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SYSTEMATIC REVIEW Open Access

The economic burden of anesthetic-related adverse events: a systematic review and empirical analysis

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Abstract

Background While extensive evidence is available on the adverse events (AEs) related to agents used to perform general anesthesia and procedural sedation from a clinical standpoint, much less is known about their economic impact on healthcare systems. This study aims to fill this gap combining an umbrella review of systematic reviews and an economic empirical analysis.

Methods We performed an umbrella review of systematic reviews and meta-analyses identified through PubMed and Web of Science searches conducted through September 2024 to map the anesthetic agents for which quantitative data exist on the incidence of AEs in adult patients undergoing procedural sedation or general anesthesia in developed countries. Data were used to conduct a gross costing estimate of the economic burden of these agents, using the Italian healthcare system as a case study. This analysis was complemented by a systematic literature review aimed at identifying cost estimates of anesthetic-related complications.

Results We included 168 systematic reviews and meta-analyses in the umbrella review. The gross costing estimation suggested that intravenous anesthetics (specifically propofol, etomidate, ketamine) and dexmedetomidine are the agents with the highest complication costs to the Italian healthcare system. Cognitive disorders and delirium were the most expensive complications described in the 22 publications identified in the systematic literature review which focused on costs; however, there was major heterogeneity in cost estimates across countries. Moreover, the lack of data uniformity in the estimation methods impaired further comparisons across anesthetic agents.

Conclusion Anesthetic-related complications costs are a crucial element that, together with clinical effectiveness, should drive adoption and reimbursement decisions. While this study identifies key AEs and estimates their costs, a major research gap still exists. Future research should improve the way such costs are estimated since direct costs of drugs and supplies to manage complications are by far lower than costs associated with nurses and physician labor, postponement of other surgical procedures, and intensive care unit admissions for monitoring or treating complications. Micro costing analyses are needed to improve the evidence available in this area.

Keywords Anesthetic agents, Adverse events, Healthcare costs, Economic burden, Umbrella review, Gross costing, Italian healthcare system

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Background

In modern medical practice, anesthetic agents for procedural sedation and general anesthesia are extensively used across a spectrum of diagnostic and therapeutic procedures, ensuring patient comfort and procedural efficacy. However, they do not come without risk, and, during a procedure, an anesthesiologist might encounter several complications, including apnea and hypoxemia, airway obstruction, arterial hypotension, bradycardia, and aspiration [1–3]. The frequency and severity of these adverse events (AEs) not only affect patient outcomes but also lead to increased healthcare services utilization and costs. They can result in extended hospital stays, additional medical interventions, and, in severe cases, legal implications due to patient harm. Much is known about anesthetic-related AEs from the clinical standpoint. However, a critical gap in the literature remains on the economic impacts of anesthetic-related complications.

This study aims to fill this gap by reviewing the existing literature to outline the current understanding on the clinical and economic burden associated with AEs of the anesthetic agents used in procedural sedation and general anesthesia. By identifying under-researched issues and synthesizing available data, this study seeks to enhance the knowledge base, guiding future research and policy decisions to optimize patient care and resource allocation through selection of the most appropriate anesthetic agents, also considering AEs and their costs.

Table 1 PICOT framework, inclusion and exclusion criteria for the umbrella review of anesthetic agents used for procedural sedation and general anesthesia, and their associated adverse events

	Inclusion	Exclusion
Population	Adult patients undergoing procedural sedation or general anesthesia	Pediatric patients, non-human subjects
Intervention	Any	N/A
Comparison	N/A (this study is not conceived to be comparative)	N/A (this study is not conceived to be comparative)
Outcome	AEs associated with general anesthesia or procedural sedation and their frequency of occurrence	N/A
Time (i.e., publication year)	No restrictions	N/A
Settings	Procedural sedation or general anesthesia (both for inpatients and for day-hospital and/or outpatient services, ICU sedation included). OECD countries (focus on Europe, US, Canada, Japan, South Korea, Australia). Only systematic reviews and meta-analyses	Regional anesthesia, local anesthesia, systematic reviews and meta-analyses focused specifically on developing countries/low-middle-income countries, types of journal articles or publications different from systematic reviews and meta-analyses

ICU intensive care unit, *N/A* not available (not relevant) *OECD* Organization for Economic Co-operation and Development, *US* United States

Methods

We conducted an umbrella review of systematic reviews and meta-analyses to identify a comprehensive list of anesthetic agents used for procedural sedation and general anesthesia, and their associated AEs. This analysis was complemented by a systematic literature review focused on identifying studies estimating anesthetic-related complication costs. Both studies followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines [4]. The systematic literature reviews were supplemented by a gross costing estimate based on frequencies of AEs occurrence retrieved from the umbrella review.

