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Association Between Deep Palliative Sedation and Survival in Patients with Advanced Cancer: A Systematic Review and Meta-Analysis

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ABSTRACT

Deep palliative sedation is used to relieve refractory symptoms at the end of life, but concern that it may shorten survival persists. To synthesise comparative evidence on the association between deep palliative sedation and survival in adults with advanced cancer. Systematic review and meta analysis reported according to PRISMA 2020. Adults with advanced or terminal cancer in hospice, palliative care unit, hospital, and home settings. PubMed, Embase, and Cochrane CENTRAL were searched, with Google Scholar and citation chasing. Cohort studies comparing survival between sedated and unsedated patients were included. Hazard ratios (HRs) were pooled by random effects. Mean survival differences were pooled exploratorily. Risk of bias used ROBINS I, certainty GRADE. Twenty three cohort studies (10,911 patients; 2,487 sedated) were included. Five studies (5172 patients) gave HRs, with a pooled HR for death of 0.96 (95% CI 0.88 to 1.04; $I^2 = 0\%$). The HR was 1.02 (0.91 to 1.16) in two studies defining continuous deep sedation and 0.90 (0.80 to 1.01) in three studies of mixed depth. No study reported significantly shorter survival with sedation. In six studies counting survival from admission, sedated patients appeared to live 2.8 days longer (95% CI 0.9 to 4.8), a pattern consistent with immortal time bias. Twenty studies were at serious and three at moderate risk of bias. Observational evidence does not show that deep palliative sedation shortens survival in advanced cancer. Certainty is low, and a small effect cannot be excluded.

INTRODUCTION

Patients with advanced cancer often develop distressing symptoms in the last days of life, including agitated delirium, dyspnoea, and pain. When these symptoms remain refractory to intensive palliative treatment, sedative medication may be used to lower consciousness and relieve suffering, a practice called palliative sedation (Cherny & Radbruch, 2009). Palliative sedation varies in depth and duration. Continuous deep sedation, in which consciousness is reduced to stupor or coma and maintained until death, is the form that raises the most ethical debate (Morita *et al.*, 2017).

The central concern is that sedation, particularly when deep and continuous, might shorten life, through the pharmacological effects of the drugs or through the withholding of artificial hydration. Earlier syntheses found no evidence of a detrimental effect on survival (Beller *et al.*, 2015; Maltoni *et al.*, 2012a). However, those reviews drew mostly on small studies from single centres with differing definitions of sedation, and they combined studies without a quantitative effect estimate. Most studies also measured survival from admission to a service rather than from the start of sedation. This choice is problematic for two reasons. Patients who survive longer have more time in which to become sedated, which can make sedation look protective. Sedated patients are also often the sickest and most symptomatic, which can mask harm (Morita *et al.*, 2017; Suissa, 2008).

Since 2015, several larger cohort studies have used propensity weighting and survival origins closer to the start of sedation to address these problems, and further comparative cohorts have appeared in the last five years. This systematic review and meta analysis therefore aimed to synthesise comparative evidence on the association between deep palliative sedation and survival in adults with advanced cancer, to estimate the pooled hazard ratio where adjusted estimates exist, to separate studies that defined continuous deep sedation from those of mixed or unspecified depth, and to judge the certainty of the evidence.

MATERIALS AND METHODS

Protocol and Reporting

This review followed the PRISMA 2020 statement (Page *et al.*, 2021) and, for studies that could not be pooled, the SWiM guideline (Campbell *et al.*, 2020). Methods followed the Cochrane Handbook where applicable (Higgins *et al.*, 2023).

Eligibility Criteria

Studies were eligible if they enrolled adults with advanced or terminal cancer, compared survival between patients who received palliative sedation and patients who did not, and reported survival time or the hazard of death. Deep palliative sedation was defined as the use of sedative drugs to reduce consciousness to a deep level, continuously or until death, in order to relieve refractory symptoms. Studies of palliative sedation of mixed or unspecified depth were

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eligible when the sedated group could include continuous or deep sedation, and were analysed as a separate stratum. Prospective and retrospective comparative cohort studies were included. Studies without an unsedated comparison group, studies without a survival outcome by sedation status, studies of sedation for procedures or intensive care, and reviews were excluded.

