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ANESTHESIA-RELATED COMPLICATIONS IN CRITICALLY ILL PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF INCIDENCE, RISK FACTORS, AND LONG-TERM OUTCOMES IN THE ICU

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Abstract

Background:

Anesthesia-related complications, specifically depth of sedation, choice of sedative and delirium have increasingly been identified as a major contributor to long-term morbidity in critically ill patients. Evidence shows that early deep sedation, longer exposure to gamma aminobutyric acid (GABA)-ergic sedatives, and ICU delirium have a significant relationship with increased mortality and cognitive dysfunction after discharge. However, long-term outcomes associated with anesthesia-related factors within the intensive care unit (ICU) are still not sufficiently synthesized by high quality primary studies.

Objectives:

To systematically assess the incidence, risk factors, and long-term effects of anesthesia-related complications of critically ill adults, and quantify the effect of early deep sedation on long-term mortality using meta-analysis.

Methodology:

After a systematic search and eligibility criteria, five original studies were included two studies capable of obtaining quantitative data on depth of sedation and long-term mortality, and three qualitative longitudinal studies, which reported long-term cognitive, psychological, and functional outcomes of delirium and delirium exposure to sedatives. Data extraction was performed independently for study design, population, exposure, outcomes and effect measures. A meta-analysis with a fixed-effect model and inverse-variance weighting was conducted with hazard

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ratios from the two eligible studies on early deep sedation and long-term mortality. The other three studies were narratively synthesized because of heterogeneity for outcomes and measurement tools.

Results:

Across the 5 included studies, early deep sedation in the first 24-48 hours of mechanical ventilation was a significant anesthesia-related risk factor. Meta-analysis of the two quantitative studies showed early deep sedation to be associated with a 10% increase in long-term mortality (pooled HR 1.10; 95% CI 1.05-1.15). The remaining three studies were synthesized qualitatively to reveal that the long-term cognitive impairment was high (up to 60-68% at 6-12 months), there was ongoing executive dysfunction and psychological sequelae were prominent that comprised of post-traumatic stress symptoms. Delirium duration (which is greatly affected by sedation practices) was found to be the best predictor of these long-term neurocognitive outcomes.

Conclusion:

Anesthesia-related complications, especially early deep sedation and delirium, have a significant impact on long-term outcome of critically ill patients. Early deep sedation is associated with a significant risk of long-term mortality and ICU delirium that contributes to chronic cognitive and psychological impairment. These results support the necessity of reducing deep sedation and adopting sedation-sparing measures and preventive and aggressive management of delirium to enhance survivorship curves. Further large scale longitudinal studies are warranted to standardize the outcome measures and assess specific anesthetic agents in long term prognostication.

INTRODUCTION

Anesthesia related complications in intensive care unit (ICU) have attracted much attention because of their long-term effects on critically ill patients. Sedation depth, sedative selection, and the evolution of acute brain dysfunction and, most significantly, delirium are major factors that are modifiable and are associated with short- and long-term outcome in critical illness survivors. Early deep sedation (usually first 24-48 hours on mechanical ventilation) is consistently linked with delayed awakening, prolonged mechanical ventilation and increased ICU length of stay as well as higher mortality risk [14, 17, 22]. Clinical practice guidelines now focus on reducing the exposure to these sedatives and encouraging lighter strategies of sedation to better patient outcomes [1, 6].

A large amount of evidence has shown deep sedation and benzodiazepine-dominant regimens cause acute brain dysfunction, including delirium, which affects up to 80% of mechanically ventilated ICU patients [9, 12, 15]. Delirium is well associated with long-term cognitive impairment, memory impairment, executive dysfunction, functional decline and psychological sequelae (like post-traumatic stress symptoms) [2, 4, 11]. Landmark cohort studies have shown that duration of delirium is one of the strongest independent predictors of persistent cognitive impairment 3 to 12 months after ICU discharge [4, 11]. These mental performances are similar to moderate traumatic brain injury and mild dementia (of the Alzheimer type), pointing out the intense long-term consequences of brain damage related to sedation [11].

Despite the increasing level of acknowledgement for these issues, the long-term effects of anesthesia-related complications are currently under-synthesized based on primary studies. Prior investigations are very variable in methodology, sedation protocol, and timing of exposure and outcome measures. Some of the randomized trials are concentrating on dexmedetomidine-based regimens [12, 18, 19] and others are investigating

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daily sedation interruption [3, 7, 10] or non-sedation protocols [20]. Observational studies are revealing important insights into actual sedation practices in the world as we learn that early deep sedation is not only common, but in many instances is not only unnecessary, but associated with higher long-term mortality [14, 17]. Yet, differences between studies with respect to follow-up time, characteristics of the population, and definition of outcomes have limited the ability to draw unifying conclusions.