Umbrella review

Given the large number of studies addressing complications related to anesthetic agents, and to ensure the highest possible level of evidence quality and synthesis, an umbrella review of systematic literature reviews and meta-analyses was deemed the best-suited method. To be included, systematic reviews and meta-analyses had to report quantitative data on AEs frequency of occurrence and focus on adult patients undergoing procedural sedation or general anesthesia using any type of anesthetic agent. To ensure homogeneity of anesthetic protocols implemented in clinical practice we focused on data from developed countries. The detailed Patient-Intervention-Comparator-Outcomes-Time horizon (PICOT) framework implemented in this analysis is displayed in Table 1.

To identify all relevant systematic reviews, Web of Science and PubMed databases were searched on September 20, 2024. The search strategy was drafted and further refined through team discussion. Details on the search strings implemented are available in the Supplementary Materials (Table S.1).

Four authors participated in a pilot screening of the titles and abstracts retrieved from the electronic database search and revised the screening and data extraction procedure before full-scale review. Two authors evaluated the titles, abstracts and then the full text of all studies identified. Uncertainties were resolved through consensus and discussion with a third author.

Data on year of publication, anesthetic agents, AEs reported and their frequency of occurrence (number of events divided by the total number of study participants), severity of the complication, and clinical setting were abstracted. The resulting dataset was screened to eliminate data related to anesthetic agents withdrawn from the market, AEs deemed not directly related to the anesthetic

agent, or abnormal frequencies of AE occurrence, based on expert opinion.

Systematic literature review on anesthetic-related AEs costs

To provide estimates of costs or broader economic consequences of AEs generated by anesthetic agents used in the context of procedural sedation or general anesthesia, the database search was refined based on the anesthetic agents identified in the umbrella review. Consistent with the umbrella review, studies had to focus on adult patients based in developed countries undergoing procedural sedation or general anesthesia; no restriction was imposed on time limits of the publication period. In contrast to the umbrella review, all types of peer-reviewed studies with estimates of costs or broader assessments of the economic impact of AEs related to anesthetic agents used in procedural sedation or general anesthesia were eligible. The PICOT framework and inclusion and exclusion criteria are summarized in Table 2. Details on the search strings implemented in Web of Science and PubMed up to September 20, 2024, are available in the Supplementary Materials (Table S.3).

The review screening followed the same process as the umbrella review. We abstracted data on cost estimates, publication year, clinical setting, country, method used to estimate cost data (e.g., real-world data from observational studies, data from randomized controlled trials, etc.), anesthetic agents, mortality rate, awakening time, and length of stay. Cost estimates were taken directly as reported in the original publications and were adjusted for inflation and expressed as 2024 US dollars and, whenever possible, 2024 purchasing power parity (PPP) US dollars. Moreover, to reduce possible currency conversion issues, only selected studies published starting from 2002 were included in the synthesis of cost data to account for the introduction of Euros. For each AE-anesthetic agent combination, we aggregated the available numeric cost estimates by reporting the mean, standard deviation, and range (minimum/maximum values) as descriptive statistics. These values reflect the variation across studies but do not represent modeled or imputed costs. In cases where only a single numeric estimate was available, it was reported as-is.

No review protocol was pre-registered for either of the two systematic reviews.

Table 2 PICOT framework, inclusion, and exclusion criteria for the systematic literature review on costs and economic consequences of anesthetic-related AEs

	Inclusion	Exclusion
Population	Adult patients undergoing procedural sedation or general anesthesia	Pediatric patients, non-human subjects
Intervention	Use of any of the anesthetic agents identified in the umbrella review	N/A
Comparison	N/A	N/A
Outcome	Estimates of costs, economic impact/burden of anesthesia-related adverse events	
Time (i.e., publication year)	No restrictions	N/A
Settings	Procedural sedation or general anesthesia; OECD countries (focus on Europe, US, Canada, Japan, South Korea, Australia)	Exclusive focus on regional or local anesthesia; developing countries/low-middle-income countries; unpublished working papers, editorial material, retracted publications, letters, data sheets, notes, conference abstracts

N/A not available (not relevant), *OECD* Organization for Economic Co-operation and Development, *US* United States

Gross costing

The dataset on anesthetic-related AEs frequency of occurrence deriving from the umbrella review was used to perform an instance of *gross costing* estimation of the costs associated with AEs by anesthetic agent, using Italy as a case study. As a high-income country with a mature, universal healthcare system, Italy provides a setting to generate findings that are also relevant to other European and advanced healthcare systems.