Information Sources and Search Strategy

MEDLINE through PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched, using combinations of terms for palliative, terminal, and continuous deep sedation, survival, and cancer. The full strategies for each database are given in Appendix 1. Google Scholar was also searched for extracting information sources with the same search strings.

Study Selection and Data Extraction

One reviewer screened titles and abstracts and then assessed full reports against the eligibility criteria. Duplicate records were removed, and where two reports described overlapping populations the report with an unsedated comparison group was retained. For each study the reviewer extracted country, setting, design, enrolment period, sample size by sedation status, definition and depth of sedation, the origin of the survival time, and the effect measure with its confidence interval, together with the variables used for matching or adjustment. Hazard ratios and confidence intervals were taken directly from the reports, and a 90% confidence interval was converted to a 95% interval from its reported limits (Tierney *et al.*, 2007). Data were extracted from the full reports where available. For older reports, data were taken from the published abstract and from the structured data tables of the Cochrane review (Beller *et al.*, 2015), including means and standard deviations. A missing standard deviation was derived from the reported 95% confidence interval. When several estimates were available for one study, the primary analysis used the estimate adjusted for the most confounders by weighting, matching, or regression, and the others were examined in sensitivity analyses.

Risk of Bias and Certainty of Evidence

Risk of bias was assessed with ROBINS I (Sterne *et al.*, 2016). Judgements were made for confounding, selection of participants and time origin, classification of the intervention, missing data, and outcome measurement, and were combined into an overall rating. Particular attention was paid to immortal time bias (Suissa, 2008), which arises when survival is counted from a point before sedation can occur. Certainty of evidence for the primary outcome was graded using GRADE (Guyatt *et al.*, 2008).

Statistical Analysis

The primary analysis pooled hazard ratios for death. Hazard ratios were log transformed and combined by inverse variance with a DerSimonian and Laird random effects model (DerSimonian & Laird, 1986). Studies were stratified by whether continuous deep sedation was explicitly defined. Heterogeneity was quantified with Cochran Q, I^2, and tau squared (Higgins *et al.*, 2003). Because few studies were available, a Hartung Knapp adjustment was applied as a sensitivity analysis (IntHout *et al.*, 2014). Further sensitivity analyses used unweighted, unadjusted, or unmatched estimates, the adjusted estimate from the Italian matched cohort, the estimate from the Japanese EASED cohort restricted to patients who reached a Richmond Agitation Sedation Scale score of minus 4 or lower, and leave one out analysis. As an exploratory secondary analysis, differences in mean survival were pooled for studies that reported means with standard deviations and group sizes. Because these studies counted survival from admission, the analysis was interpreted as a test for bias, not as an estimate of effect.

RESULTS AND DISCUSSION

Study Selection

The selection process is shown in Figure 1. In total, 32 reports were assessed in full, and nine were excluded.

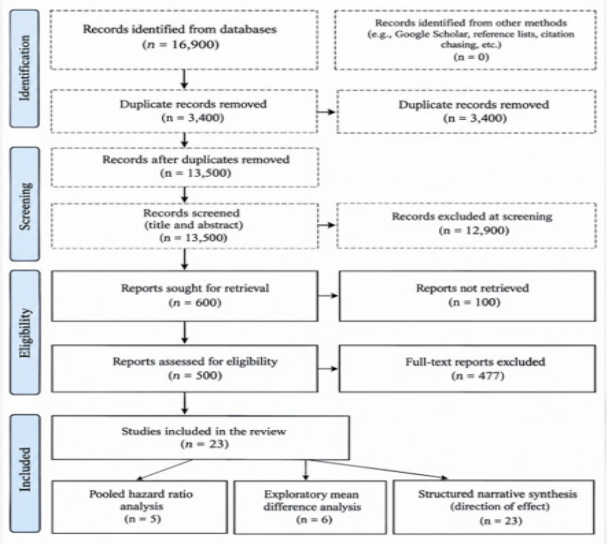


Figure 1: PRISMA 2020 flow diagram of study selection.

