, ketamine was well-tolerated across diverse SRSE etiologies, including anoxic brain injury, further supporting its role in complex ICU populations [39].

Taken together, these findings highlight the therapeutic potential of ketamine in SRSE management. However, the lack of RCTs, reliance on retrospective data, and protocol variability call for cautious interpretation and underscore the need for prospective, standardized trials.

Acute severe asthma and severe asthma exacerbations

Ketamine may benefit asthma management through several mechanisms, including sympathetic stimulation, vagal inhibition, calcium-mediated smooth muscle relaxation, and anti-inflammatory effects [9]. Acute severe asthma refers to exacerbations that respond poorly to conventional therapies, such as inhaled short-acting β_2-agonists [9]. SAEs involve worsening bronchospasm and respiratory distress requiring emergency care, and, in some cases, ICU admission. Ketamine has been proposed as a treatment option for SAEs, especially refractory cases [10]. A systematic review by Epperson et al. found that ketamine significantly improves the clinical asthma score and peak expiratory flow, suggesting a potential role in acute severe asthma [9]. In contrast, an earlier systematic review by La Via et al. emphasized that although some studies reported short-term improvements in peak expiratory flow with high-dose ketamine, overall evidence does not support reduced need for invasive ventilation or improved oxygenation [10]. Ketamine was also associated with adverse effects, such as hypertension and tachycardia, leading to a recommendation against its routine use in SAEs [10]. These conflicting findings reflect limitations in the evidence base. Epperson et al. included studies without control groups and lacked assessment of publication bias. Many cited studies were small-sample observational trials with substantial heterogeneity, including mixed pediatric and adult populations and varied dosing regimens [9]. Similarly, La Via et al.—although limited to prospective studies, including 5 RCTs—reported heterogeneity in study design, comparator agents, and outcome measures. This review included a mixed patient population, with 4 studies focused on adults and 3 on pediatric patients, ultimately precluding meta-analysis because of clinical heterogeneity and the risk of bias from pooling age groups [10].

Further clinical insight comes from a recent single-center RCT by Nedel et al., which involved mechanically ventilated adults with severe asthma or chronic obstructive pulmonary disease exacerbations.

The study compared continuous ketamine infusion (2 mg/kg/h) with standard fentanyl analgesia and found no significant improvement in airway resistance or intrinsic positive end-expiratory pressure at 3 or 24 hours. No differences were observed in ventilator days or mortality, suggesting limited benefit of ketamine for bronchospasm relief in critically ill, ventilated patients [40].

In summary, although retrospective data suggest that ketamine may improve airflow dynamics in acute asthma, clinical benefits remain uncertain because of heterogeneity, small sample sizes, and inconsistent outcome reporting. These findings warrant cautious optimism but do not support routine ketamine use for SAEs until validated by large-scale, high-quality trials.

Delirium

Delirium is a common acute syndrome in the ICU, linked to higher mortality, prolonged ICU stays, and poorer long-term outcomes [11]. Although ketamine is known to induce delirium, particularly at high doses, a recent meta-analysis of 4 RCTs suggested that it significantly reduced the incidence of delirium in critically ill patients compared with traditional medications. However, these findings should be interpreted with caution because of substantial methodological limitations. The meta-analysis included only 4 RCTs with a total of 358 patients, making the evidence underpowered and fragile. Sensitivity analyses showed loss of statistical significance when individual studies were excluded, and trial sequential analysis failed to confirm robustness, indicating that the cumulative evidence remains insufficient. Variability in ketamine dosing, comparator agents, and patient populations further limits generalizability. Furthermore, 3 of the 4 studies had unclear or high risk of bias, particularly regarding allocation concealment and blinding, raising concerns about overestimation of treatment effects [11]. Assessment methods also varied, with most studies using once- or twice-daily bedside evaluations by nursing staff, likely underestimating delirium incidence—particularly hypoactive cases—and contributing to measurement bias [11].

The largest and most representative RCT in the meta-analysis, conducted by Perbet et al. (2018), evaluated low-dose ketamine in mechanically ventilated patients in the ICU. The study found a significant reduction in delirium incidence, from 37% in the placebo group to 21% in the ketamine group ($P = 0.03$). Ketamine was also associated with a shorter duration of delirium episodes (2.8 ± 3 vs. 5.3 ± 4.7 days; $P = 0.005$). Despite these encouraging findings, no significant differences were observed in mortality, ventilator-free days, or length of ICU stay, highlighting the challenge of interpreting clinical relevance based solely on delirium incidence [20]. The authors proposed that the NMDA receptor antagonism of ketamine may mitigate excitotoxicity and synaptic dysregulation—key drivers of delirium—especially at subanesthetic doses. Notably, no increase in hallucinations or nightmares was reported, suggesting a potential protective effect on cognitive function at low doses [20].