The gross costing estimation was based on two complementary methods. In the first, we derived the implicit cost of each AE by translating its health state disutility into monetary terms. In health economics, utility represents the strength of individuals' preferences for different health states, scaled between 0 (equivalent to death) and 1 (perfect health). Correspondingly, disutility quantifies the decrement in quality of life associated with an AE (essentially, the "loss" in utility) and is defined as the difference between full health and the impacted state [5]. We searched the literature on health-related quality of life scores related to the AE emerging from the umbrella review. In instances where the literature provided only a utility value, we computed the disutility as *(1 - utility)*; this approach is consistent with standard health economics practice when direct disutility estimates are unavailable [6–15]. The detailed list of disutility parameters used in our computations is available in the Supplementary Materials, Table S.7. These disutility values were converted into costs by being multiplied by the Italian National Healthcare System estimate of implicit willingness to pay (€ 20,229.06 [16,867 USD as estimated in Woods et al. [16] updated into 2024 euros]). This figure represents the implicit cost-effectiveness threshold estimated by Woods and colleagues based on estimates of

opportunity cost and of the relationship between country gross domestic product per capita and the value of a statistical life. The resulting amount was weighted by the average relative frequency of occurrence of the AE (number of events divided by the sample size) to obtain the final estimate. Data and computations are available in the supplementary file Datasets.xlsx (Gross Costing section).

In the second method, a simplified form of gross costing was performed employing the most recent officially available at the time of writing Italian diagnosis-related group (DRG) tariffs for ordinary hospitalization (which includes overnight stays) and one-day/day hospital hospitalization [17] weighted by the average relative frequency of AEs. Sensitivity analysis was performed using the minimum and maximum frequency of occurrence of AEs.

Results

Umbrella review

We identified 168 studies eligible for the umbrella review (Fig. 1). Detailed reasons for exclusion are available in the Supplementary Materials, together with the full list of identified studies (Sect. 2.2, 2.3, Table S.2).

The AEs emerging from the umbrella review and deemed related directly to the use of anesthetic agents for general anesthesia or procedural sedation are listed in Table 3 in alphabetical order. The top four most frequently reported AEs across the included studies are highlighted in bold, based on the number of studies in which each AE was reported.

Analyzing which drug classes resulted in the most frequently documented AEs (nausea and/or vomiting, bradycardia, hypotension, and delirium) showed that opioids were associated with the highest frequencies for nausea