Seven of these had no unsedated comparison group (Ahn *et al.*, 2021; Cameron *et al.*, 2004; Claessens *et al.*, 2012; Cowan *et al.*, 2006; Da Costa Miranda *et al.*, 2011; Fainsinger *et al.*, 2000; Good *et al.*, 2005), and two reported no survival outcome by sedation status (Table 1) (Caraceni *et al.*, 2012; Marinelli *et al.*, 2023). Twenty three cohort studies were included (Alonso-Babarro *et al.*, 2010; Bulli *et al.*, 2007; Chiu *et al.*, 2001; de Araujo *et al.*, 2022; Fainsinger *et al.*, 1998; Gu *et al.*, 2015; Kohara *et al.*, 2005; Maeda *et al.*, 2016; Maltoni *et al.*, 2009, 2012b; Mercadante *et al.*, 2009, 2012; Müller-Busch *et al.*, 2003; Park *et al.*, 2021; Prado *et al.*, 2018; Radha Krishna *et al.*, 2012; Rietjens *et al.*, 2008; Stone *et al.*, 1997; Sykes & Thorns, 2003; Tan *et al.*, 2023; Tin *et al.*, 2019; Vitetta *et al.*, 2005; Yokomichi *et al.*, 2022).

Table 1: Reports excluded after full report assessment

Report	Reason For Exclusion
Ahn *et al.* (2021)	No unsedated comparison group; all 106 patients received continuous deep sedation
Cameron *et al.* (2004)	No unsedated comparison group for survival
Claessens *et al.* (2012)	No unsedated comparison group for survival; consciousness outcomes
Cowan *et al.* (2006)	No unsedated comparison group for survival
Da Costa Miranda *et al.* (2011)	No unsedated comparison group for survival
Fainsinger *et al.* (2000)	No unsedated comparison group; descriptive multicentre study
Good *et al.* (2005)	Survival related to opioid and sedative dose; no unsedated group (94% received sedatives)
Caraceni *et al.* (2012)	Compared symptom prevalence; no survival outcome by sedation status
Marinelli *et al.* (2023)	Reported rates of home sedation; no survival comparison by sedation status

Study Characteristics

The included studies enrolled 10,911 patients, of whom 2,487 (23%) were sedated (Table 2). Seven were prospective and sixteen retrospective. They were conducted in Italy (five), Japan (three), China (two), Brazil (two), and the United Kingdom (two), with one each in

Table 2: Characteristics of the 23 included studies

Study	Country and setting	Design and period	Sedated / total	Sedation definition and depth	Survival origin	Result (sedated vs unsedated)
Maltoni *et al.* (2009)	Italy; four hospices	Prospective matched cohort; 2005 to 2006	267 / 518	Mixed depth; 37.8% deep, 43.8% continuous	Hospice admission	HR 0.92 (90% CI 0.80 to 1.06); adjusted HR 0.86 (0.74 to 1.00)
Mercadante *et al.* (2009)	Italy; acute palliative care unit in a cancer centre	Prospective cohort; 1 year	42 / 77	Controlled midazolam sedation, intermediate then definitive or definitive	Admission	Admission time 6.6 vs 3.3 days (P = 0.003)
Mercadante *et al.* (2012)	Italy; three home palliative care units	Retrospective cohort; 6 months	49 / 370	Nonopioid sedatives; depth not graded	Not stated	Mean 38 vs 35 days (P = 0.98)
Prado *et al.* (2018)	Brazil; tertiary cancer centre	Retrospective cohort; deaths 2012 to 2014	203 / 374	Continuous infusion of midazolam or neuroleptic; depth not graded	Admission	Median 33.6 vs 16 days (P < 0.001)
Gu *et al.* (2015)	China; cancer centre palliative ward	Retrospective cohort; 2007 to 2011	82 / 244	All began intermittent; 20 moved to continuous	Admission	Mean 27.4 vs 21.6 days (P = 0.066)
Maeda *et al.* (2016)	Japan; 58 services (hospital teams, units, home)	Prospective cohort, secondary analysis; 2012 to 2014	269 / 1827	Continuous deep sedation: total loss of consciousness until death	Enrolment	HR 1.01 (0.87 to 1.17); propensity weighted