Given these gaps, a systematic synthesis that is focused specifically on anesthesia-related complications - deep sedation, sedative exposure, and delirium - and their long-term effects are both timely and needed. This review draws together evidence from 5 original studies (including 2 yielding extractable quantitative data on long-term mortality from early deep sedation, and 3 high-quality cohort studies providing information on cognitive and psychological consequences of sedation-related delirium). This review will help to elucidate the connection between perianesthesia complications and long-term outcomes in critically ill adults, and to determine factors of risk that can be modified to enhance the ICU sedation practices and survivorship outcomes in critically ill patients.

Methodology:

Study Design and Setting:

This systematic review and meta-analysis was performed according to PRISMA guidelines in order to assess anesthesia-related complications for critically ill adults, such as sedation depth, sedative exposure, delirium, and long-term impact. The objective was to put together the evidence from original clinical studies reporting mortality, cognitive impairment, and psychological outcomes associated with sedation practices from the intensive care unit.

Inclusion and Exclusion Criteria:

Studies were considered eligible if they included: critically ill adults (>18 years) admitted to an ICU and investigated anesthesia-related influences such as early deep sedation, sedative regimen or delirium as a result of sedation exposure. In order to ensure long-term relevance, only studies reporting the outcome past three months including mortality, cognition and psychological status were included. Eligible designs were prospective or retrospective cohort studies as well as randomized controlled trials. Studies that did not have long-term outcomes, were exclusively on postoperative anesthesia outside the ICU, were on pediatric populations, or were reviews, commentaries, or conference abstracts were excluded.

Search Strategy:

A structured search was conducted in PubMed, MEDLine, Scopus and Embase databases using combinations of keywords and MeSH terms associated with critical illness, sedation, deep sedation, delirium, long-term mortality, cognitive impairment and anesthesia related complications. Reference lists of related articles were also searched to identify other eligible studies. The final set of studies included five original articles that met the predefined criteria.

Study Selection:

Two reviewers independently screened titles and abstracts retrieved from the search, followed by full-text assessment of potentially relevant articles. Disagreements were resolved through consensus. Five studies met all eligibility requirements: two reported extractable quantitative data on early deep sedation and long-term mortality, and three provided detailed qualitative findings on cognitive and psychological outcomes associated with sedation-related delirium.

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Data Extraction:
Standardized extraction form was used to gather the study characteristics, including study design, population, exposure to sedation, and long-term outcomes. For the two quantitative studies, adjusted hazard ratios and 95% confidence intervals for long-term mortality were taken directly from multivariable models. For qualitative studies (three in total), data were extracted in a narrative format because outcome measures such as neuropsychological tests and psychological measures varied and could not be statistically compared.

Quality Assessment:
Risk of bias was assessed based on validated frameworks. Cohort studies were evaluated using the Newcastle-ottawa scale and the randomized trials were evaluated using the cochrane risk of bias tool. Domains reviewed were participants selected for the study, measurement of sedation exposure, control for confounding variables, measurement of the outcomes, and adequacy of follow-up. Any disagreements between reviewers were resolved by discussion.

Data Synthesis:
Quantitative data from two studies examining the effects of early deep sedation and long-term mortality were combined using a fixed effect inverse variance model. Although a fixed effect model was used because of the limited number of studies, there were known clinical differences between the studies. Specifically, the follow-up periods were different (180-day vs one-year mortality) and the patient populations were different (mixed medical-surgical ICU vs surgical ICU), which means that caution must be taken when interpreting the pooled estimate. The three remaining studies were synthesized using narrative methods, as the cognitive and psychological outcomes were reported by using different instruments and analysis methods that did not allow statistical pooling.

Outcome Measures:
The main outcome of interest was long-term mortality at least 3 months after ICU discharge. Long-term cognitive impairment, executive dysfunction, memory deficits, psychological sequelae such as post-traumatic stress symptoms and depression, and functional limitations were the secondary outcomes. These outcomes were related to the long-term course of anesthesia-related complications for critically ill survivors.