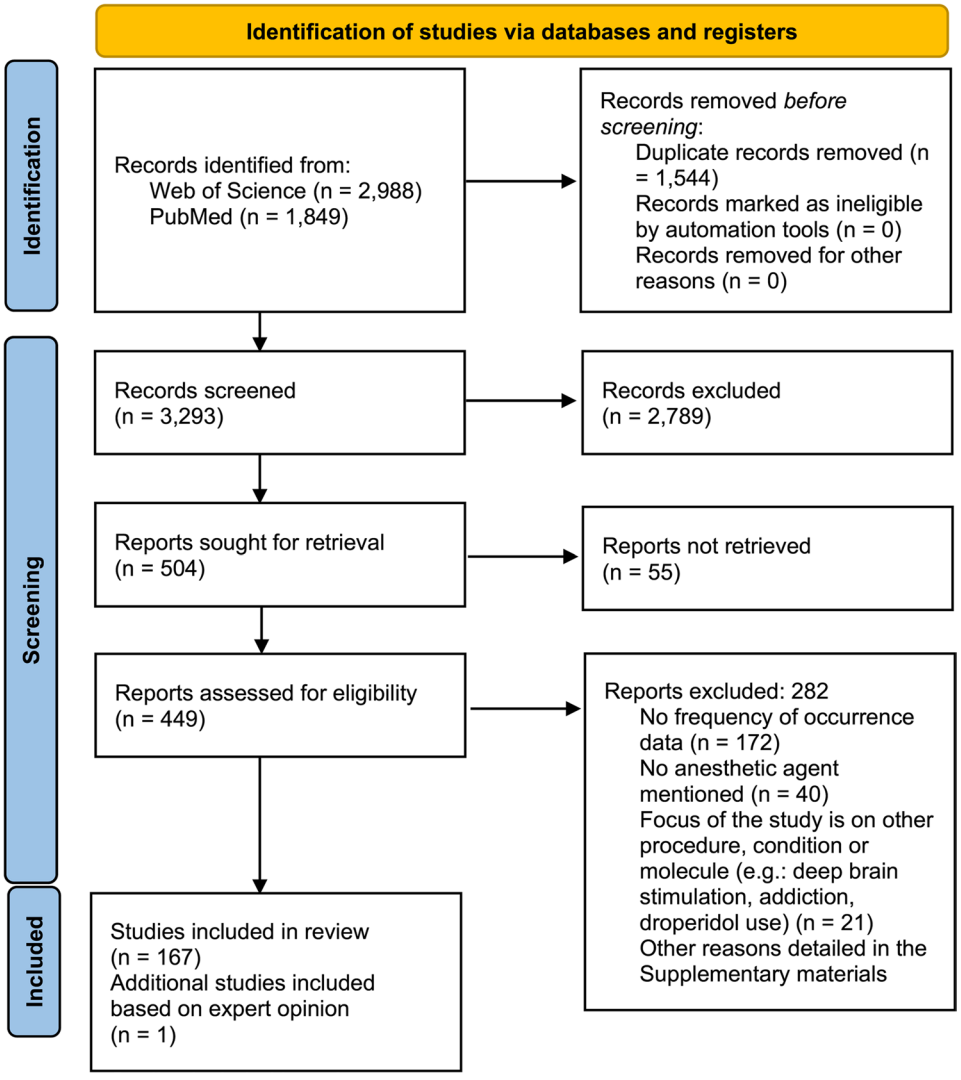

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart synthesizing the review screening process for the umbrella review

Table 3 AEs identified in the umbrella review; the top four most frequently reported AEs highlighted with bold text

Adrenal insufficiency	Cough	Intraoperative chocking
(Emergence) Agitation	**Delirium (4th)**	Laryngospasm
Airway obstruction	Dizziness	Muscle rigidity
Apnea	Drowsiness	Myoclonus
Arrythmia	Fever	**Nausea and/or vomiting (1st)**
(Intraoperative) Body movements	Hallucination	Pain on injection
	Headache	Pneumonia
Bradycardia (2nd)	Hypersalivation	Tachycardia
Bradypnea	Hypertension	Truncal rigidity
Cardiac depression	**Hypotension (3rd)**	Urinary retention
Chest tightness	Hypoxemia	Visual disturbance
Cognitive dysfunction	Hypoxia	

[1] This list includes synonyms or semantically related terms used to indicate the same adverse event. The precise name used to identify the adverse event used by the authors of the articles included in the umbrella review is reported in the ancillary files

and/or vomiting (fentanyl 31.56% [range 8%–70%]), remifentanil (27.30% [0%–70%]). Phenol derivatives were associated with some of the highest frequencies for bradycardia (ciprofol 14.07% [12.76%–14.75%], propofol 7.10% [0%–17.10%] for bradycardia). Phenol derivatives were also frequently inducing hypotension (ciprofol 30.77% [24.67%–34.48%], propofol 14.30% [0%–65%]). Dexmedetomidine was another agent also frequently implicated in bradycardia (14.07% [12.76%–14.75%]) and hypotension (20.40% [0%–61.78%]). Finally, the highest frequencies of occurrence for delirium were documented for ketamine (27.18% [15.71%–38.66%]) and dexmedetomidine (15.76% [11.03%–25.15%]).

Systematic literature review on anesthetic-related AEs costs

We identified 22 studies from the systematic literature review on anesthetic-related AEs costs (Fig. 2); the full list of contributions included in the review and reasons for exclusion are available in the Supplementary materials (Sect. 2.2, 2.3, Table S.4).

Studies were conducted mainly in the US and Europe. Major variability was recorded in the severity of the clinical setting, ranging from ambulatory procedures to major surgeries (major abdominal surgery, liver surgery, major orthopedic, abdominal, gynecologic or noncardiac thoracic surgery). Overall, the anesthetic agents most frequently analyzed, alone or in combination, were midazolam, propofol, dexmedetomidine, fentanyl, remifentanil, volatile agents (desflurane, sevoflurane, isoflurane, nitrous oxide). Most studies ($n = 14$ [18–31]) featured some form of aggregate measure of costs (recovery costs, intensive care unit/post-anesthesia care unit costs, perioperative costs, or total estimates of costs incurred for the complications). Studies that featured cost estimates associated with specific AE costs most frequently focused on nausea and/or vomiting, using estimates of (additional) antiemetic drugs required and pain (additional analgesics required); two studies focused specifically on delirium and/or post-operative cognitive disorder [31, 32].