Park *et al.* (2021)	South Korea; palliative care unit	Retrospective cohort; 2012 to 2016	311 / 974	Continuous deep sedation: stupor or coma until death	Start of sedation (actual or estimated)	Time ratio 1.41 (1.21 to 1.64); adjusted 1.22
Yokomichi *et al.* (2022)	Japan; 23 palliative care units	Prospective cohort; 2017	156 / 1625	Continuous deep sedation by intention	Day PPS fell to 20	HR 1.06 (0.85 to 1.33); inverse probability weighted
Alonso-Babarro *et al.* (2010)	Spain; home palliative care, Madrid	Retrospective cohort; 2002 to 2004	29 / 245	Midazolam protocol; depth not graded	Start of palliative team care	Mean 63.9 vs 63.3 days
Bulli *et al.* (2007)	Italy; four home and hospice teams, Florence	Prospective case series; 2000 and 2003 to 2004	136 / 1075	Continuous deep sedation	Start of palliative team care	Median 23 vs 23 days (2000); 24 vs 17 days (2003 to 2004)
Chiu *et al.* (2001)	Taiwan; hospice and palliative care unit	Prospective case series; 1998 to 1999	70 / 276	Sedation; depth not graded	Start of palliative team care	Mean 28.5 vs 24.7 days (not significant)
Fainsinger *et al.* (1998)	South Africa; hospice	Retrospective chart review	23 / 76	Continuous midazolam in 61%, intermittent in 30%	Hospice admission	Mean 9 vs 6 days
Kohara *et al.* (2005)	Japan; palliative care unit	Retrospective chart review; 1999	63 / 124	Sedation; depth not graded	Hospice admission	Mean 28.9 vs 39.5 days (not significant)
Maltoni *et al.* (2012b)	Italy; two palliative care units	Prospective cohort; 2009 to 2010	72 / 327	Midazolam; depth not graded	Admission	Mean 11 vs 9 days
Müller-Busch *et al.* (2003)	Germany; palliative care unit	Retrospective chart review; 1995 to 2002	80 / 548	Mostly midazolam; depth not graded	Admission	Median 15.5 vs 14.0 days
Radha Krishna *et al.* (2012)	Singapore; oncology ward	Retrospective chart review; 2006 to 2007	68 / 238	Midazolam or haloperidol; depth not graded	Admission	Log rank P = 0.78; about 8 days in both groups
Rietjens *et al.* (2008)	Netherlands; acute palliative care unit	Retrospective chart review; 2001 to 2005	68 / 157	Continuous deep sedation before death	Admission	8 vs 7 days (P = 0.12)
Stone *et al.* (1997)	United Kingdom; hospital team and hospice	Retrospective chart review; 1994 to 1995	30 / 115	Sedation for uncontrolled symptoms; mostly midazolam	Admission	Mean 18.6 vs 19.1 days
Sykes and Thorns (2003)	United Kingdom; hospice	Retrospective chart review; 1999	80 / 237	Sedation in the last 48 hours (n = 64) or last 7 days (n = 16)	Hospice admission	Mean 14.3 (48 hours) and 36.6 (7 days) vs 14.2 days
Vitetta *et al.* (2005)	Australia; hospice	Retrospective chart review	68 / 102	Haloperidol, midazolam, or clonazepam; depth not graded	Hospice admission	Mean 36.5 vs 17.0 days
Tin *et al.* (2019)	Hong Kong; oncology ward	Retrospective review	81 / 180	Midazolam infusion; depth not graded	Admission to ward	Median 11 vs 9 days (P = 0.65)