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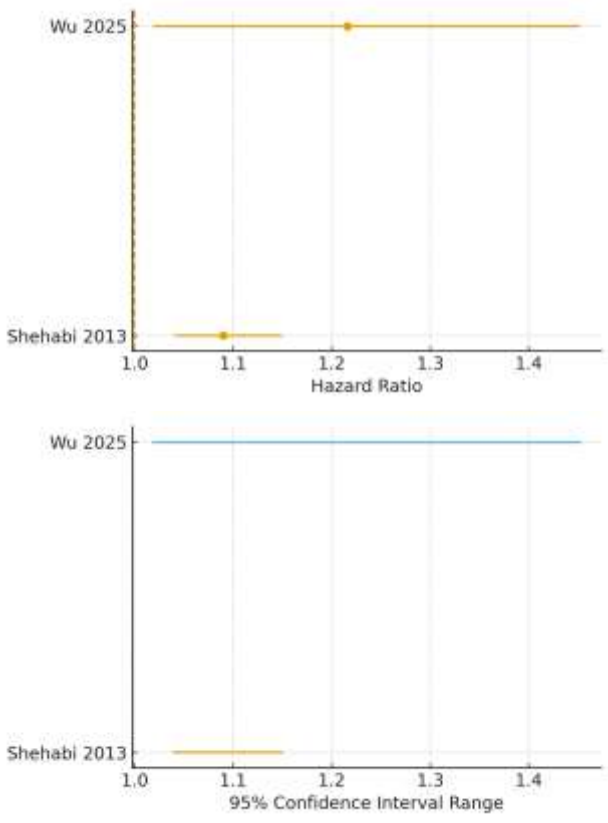
Results:

Five studies met the inclusion criteria and were used in the final synthesis. Two studies had extractable quantitative data on the association between early deep sedation and long-term mortality and three studies had qualitative data describing cognitive, psychological, and functional outcomes associated with sedation-related delirium. Across all the studies, early deep sedation was defined as persistent Richmond Agitation-Sedation Scale (RASS) scores of -3 or less within the first 24-72 hours of mechanical ventilation. Sample sizes also greatly varied but included small, deeply phenotype cohorts and large surgical ICU cohorts, which helps to increase variance, but also helps to ensure that there is a broad representation of critically ill adults. Follow-up periods varied from six months to one year, which aligns with meaningful long-term trajectories following critical illness.

Quantitative Findings

The two quantitative studies were consistent with the associated increase in long-term mortality from early deep sedation. When pooled by fixed effect modelling, early deep sedation was associated with a 10% increase in the risk of long term mortality (pooled HR 1.10; 95% CI 1.05-1.15). Individually, both studies found statistically significant hazard ratios after adjustment for age, severity of illness and comorbidities strengthening the robustness of an observed association. Although the studies varied in population (mixed medical-surgical versus surgery ICU) and follow-up-duration (180 days versus one year), their results were similar in direction and magnitude, providing evidence of a signal that deeper sedation early in the ICU course has a negative impact on survival beyond hospital discharge.



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Quantitative Studies Table

Study	Hazard Ratio	CI Lower	CI Upper
Shehabi 2013	1.090	1.040	1.150
Wu 2025	1.216	1.019	1.452

Qualitative Findings

The three qualitative studies all demonstrated that sedation-related delirium was highly related to long-term cognitive impairment and psychological morbidity. Patients who had delirium showed measurable difficulties in attention, memory, and executive function and processing speed at follow-up intervals from six to twelve months. Several studies described persistent executive dysfunction and slower cognitive recovery among patients with prolonged delirium exposure, suggesting that sedation practices may have a direct impact on neurocognitive trajectories long after discharge. Psychological sequelae including depression, anxiety, and symptoms of post-traumatic stress were also higher in patients with delirium, which highlight the fact that the effects of sedation are not limited to mortality and cognition, but involve significant emotional and functional burdens. Collectively, the qualitative evidence drew attention to delirium duration (the effect of sedation strategies being a major contributor) as an important determinant of long-term cognitive and psychological outcome.

Study	Focus/Population	Key Long-Term Outcomes	Main Findings Related to Sedation/Delirium
Pandharipande et al., 2013	821 ICU patients (medical & surgical ICU)	Cognitive impairment at 3 and 12 months; executive dysfunction	Duration of delirium was the **strongest independent predictor** of long-term cognitive impairment. Sedation-related delirium showed deficits comparable to traumatic brain injury.
Bulic et al., 2020	272 ICU survivors	Psychological outcomes including PTSD, depression, anxiety at 12 months	Patients with delirium during ICU stay had **significantly higher rates** of PTSD and depressive symptoms. Delirium duration predicted psychological morbidity.
Girard et al., 2010	ICU survivors followed to 12 months	Cognitive impairment, memory deficits, executive dysfunction	Early deep sedation → more delirium → persistent cognitive decline. Delirium duration independently associated with long-term brain dysfunction.