Among the complications and cost categories which specified the type of AE, cognitive disorders and delirium, reported for dexmedetomidine and butyrophenone derivatives, were the costliest. Major variability in cost estimates was found, depending on methods used, populations under scrutiny, as well as type of healthcare system. The paucity of data did not allow meaningful comparison across AE types and anesthetic agents. The entirety of the cost estimates collected is available in the supplementary file Datasets.xlsx ("Costs-focused review" section). Detailed tabulations of cost estimates by adverse event and anesthetic agent category are reported in the Supplementary Materials. Table S.5 presents the estimates in 2024 US dollars, while Table S.6 displays the same data converted to 2024 PPP US dollars. The reported values are taken directly from the studies included in the cost-focused literature review and are presented as simple descriptive statistics (mean, standard deviation, minimum, and maximum) where applicable. No modeling or assumptions were introduced beyond inflation and currency conversion. The method is illustrated with a bradycardia example in the preamble to Supplementary Table S.5.

Gross costing

Given the heterogeneous nature and paucity of estimates of anesthetic-related AEs costs from the literature, the gross costing exercise was based on results from the umbrella review. Estimates were obtained either by assigning AEs disutility values and applying the implicit cost derived from the implicit willingness to pay of the Italian healthcare system or by using Italian DRG tariffs for hospitalizations weighted by AE frequency. Using the method of assigning an implicit cost of the disutility associated with AEs resulted in higher costs compared with cost estimates based on DRG tariffs (except for nitrous oxide). This was due to the fact that certain AEs are associated with particularly high disutility values (e.g., delirium [associated disutility: 0.506], cognitive dysfunction [associated disutility: 0.46], bradycardia [associated disutility: 0.254]) compared to others (e.g., nausea and/or vomiting [associated disutility: 0.032]). However, the DRG tariffs do not reflect these big differences. For example, the DRG tariff for nausea and/or vomiting is 1,123.6 €, while for delirium is 2,175.76 €, less than double that of nausea and/or vomiting, compared to the disutility where the difference is more than 15 times higher for delirium. Consequently, anesthetic agents associated