de Araujo *et al.* (2022)	Brazil; palliative care unit	Retrospective cohort; 5 years	92 / 906	Palliative sedation; depth not graded	Hospital admission	Median 9.3 vs 8.2 days; adjusted HR 0.93 (0.74 to 1.15)
Tan *et al.* (2023)	China; palliative ward	Retrospective cohort; 2018 to 2022	148 / 296 (matched)	Continuous palliative sedation, 92.8% light	Admission	Matched median 10 vs 9 days; HR 0.82 (0.64 to 1.04)

Note: HR, hazard ratio; PPS, Palliative Performance Scale. Results are as reported by the original authors. For older reports, values were taken from the abstract or the Cochrane data tables (Beller et al., 2015).

South Korea, Spain, Taiwan, South Africa, Germany, Singapore, the Netherlands, Australia, and Hong Kong. Settings included hospices, palliative care units, oncology wards, hospital teams, and home care. Midazolam was the most frequent sedative, with neuroleptics and diazepam used in several services.

Five studies defined continuous deep sedation explicitly. Maeda and colleagues required total loss of consciousness until death (Maeda *et al.*, 2016), Park and colleagues required stupor or coma maintained until death (Park *et al.*, 2021), Yokomichi and colleagues defined it by the intention to keep the patient continuously unconscious (Yokomichi *et al.*, 2022), Rietjens and colleagues studied continuous deep sedation before death (Rietjens *et al.*, 2008), and Bulli and colleagues reported continuous deep sedation in home and hospice teams (Bulli *et al.*, 2007). The other eighteen studies included sedation of mixed or unspecified depth. In the Italian hospice study, 23.6% of sedated patients received continuous deep sedation (Maltoni *et al.*, 2009). In the Shanghai study, all sedation began as intermittent sedation and 20 of 82 patients moved to continuous sedation (Gu *et al.*, 2015). In the Chengdu study, 92.8% of sedation was continuous light sedation (Tan *et al.*, 2023). Where reported, the median time from the start of sedation to death was between 22 hours and 5 days.

Survival was counted from admission, referral, or enrolment in twenty studies, from the day the Palliative Performance Scale fell to 20 in the Yokomichi study (Yokomichi *et al.*, 2022), and from the start of sedation (actual for sedated patients, estimated for unsedated patients) in the Park study (Park *et al.*, 2021). The origin was not stated in the Italian home care study (Mercadante *et al.*, 2012).

Risk of Bias

Three studies were at moderate risk of bias overall (Maeda *et al.*, 2016; Maltoni *et al.*, 2009; Yokomichi *et al.*, 2022) and twenty were at serious risk (Table 3). The main concerns were confounding by indication in unadjusted

Table 3: Risk of bias (ROBINS I, reviewer judgements)

Study	Confounding	Selection and time origin	Classification of intervention	Missing data	Outcome measurement	Overall
Maltoni *et al.* (2009)	Moderate	Moderate	Moderate	Low	Low	Moderate
Mercadante *et al.* (2009)	Serious	Serious	Low	Low	Low	Serious
Mercadante *et al.* (2012)	Serious	Moderate	Moderate	Low	Low	Serious
Prado *et al.* (2018)	Serious	Serious	Moderate	Low	Low	Serious
Gu *et al.* (2015)	Serious	Serious	Moderate	Low	Low	Serious
Maeda *et al.* (2016)	Moderate	Moderate	Moderate	Moderate	Low	Moderate
Park *et al.* (2021)	Serious	Serious	Moderate	Moderate	Low	Serious
Yokomichi *et al.* (2022)	Moderate	Moderate	Moderate	Low	Low	Moderate
Alonso-Babarro *et al.* (2010)	Serious	Serious	Moderate	Low	Low	Serious
Bulli *et al.* (2007)	Serious	Serious	Moderate	Low	Low	Serious
Chiu *et al.* (2001)	Serious	Serious	Moderate	Low	Low	Serious
Fainsinger *et al.* (1998)	Serious	Serious	Moderate	Low	Low	Serious
Kohara *et al.* (2005)	Serious	Serious	Moderate	Low	Low	Serious
Maltoni *et al.* (2012b)	Serious	Serious	Moderate	Low	Low	Serious
Müller-Busch *et al.* (2003)	Serious	Serious	Moderate	Low	Low	Serious