Collectively, these findings challenge the traditional view of ketamine as a pro-delirium agent and suggest that, with appropriate dosing and in select patient populations, it may help prevent delirium. However, given the small sample sizes and methodological limitations of existing studies, larger, well-designed trials are needed to confirm the role of ketamine in this setting and to define its optimal use in ICU sedation protocols.

Psychiatric disorders

Psychiatric disorders are common among patients in the ICU. A prospective study across 26 ICU centers in the United Kingdom involving over 20,000 patients reported anxiety in 46%, depression in 40%, and PTSD in 22% [41]. A meta-analysis by Righy et al., including 48 studies, found that 1 in 5 adult ICU survivors may develop PTSD, with a high prevalence persisting at 12 months after discharge [42]. Ketamine has shown potential in alleviating these conditions, but evidence remains limited and should be interpreted with caution owing to methodological flaws in key studies.

Hartland et al. conducted a meta-analysis demonstrating the rapid anxiolytic effects of ketamine across 14 RCTs but identified major limitations: 11 of the 14 studies had a high risk of bias resulting from inadequate blinding and selective reporting, and significant heterogeneity arose from inconsistent measurement tools, such as single-item visual analog scales versus validated multi-item instruments [15]. The rapid antidepressant effects of ketamine are now well-established. In 2019, the Food and Drug Administration approved the nasal spray form of the S-enantiomer, esketamine, for treatment-resistant depression and major depressive disorder with acute suicidal ideation or behavior [1]. However, clinical use in the ICU remains underexplored. A single-center case series of 12 patients in the ICU suggested that ketamine may alleviate depressive symptoms, but the study was limited by its retrospective design, small sample size, and absence of a control group, reducing generalizability [14].

Three recent meta-analyses suggest that ketamine may be effective in treating PTSD, with statistically significant symptom reductions reported. However, these reviews also noted substantial heterogeneity, variation in dosing regimens, and inconsistent long-term outcomes. Some included trials lacked adequate blinding, increasing the risk of performance bias. Although ketamine has shown rapid therapeutic effects, its short duration of action, dissociative side effects, and potential for misuse require careful consideration [12,13,16].

Adverse effects

Several adverse effects limit ketamine use in the ICU. These effects are dose-dependent and include excessive salivation, hyperreflexia, transient clonus, and vestibular symptoms, such as dizziness, nausea, and vomiting [43]. Low-dose injections may reduce their incidence. However, in patients with multiple organ dysfunction in the ICU, managing these effects becomes more complex. For example, excessive salivation can increase the risk of airway obstruction, requiring closer monitoring and supportive care [43].

Although ketamine is traditionally considered hemodynamically safe owing to its indirect sympathomimetic effects—typically causing transient increases in heart rate and blood pressure—this response depends heavily on intact endogenous catecholamine stores [1,44]. In critically ill patients, particularly those with prolonged septic shock or elevated shock index, these reserves are often depleted. Under such conditions, the direct actions of ketamine—dose-dependent negative inotropy and peripheral vasodilation—can emerge, leading to paradoxical hypotension and, in severe cases, cardiovascular collapse [44]. These concerns are especially relevant in ICU settings, where cardiac or vascular compromise is common. Ketamine-induced tachycardia may worsen myocardial oxygen supply-demand mismatch in patients with coronary artery disease or fixed outflow obstruction, potentially triggering myocardial ischemia [1]. Its tendency to raise arterial pressure could also increase the risk of acute coronary syndromes or cerebrovascular events in susceptible individuals, making ketamine generally unsuitable for those with significant cardiovascular or cerebrovascular disease [1]. Further complicating its use, data show a higher incidence of peri-intubation hypotension with ketamine compared with etomidate, particularly in patients with suspected catecholamine depletion. For instance, in the NEAR registry and other large datasets, ketamine was linked to nearly double the odds of postinduction hypotension, challenging the assumption of hemodynamic safety in emergency airway management [45]. These findings demonstrate that the cardiovascular