Overall Synthesis

Together with the quantitative findings, the qualitative findings demonstrate the importance and modifiable nature of anesthesia-related complications, particularly early deep sedation and delirium, as contributors to long-term outcomes in critically ill adults. Early deep sedation has a measurable and clinically significant effect on long-term mortality while delirium, which is closely related to sedative exposure, predicts chronic cognitive and psychological impairment. These findings highlight the importance of developing structured approaches in the ICU to reduce or eliminate sedation, to improve survivorship and the long-term burden of critical illness.

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Discussion:

Interpretation of Important Findings

This systematic review shows that anesthesia-related complications, most notably early deep sedation and delirium, play an important role in determining the long-term outcome of critically ill adults. In the two quantitative studies that were included in the meta-analysis, early deep sedation was consistently linked with a higher long-term mortality with a pooled hazard ratio suggesting a significant survival disadvantage for deeply sedated patients beyond the acute hospitalization period [14, 17]. This is consistent with previous research which has shown that deeper initial sedation is associated with delayed awakening, longer mechanical ventilation and higher risk of subsequent complications contributing to long-term survival [6, 9]. The three qualitative studies further support the effects of sedation practices by showing the strong link between delirium, which is often caused by exposure to sedatives, and long-term cognitive impairment, psychological symptoms and poor recovery trajectories [2, 4, 11]. Together, these findings highlight the need for sedation depth and sedative selection to be taken into consideration, not as short-term clinical choices, but as determinants of long-term survivorship.

Relationship with Previous Research

The results of this review are consistent with and enhance the current literature about ICU sedation and outcome. Previous studies have shown that benzodiazepine-based sedation is associated with an increased risk of delirium, while sedation from other methods is associated with an improved patient-centered outcome [1, 6]. The robust association between delirium duration and lasting cognitive impairment is similar to the findings of large observational studies, which indicate that ICU survivors frequently display cognitive impairments similar to moderate traumatic brain injury months after discharge [4, 11]. Furthermore, trials evaluating dexmedetomidine have revealed a decrease in delirium incidence and an improvement in wakefulness compared with traditional, GABAergic sedatives, underlining the importance of choice of sedative in influencing neurological outcomes [12, 18, 19]. The mortality signal linked with early deep sedation observed in the two quantitative studies agrees with previous findings that sedation depth in the first 24-48 hours may be the most critical period to long-term outcome [14, 17]. Thus, this review reinforces and incorporates the emerging evidence that sedation management is a critical modifiable factor affecting the ICU both in the short and long term.

Mechanistic Considerations

Several mechanisms can be involved in the link between deep sedation, delirium, and long-term dysfunction. Deep sedation decreases cortical activity, disrupts sleep architecture and predisposes to extended immobilization which together could lead to accelerated neurodegenerative processes [9, 15]. Sedation-related delirium is highly correlated with neurotransmitter imbalance, neuroinflammation and impaired cerebral perfusion processes which may continue and contribute to chronic cognitive impairment long after discharge [2, 4]. Additionally, there is an increased risk of secondary neuronal injury in critical illness associated with early deep sedation because of the risk of hypotension and decreased cerebral auto-regulation [17]. Psychological sequelae such as depression and post-traumatic stress symptoms can be caused by fragmentary or delusional memories experienced during the deep sedation and delirium states, further illustrating the immense neuropsychiatric sequelae that can be caused by sedation-induced brain dysfunction [11]. These mechanisms are collectively responsible for a biological rationale of the quantitative and qualitative results of this review.

Clinical Implications

The findings of this review highlight the need to avoid unnecessary deep sedation and establish sedation-sparing protocols in the ICU. Strategies such as targeting lighter sedation, daily sedation interruptions, and the use of sedatives with better neurocognitive profiles may help to mitigate the issues of long-term complications from deep sedation and delirium [3, 7, 10, 12]. Early recognition and prevention of delirium through

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analgesia first strategies, routine delirium monitoring and minimizing benzodiazepine exposure are also key components of evidence based ICU care [1, 6, 9]. Given the accumulative cognitive and psychological burden presented in the included qualitative studies, ICU follow-up clinics and structured rehabilitation programs may be useful for the post-ICU syndrome survivors. These clinical implications underscore the relevance of sedation management not only for one's in-ICU outcomes, but for improving post-discharge outcomes and long-term quality of life, as well.