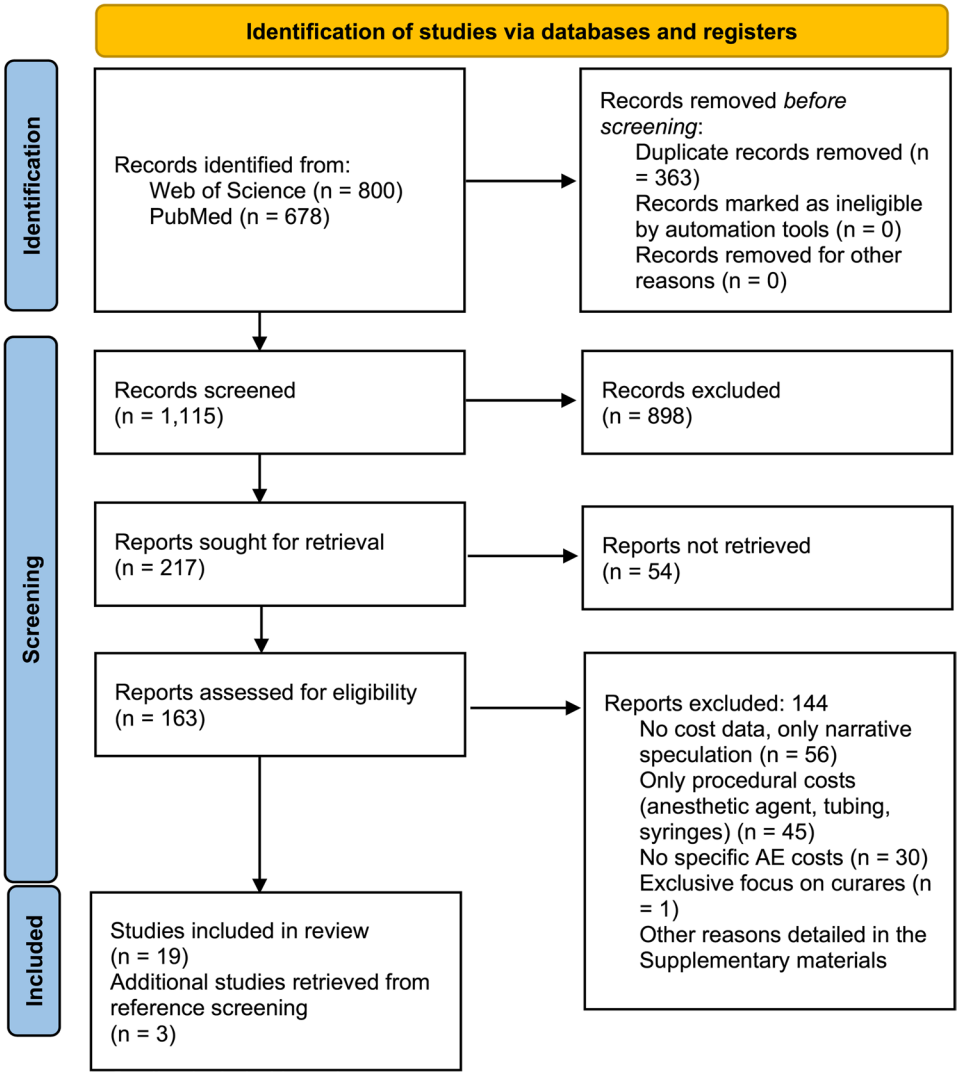

Fig. 2 PRISMA flowchart synthesizing the review screening process for the costs-focused literature review

with high frequencies of AEs entailing large disutilities end up being more penalized in the "implicit cost of the disutility" method compared to the DRG method.

Figure 3 reports the estimates of costs associated with AEs by anesthetic agent resulting from the umbrella review in the Italian context. Propofol appeared to be the anesthetic agent associated with the highest costs, followed by etomidate, ketamine, dexmedetomidine, and fentanyl. The complete table featuring numeric values, sensitivity analysis, and the complete datasets are available in the Supplementary Materials (Table S.7, S.8, S.9) and ancillary files.

Discussion and conclusion

Despite a growing body of knowledge about anesthetic-related AEs from a clinical standpoint, much less is known about their economic impacts, even though it is arguably crucial that payers, policymakers and clinicians make decisions about preferred anesthetic agents based on safety and associated cost burdens. This umbrella review of systematic reviews and meta-analyses mapped the set of anesthetic agents and related AEs for which quantitative data exist on their frequency of occurrence. These data were used to perform an exploratory assessment of the magnitude of costs generated by AEs in the Italian context. This gross costing exercise unveiled that propofol, etomidate, ketamine, and dexmedetomidine were associated with the highest cost estimates.

The systematic literature review which focused on contributions featuring explicit estimations of costs, revealed that the economic burden of anesthesia-related adverse events remains an understudied area, with a crucial lack of methodological guidelines on how cost data should be estimated and reported. Many studies use aggregate measures (e.g., total AE-related costs, total perioperative costs) or bundles of anesthetic agents and few look