Radha Krishna *et al.* (2012)	Serious	Serious	Moderate	Low	Low	Serious
Rietjens *et al.* (2008)	Serious	Serious	Moderate	Low	Low	Serious
Stone *et al.* (1997)	Serious	Serious	Moderate	Low	Low	Serious
Sykes and Thorns (2003)	Serious	Serious	Moderate	Low	Low	Serious
Vitetta *et al.* (2005)	Serious	Serious	Moderate	Low	Low	Serious
Tin *et al.* (2019)	Serious	Serious	Moderate	Low	Low	Serious
de Araujo *et al.* (2022)	Serious	Serious	Moderate	Low	Low	Serious
Tan *et al.* (2023)	Serious	Serious	Moderate	Low	Low	Serious

Note:. Selection and time origin was rated serious where survival was counted from admission, because sedated patients accrue immortal time. Classification was rated moderate where depth was mixed, unspecified, or defined by intention.

comparisons, admission based survival origins that expose sedated patients to immortal time, baseline imbalance in age or performance status between groups, and, in the Park study, an estimated sedation start for unsedated patients derived from a model with an accuracy of 52.8% (Park *et al.*, 2021).

Pooled Analysis of Hazard Ratios

Five studies with 5172 patients, of whom 932 were sedated, provided hazard ratios (de Araujo *et al.*, 2022; Maeda *et al.*, 2016; Maltoni *et al.*, 2009; Tan *et al.*, 2023; Yokomichi *et al.*, 2022). The pooled hazard ratio for death with sedation compared with no sedation was 0.96

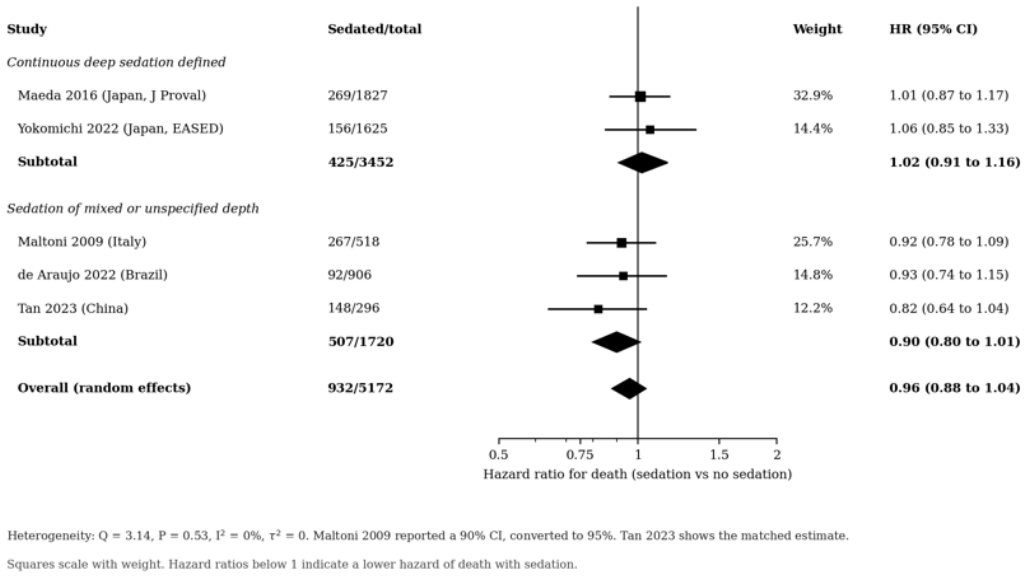


Figure 2: Forest plot of the association between deep palliative sedation and the hazard of death