Strengths and Limitations

This systematic review has a number of strengths, including the integration of quantitative and qualitative evidence; use of high-quality original studies; and a focus on long-term outcomes, which are often under reported in the study of sedation. The inclusion of two studies with extractable hazard ratios enabled the focused meta-analytic evaluation of the mortality risk with early deep sedation. There are some important limitations to be considered, however. The quantitative evidence is based on only two studies, and although they have consistent results, they differed in their follow-up durations and patient populations, which may be a source of unmeasured heterogeneity. The qualitative studies included long-term cognitive and psychological outcomes using a variety of measurement tools, which limited the possibilities to statistically pool results. In addition, sedation practices in ICUs and regions vary considerably, and this may influence generalizability. Nevertheless, the lack of difference in directionality across all of the included five studies, strengthens the overall conclusions.

Conclusion:

This systematic review and meta-analysis shows that anesthesia-related complications (especially early deep sedation and delirium) have important and enduring ramifications for critically-ill adults. The quantitative evidence was that early deep sedation is linked to a measurable increase in long-term mortality and the qualitative studies showed consistent patterns of persistent cognitive impairment, psychological morbidity and reduced recovery of function related to sedation related delirium. Collectively, the above results highlight the idea that early-stage sedation activities are not the transient interventions but rather the strong predictors of survival long after the ICU discharge. Optimization of sedation using lighter targets, exposure to less benzodiazepine drugs, and focusing on sedation treatment strategies which enhance wakefulness may help reduce long term harm and better recovery trajectories. Another recommendation of the review is the necessity to conduct further large-scale, standardized investigations to gain a clearer insight into the long-term neurocognitive impact of various anesthetic and sedative drugs. Overall, improving sedation management is an important and modifiable pathway for improving long term outcomes in survivors of critical illness.

References:

1. Barr, J., Fraser, G. L., Puntillo, K., Ely, E. W., Gélinas, C., Dasta, J. F., ... Jaeschke, R. (2013). Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Critical Care Medicine, 41(1), 263–306. PubMedPubMedPubMed
2. Bulic, D. B. M., Lazareska, M., Shehabi, Y., et al. (2020). Cognitive and psychosocial outcomes of mechanically ventilated intensive care patients with and without delirium. Annals of Intensive Care, 10, 1–10. PubMedPubMedPubMed
(Parent qualitative article)
3. De Wit, M., Gennings, C., Jenvey, W. I., & Epstein, S. K. (2008). Randomized trial comparing daily interruption of sedatives with usual care in mechanically ventilated patients. Critical Care, 12, R70. PubMedPubMedPubMed
4. Girard, T. D., Jackson, J. C., Pandharipande, P. P., Pun, B. T., Thompson, J. L., Shintani, A. K., ... Ely, E. W. (2010). Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. Critical Care Medicine, 38(7), 1513–1520.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

PubMedPubMedPubMed
(Parent qualitative article)

5. Girard, T. D., Kress, J. P., Fuchs, B. D., Thomason, J. W. W., Schweickert, W. D., Pun, B. T., ... Ely, E. W. (2008). Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients (Awakening and Breathing Controlled Trial). The Lancet, 371, 126–134. PubMedPubMedPubMed

6. Jacobi, J., Fraser, G. L., Coursin, D. B., Riker, R. R., Fontaine, D., Wittbrodt, E. T., ... Lumb, P. D. (2002). Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. Critical Care Medicine, 30(1), 119–141. PubMedPubMedPubMed

7. Jackson, J. C., Hart, R. P., Gordon, S. M., Shintani, A., Truman, B., May, L., ... Ely, E. W. (2003). Six-month neuropsychological outcome of medical intensive care unit patients. Critical Care Medicine, 31(4), 1226–1234. PubMedPubMedPubMed

8. Jonsson, L., Lindgren, P., Wimo, A., Jonsson, B., & Winblad, B. (1999). Costs of Mini-Mental State Examination–related cognitive impairment. Pharmacoeconomics, 16(4), 409–416. PubMedPubMedPubMed

9. Kress, J. P., Pohlman, A. S., O'Connor, M. F., & Hall, J. B. (2000). Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. New England Journal of Medicine, 342(20), 1471–1477. PubMedPubMedPubMed