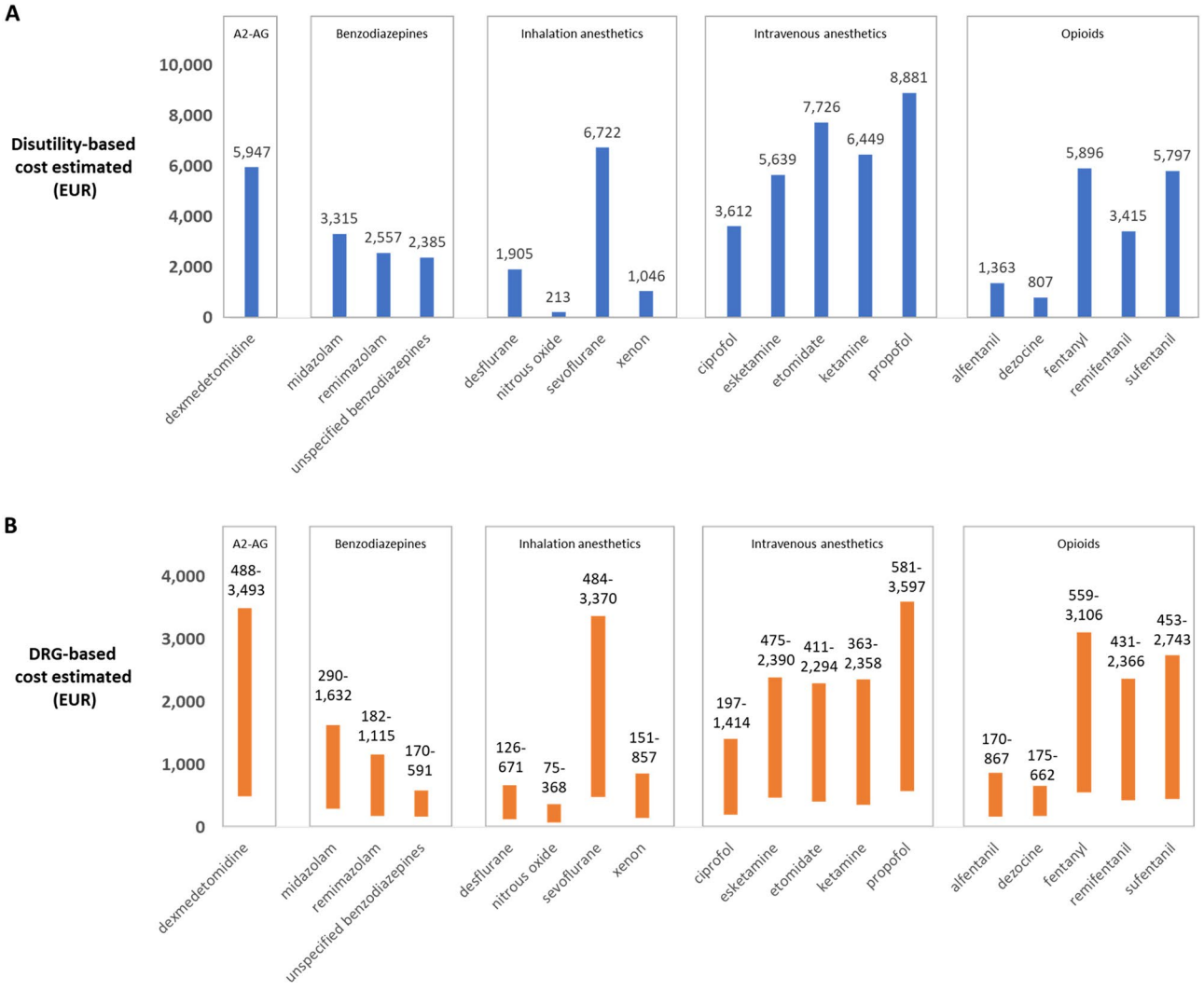

Fig. 3 Disutility-based estimates **(A)** and DRG-based estimates **(B)** of average costs per episode associated with AEs for anesthesia agents, derived from AE frequency data collected from the umbrella review. In B, the top of range is based on day ordinary hospitalization (which includes overnight stays) and bottom of range based on one-day/day-hospital hospitalization hospital DRGs. Note: *A-2 Ag* = Alpha-2 agonist

at specific AEs, impairing the possibility to make comparisons across anesthetic agents. From the evidence available, cognitive disorders and delirium, which are particularly associated with dexmedetomidine, haloperidol, and ketamine [33], appear to be the most expensive complications to be addressed. Major heterogeneity in costs estimates exists across countries and healthcare systems. It is worth remarking that no data is available to compare costs of complications based on survival of the patient. Indeed, severe (e.g., leading to death) but rare complications exist which can – although with caution – be attributed to single anesthetic agents [34]. At the same time, there are many, frequent, mild complications that can be attributed with more certainty to single anesthetic agents and may therefore justify the use of safer, but more expensive agents.

This study comes with a set of limitations worth acknowledging. Although systematic reviews and meta-analyses represent the highest level of quality in clinical research, results of the gross costing estimates are endogenous to the AEs examined in these systematic reviews. This is particularly true for systematic reviews addressing specific combinations of anesthetic agents or focusing on specific sets of complications. Consequently, heterogeneity in terms of clinical settings and patient populations affects our estimates, encouraging caution in results interpretation, especially for comparisons across anesthetic agents.