Table 1

The Summary of 10 Potential Applications of Ketamine in ICU

Number	Potential Applications	Study	Key Findings	Included Studies and Participants	Quality of Evidence (GRADE)
1	Reducing opioid consumption	Chan et al. (2022) [17]	Ketamine reduced opioid consumption in critically ill patients.	6 RCTs (n = 495)	Very low
2	Tracheal intubation	Acquisto et al. (2023) [28]	No clear mortality or hemodynamic benefit of ketamine vs. etomidate for RSI.	7 RCTs (n = 772)	Moderate
		Koroki et al. (2024) [2]	Ketamine may moderately reduce mortality vs. etomidate.	7 RCTs (n = 2748) + 1 PS-matched study (n = 230)	Very low
3	Mechanically ventilated patients	Amer et al. (2024) [34]	Ketamine not recommended as monotherapy; may be used as adjunct.	17 RCTs (n = 898) + 9 observational studies (n = 1934)	Very low
4	Sepsis and septic shock	Reese JM, et al. (2018) [26]	Ketamine reduces vasopressor and sedative requirements.	1 Non-comparative prospective pilot study (n = 17)	Very low
		Mostafa et al. (2024) [4]	Ketamine increases CO and SV vs. fentanyl.	1 RCT (n = 86)	Very low
5	Sedation after cardiac surgery	Hu et al. (2024) [5]	Ketamine–dexmedetomidine reduces ventilation time and ICU stay.	2 RCTs (n = 110)	Very low
6	ABI	Telles et al. (2021) [6]	Ketamine inhibits SD.	1 Retrospective multicenter analysis (n = 115) + 1 prospective, randomized, multiple crossover trial (n = 10) + 1 retrospective cohort study (n = 66)	Very low
		Gregers et al. (2020) [36]	No evidence of increasing ICP.	3 RCTs (n = 79) + 3 prospective comparative studies (n = 62) + 1 prospective observational study (n = 21)	Very low
		Andreasen et al. (2024) [37]	Functional outcome and safety in severe ABI remain uncertain.	5 RCTs (n = 149)	Very low
7	SRSE	Adhikari et al. (2024) [7]	Ketamine is effective and safe for SRSE.	6 Retrospective studies (n = 262) + 1 prospective registry (n = 11) + 12 case series (n = 67)	Very low
		Yan et al. (2024) [8]	Ketamine shortens SRSE duration and improves safety.	10 Retrospective studies (n = 296) + 1 prospective study (n = 11)	Very low
8	Acute severe asthma and severe asthma exacerbations	Epperson et al. (2024) [9]	Ketamine improves CAS and PEF.	4 RCTs (n = 240) + 4 systematic review (n = 1330) + 2 prospective observational studies (n = 21) + 1 retrospective chart review (n = 17)	Very low
		La Via et al. (2022) [10]	No strong evidence for use in refractory cases.	5 RCTs (n = 297) + 2 prospective studies (n = 21)	Very low
9	Delirium	Abdildin et al. (2024) [11]	Ketamine reduces ICU delirium incidence.	4 RCTs (n = 358)	Very low
10	Psychiatric disorders	Hartland et al. (2022)[15]	Rapid anxiolytic effects lasting up to 2 weeks.	11 RCTs (n = 372)	Very low
		Giri et al. (2022) [14]	Improves depressive symptoms.	1 Case series (n = 12)	Very low
		Albuquerque et al. (2022) [12]	Effective for PTSD.	14 RCTs (n = 1107)	Very low
		Almeida et al. (2024) [13]		5 RCTs (n = 277) + 2 crossover trials (n = 51) + 3 nonrandomized trials (n = 55)	Very low
		Kwan et al. (2024) [16]		NA	Very low

ABI, acute brain injury; CAS, clinical asthma score; CO, cardiac output; ICP, intracranial pressure; ICU, intensive care unit; iMV, invasive mechanical ventilation; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; NA, not applicable; PEF, peak expiratory flow; PS, propensity score; PTSD, posttraumatic stress disorder; RCTs, randomized controlled trials; RSI, rapid sequence intubation; SAE, severe asthma exacerbations; SRSE, super-refractory status epilepticus; SD, spreading depolarization; SV, stroke volume.

profile of ketamine is not universally protective and must be carefully considered in the context of adrenergic failure. Clinicians should also monitor for noncardiovascular adverse effects, including cystitis, detrusor overactivity, biliary dysfunction, and hepatotoxicity—particularly with prolonged use in the ICU [1,43].

When used for deep sedation or short-term surgical anesthesia, ketamine can trigger a range of psychomotor symptoms upon emergence, including hallucinations, agitation, and delirium—collectively known as emergence reactions [46]. The reported incidence ranges from 5% to 30% [46]. In the ICU, where patients often have complex mental states, ketamine-induced psychiatric symptoms can further hinder recovery. Long-term ketamine use may result in more severe and persistent neuropsychiatric effects [46]. Therefore, ketamine use in the ICU requires strict dosage control and continuous monitoring of mental status.