(95% CI 0.88 to 1.04; Figure 2), with no heterogeneity (Q = 3.14, P = 0.53; I^2 = 0%). The two studies defining continuous deep sedation gave 1.02 (95% CI 0.91 to 1.16), and the three studies of mixed or unspecified depth gave 0.90 (95% CI 0.80 to 1.01). The upper confidence limit of the overall estimate excludes an increase in the hazard of death above 4%, well inside the margin of 1.30 that the Italian investigators set as the limit of clinically acceptable shortening (Maltoni *et al.*, 2009).

Table 4: Pooled analyses and sensitivity analyses

Analysis	Studies	Pooled estimate	95% CI	I^2
Hazard ratio, primary (random effects)	5	0.96	0.88 to 1.04	0%
Hazard ratio, Hartung Knapp adjustment	5	0.96	0.85 to 1.08	0%
Hazard ratio, continuous deep sedation defined	2	1.02	0.91 to 1.16	0%
Hazard ratio, mixed or unspecified depth	3	0.90	0.80 to 1.01	0%
Hazard ratio, unweighted, unadjusted, or unmatched estimates	5	0.92	0.82 to 1.04	57%
Hazard ratio, adjusted Maltoni estimate (0.86)	5	0.94	0.86 to 1.03	4%
Hazard ratio, Yokomichi estimate restricted to RASS minus 4 or lower (1.26)	5	0.96	0.87 to 1.07	24%

Hazard ratio, omitting Maeda 2016	4	0.93	0.84 to 1.03	0%
Hazard ratio, omitting Yokomichi 2022	4	0.94	0.86 to 1.03	0%
Hazard ratio, omitting Maltoni 2009	4	0.97	0.88 to 1.07	0%
Hazard ratio, omitting de Araujo 2022	4	0.96	0.87 to 1.05	2%
Hazard ratio, omitting Tan 2023	4	0.98	0.89 to 1.07	0%
Mean survival difference from admission, days (exploratory)	6	2.8	0.9 to 4.8	26%

Note. RASS, Richmond Agitation Sedation Scale. All estimates use random effects. The mean difference is sedated minus unsedated and is exploratory because survival began at admission

Results were stable in sensitivity analyses (Table 4). The Hartung Knapp adjustment gave an interval of 0.85 to 1.08. Unweighted, unadjusted, or unmatched estimates gave 0.92 (95% CI 0.82 to 1.04) with moderate heterogeneity ($I^2 = 57\%$), because the unmatched estimate from the Chengdu study was lower. Using the adjusted Italian estimate gave 0.94 (0.86 to 1.03), and restricting the Japanese EASED estimate to patients who actually reached deep sedation gave 0.96 (0.87 to 1.07). Omitting any single study gave estimates between 0.93 and 0.98.

Exploratory Analysis of Mean Survival

Six studies reported mean survival from admission with standard deviations and group sizes (Alonso-Babarro *et al.*, 2010; Fainsinger *et al.*, 1998; Gu *et al.*, 2015; Kohara *et al.*, 2005; Mercadante *et al.*, 2009; Müller-Busch *et al.*, 2003). Sedated patients had on average 2.8 days longer survival (95% CI 0.9 to 4.8; Figure 3), with low to moderate heterogeneity ($I^2 = 26\%$). This difference was driven by the Palermo and Shanghai cohorts, and omitting Kohara and colleagues, who found the opposite