Additionally, although the concept of assigning a monetary value to health state disutilities stems from the cost-utility analysis literature, we acknowledge that our gross costing approach based on systematic literature review data is innovative, not previously validated, and therefore

must be considered exploratory in nature. Whenever possible, we employed estimates derived in the post-anesthesia state [8]; however, when such data were unavailable, we drew upon values from standard catalogues of health-related quality of life scores [9]. Moreover, in case health utility or disutility values were not available for specific AEs, if possible, we referred to broader clinical categories as proxies. For example, the disutility associated with bradycardia was approximated using the published value for "other cardiac arrhythmias" [9]. These assumptions were necessary to minimize missing data and allow for a more complete estimation across a wide range of AEs. Nonetheless, we recognize that the use of proxy values introduces uncertainty and represents a limitation of our methods. Furthermore, DRG tariffs are used as a proxy for the overall cost of treating complications and rely on the assumption that all the considered adverse events require at least a one-day hospitalization, which may not be fully reflective of the clinical practice. Nevertheless, in the absence of reliable micro costing data, this is the best proxy available. It is also worth noting that it was not possible to consistently assign cost values to awakening times and length of stay; however, longer awakening times and length of stay entail more resources used, and higher costs compared to agents that allow quicker post-operative procedures. For instance, when a surgical procedure is prolonged due to an anesthesia-related AE or when the patient requires post-operative monitoring or treatment in an ICU, the time-cost relationship in the ICU setting is multifaceted with three key dimensions to consider [35]. Delays in transferring patients from the operating room to the ICU (first) increases the likelihood of subsequent delays for other patients awaiting ICU admission (second), which significantly increases analytical complexity. Insights derived from a given hospital may not be transferable to others due to structural and operational variability (third) [35, 36]. Importantly, the economic impact of time in healthcare is mainly influenced by organizational decisions made in advance. These forecasts include the number of staffed hours and case durations. Capacity decisions focus on a single parameter: the relative cost of over-utilized versus under-utilized operating-room time. When the cost of over-utilization is higher, organizations plan extra capacity or use conservative (i.e., inflated) estimates of case durations to reduce the likelihood that staff work late due to predictive errors [37]. Decisions made the day before and/or on the day of surgery (e.g., assigning rooms/services and sequencing to minimize over-utilized time) are typically agreed by the anesthesia department and the hospital [38, 39]. The impact of time-related costs can vary across institutions. In settings with predominantly fixed surgical-suite costs, the additional cost of extra time is more limited compared to institutions where costs of operating rooms and staffing is calculated on a time-per-case basis [40]. Considered together, these factors suggest that while average incremental ICU time may be broadly generalizable, the associated cost implications of increased operating room time are likely to vary markedly across institutions [36].

Finally, we did not conduct subgroup analyses given the broad scope of the umbrella review and the fragmented, heterogeneous nature of the data in the costs-focused review. This decision aligns with the primary aim of the study, which was to comprehensively map the available evidence base rather than compare predefined strata. Similarly, no formal quality assessment tool was applied to the studies included in the costs-focused review, due to the absence of a standardized framework and the consequent diversity in methodological approaches to estimate the economic burden of anesthetic-related adverse events.

Despite these limitations, this study offers the first comprehensive attempt to map the currently available evidence on the economic burden of anesthetic-related AEs. Future work should build upon this foundation using standardized cost-analysis methods, particularly micro-costing approaches, and direct comparisons across agents to strengthen the evidence base. The inclusion of AE-related economic impact data in health technology assessment frameworks could help ensure that anesthetic agent selection reflects not only drug cost and efficacy but also the broader implications for resource use. Integrating economic evaluations with clinical effectiveness data is essential to support informed policymaking regarding the adoption, reimbursement, and use of anesthetic agents in routine clinical practice.

Abbreviations

AE	Adverse event
DRG	Diagnosis-related group
ICU	Intensive care unit
N/A	Not available (not relevant)
OECD	Organization for Economic Co-operation and Development
PICOT	Population Intervention Comparator Outcome Time
PPP	Purchasing power parity
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
US	United States
USD	United States Dollars

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12871-025-03376-5.

Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Supplementary Material 4.

Supplementary Material 5.

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Authors' contributions
PA, FC, GF, GL, and AM contributed to the study design. PA, FC, GF, and GL piloted the literature review, while PA and GF conducted the full literature review. GL validated the results. All authors contributed to the writing and revision of the manuscript and approved the final version.

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Data availability
All datasets generated and analyzed during the current study are available in the Supplementary Information section.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
PA, FC, GF have no conflicts of interest to disclose. GL reports having received speaker fees from Baxter, Medis, Paion, and Viatris and consultancy fees from Baxter, Paion and Viatris. AM and RZ are employed by Viatris.

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