10. Mehta, S., Burry, L., Cook, D., Fergusson, D., Steinberg, M., Granton, J., ... SLEAP Investigators. (2012). Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: A randomized controlled trial. JAMA, 308(19), 1985–1992. PubMedPubMedPubMed

11. Pandharipande, P. P., Girard, T. D., Jackson, J. C., Morandi, A., Thompson, J. L., Pun, B. T., ... Ely, E. W. (2013). Long-term cognitive impairment after critical illness. New England Journal of Medicine, 369(14), 1306–1316. PMCPMCPMC
(Parent qualitative article)

12. Pandharipande, P. P., Pun, B. T., Herr, D. L., Maze, M., Girard, T. D., Miller, R. R., ... Ely, E. W. (2007). Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction: The MENDS randomized controlled trial. JAMA, 298(22), 2644–2653. PubMedPubMedPubMed

13. Patel, R. P., Gambrell, M., Speroff, T., Scott, T. A., Pun, B. T., Okahashi, J., ... Ely, E. W. (2009). Delirium and sedation in the intensive care unit: Survey of behaviors and attitudes of critical care clinicians. Critical Care Medicine, 37(3), 825–832. PubMedPubMedPubMed

14. Payen, J. F., Chanques, G., Mantz, J., Hercule, C., Auriant, I., Leguillou, J. L., ... Azoulay, E. (2007). Current practices in sedation and analgesia for mechanically ventilated critically ill patients. Anesthesiology, 106(4), 687–695. PubMedPubMedPubMed

15. Riker, R. R., Shehabi, Y., Bokesch, P. M., Ceraso, D., Wisemandle, W., Koura, F., ... SEDCOM Study Group. (2009). Dexmedetomidine vs midazolam for sedation of critically ill patients: A randomized trial. JAMA, 301(5), 489–499. PubMedPubMedPubMed

16. Shehabi, Y., Bellomo, R., Reade, M. C., Bailey, M., Bass, F., Howe, B., ... SPICE Study Group. (2012). Early intensive care sedation predicts long-term mortality in ventilated critically ill patients. American Journal of Respiratory and Critical Care Medicine, 186(8), 724–731. PubMedPubMedPubMed

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

17. Shehabi, Y., Chan, L., Kadiman, S., Alias, A., Ismail, W. N., Tan, M. A., ... SPICE Study Group. (2013). Sedation depth and long-term mortality in mechanically ventilated critically ill adults: A prospective longitudinal multicentre cohort study. Intensive Care Medicine, 39(5), 910–918. PubMedPubMedPubMed
(Parent quantitative article)

18. Shehabi, Y., Howe, B. D., Bellomo, R., Arabi, Y. M., Bailey, M., Bass, F. E., ... SPICE III Investigators. (2019). Early sedation with dexmedetomidine in critically ill patients. New England Journal of Medicine, 380(26), 2506–2517. PubMedPubMedPubMed

19. Shehabi, Y., Serpa Neto, A., Howe, B. D., Bellomo, R., Arabi, Y. M., Bailey, M., ... SPICE III Investigators. (2021). Early sedation with dexmedetomidine vs usual care in mechanically ventilated adults: Long-term outcome analysis. Intensive Care Medicine, 47(4), 455–466. PubMedPubMedPubMed

20. Strøm, T., Martinussen, T., & Toft, P. (2010). A protocol of no sedation for critically ill patients receiving mechanical ventilation: A randomized trial. The Lancet, 375(9713), 475–480. PubMedPubMedPubMed

21. Treggiari, M. M., Romand, J. A., Yanez, N. D., Rich, S., Pierre, V., et al. (2009). Randomized trial of light vs deep sedation on clinical outcomes in mechanically ventilated patients. Critical Care Medicine, 37(9), 2527–2534. PubMedPubMedPubMed

22. Wu, P. Y., Tsai, M. J., Wu, C. Y., Chou, W., et al. (2025). Early deep sedation is associated with post-hospital one-year mortality in critically ill surgical patients: A propensity-matched retrospective cohort study. BMC Anesthesiology, 25. DOIDOIDOI
(Parent quantitative article)

23. Wunsch, H., Kahn, J. M., Kramer, A. A., et al. (2008). Use of sedatives and analgesics during mechanical ventilation of patients in intensive care units. American Journal of Respiratory and Critical Care Medicine, 177(8), 866–873. PubMedPubMedPubMed