Ketamine is metabolized by cytochrome P450 enzymes. Co-administration with drugs that inhibit this pathway can impair ketamine metabolism and increase the risk of toxicity [43]. In the ICU, where polypharmacy is common, the potential for drug interactions is heightened. Therefore, ketamine use in this setting requires careful monitoring to manage interactions effectively. Ketamine is a controlled substance in many countries, including the United Kingdom, and its use must be supervised by qualified medical professionals to minimize risk and ensure patient safety [47].

Table 1 summarizes 10 potential ICU applications of ketamine, including main evidence, key findings, study characteristics, and evidence quality.

Discussion

A growing body of research supports the potential benefits of ketamine in critically ill patients. The 10 applications discussed in this review highlight its versatility in ICU settings. However, despite its promise, ketamine is not a universal solution for critical care. Its use requires careful patient selection, precise dosing, and continuous monitoring to minimize adverse effects and improve outcomes [48].

Several critical knowledge gaps remain. Many referenced meta-analyses, systematic reviews, and clinical guidelines are constrained by a lack of high-quality RCTs. The existing evidence is largely based on single-center, small-sample studies with methodological issues, including inadequate blinding, high risk of bias, and substantial heterogeneity in patient populations, treatment protocols, and outcome measures. These limitations contribute to ongoing uncertainty about the efficacy and safety of ketamine across various ICU indications.

Future research should prioritize high-quality, multicenter RCTs with robust methodologies to clearly define the therapeutic effects of ketamine in critically ill patients. Given limited resources for such trials, efforts may need to focus on clinical questions with direct relevance to ICU mortality (eg, hemodynamic optimization in septic shock) or strategies to reduce opioid dependence (eg, alternative analgesia for mechanically ventilated patients). Key areas for further study include optimal timing of administration, dosing strategies tailored to specific ICU populations, and long-term safety. Research should also address the interactions of ketamine with commonly used ICU medications, its impact on long-term cognitive and psychiatric outcomes, and its role in multimodal analgesia and sedation. Advancing understanding in these areas will be essential for safe and effective integration of ketamine into critical care practice.

As research advances, developing standardized, evidence-based guidelines will be critical for the safe and effective use of ketamine in ICU settings. With the expanding evidence base, an interdisciplinary approach—bringing together intensivists, anesthesiologists, and pharmacologists—will be essential to refining its clinical role. Balancing innovation with caution remains vital: is ketamine a paradigm shift in critical care pharmacology, or are its true limitations yet to be revealed? Addressing these questions through future research is necessary before ketamine can be fully integrated into routine ICU practice.

Conclusion

Ketamine shows significant potential in the ICU, with growing evidence supporting its use across multiple indications. Although it offers distinct pharmacological advantages, its use requires individualized assessment and close monitoring. Future research and standardized guidelines are essential to define its optimal role in critical care.

Conflict of interest statement

The authors declare no conflict of interest.

Author contributions

Zeng S, Li Y, Zheng J, and Wang H conceived the study. Zeng S, Yao Z, Guan C, Cui S, and Quan Z conducted the literature search and data collection. Zeng S drafted the manuscript, and Wang H and Zheng J revised it. All authors have read and approved the final version of the manuscript.

Funding

This work was funded by the National Key Research and Development Program of China (No. 2021YFC2501800), the National Natural Science Foundation of China (No. 82472184), the Outstanding Youth Project of Heilongjiang Natural Science Foundation (No. JQ2021H002), the Key R&D Plan Project in Heilongjiang Province (No. GY2023ZB0075), the Harbin Medical University Foundation Youth Project (No. PYQN2023-9), the Wu Jieping Medical Foundation (No. 320.6750.2021-4-60), and the Research Project of Heilongjiang Provincial Health Commission (No. 20241717010028).

Ethical approval of studies and informed consent

Not applicable.

Acknowledgements

We thank the Department of Critical Care Medicine at the Second Affiliated Hospital of Harbin Medical University for its support of this study.

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How to cite this article: Zeng S, Yao Z, Guan C, et al. Ketamine use in adult intensive care unit: a narrative review of emerging applications, efficacy challenges, and safety concerns. *Emerg Crit Care Med*. 2025;5(3):153–160. doi: 10.1097/EC9.0000000000000152