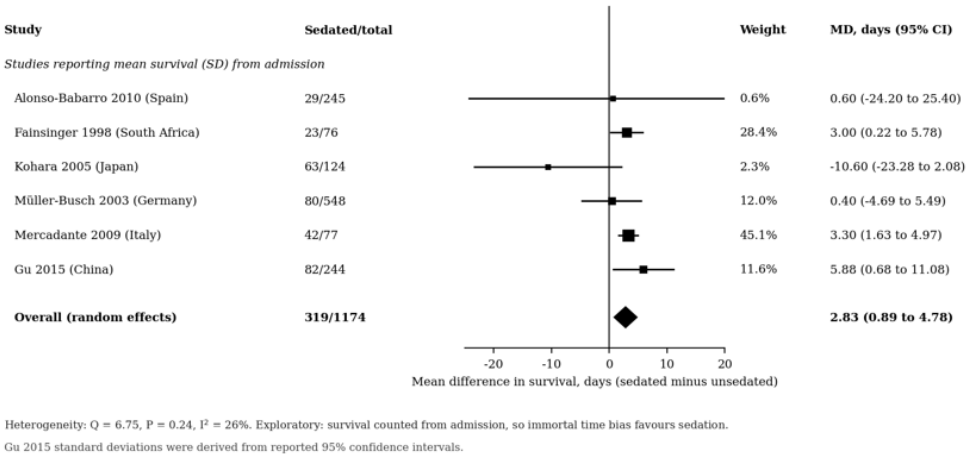


Figure 3: Exploratory forest plot of the difference in mean survival from admission between sedated and unsedated patients

direction, removed the heterogeneity. Because survival in these studies began at admission, the pattern is what immortal time bias would produce, and it should not be read as a benefit of sedation.

Direction of Effect Across All Studies

No study reported significantly shorter survival with sedation. The original authors reported significantly longer survival in four studies: the Brazilian tertiary cohort (Prado *et al.*, 2018), the Palermo unit (Mercadante *et al.*, 2009), the Korean cohort after adjustment (Park *et al.*, 2021), and, in the London hospice study, the subgroup sedated throughout the last week of life, who had been admitted earlier (Sykes & Thorns, 2003). The remaining studies reported no statistically significant difference, either in the original reports or in the Cochrane summary of the older reports (Beller *et al.*, 2015). Among the twelve older studies identified from the reference lists, the point estimate favoured sedation in eight, favoured no sedation in two (Kohara *et al.*, 2005; Stone *et al.*, 1997), and was equal or mixed in two (Table 2) (Bulli *et al.*, 2007; Radha Krishna *et al.*, 2012).

Subgroup Findings

Subgroup findings were inconsistent and exploratory. In the Yokomichi study the hazard ratio was 2.07 (95% CI 1.13 to 3.78) in lung cancer and 1.58 (95% CI 1.01 to 2.48) in moderate or severe agitated delirium, although tests for interaction were not significant (P = 0.20 and P = 0.11) (Yokomichi *et al.*, 2022). In the Maeda study the association differed by care setting (P for interaction = 0.021), with hazard ratios of 1.22 (95% CI 0.99 to 1.49) in hospital and 0.78 (95% CI 0.57 to 1.07) at home, and the volume of artificial hydration did not modify the association (P for interaction = 0.14) (Maeda *et al.*, 2016). The Chengdu study also reported a higher hazard in primary lung cancer (Tan *et al.*, 2023).

Contextual Evidence from Excluded Reports

Two reports excluded from the survival comparison still

informed interpretation. The Korean hospice cohort of 106 patients who all received continuous deep sedation had no comparator, but survival in that cohort was associated chiefly with established prognostic markers, namely performance status, the Palliative Prognostic Index, bilirubin, and ferritin (Ahn *et al.*, 2021). The Tuscan home care cohort of 143 patients reported that 38% received palliative sedation, with survival determined by performance status and ongoing anticancer treatment, but did not compare survival by sedation status (Marinelli *et al.*, 2023).

Certainty of Evidence

Certainty in the finding that sedation does not shorten survival was rated low. It was downgraded one level for indirectness, because survival was counted from admission or enrolment, or from a point preceding sedation, in most studies, and one level for imprecision, given five pooled studies and plausible values that include a small increase in hazard under the Hartung Knapp interval.

Discussion

This systematic review of 23 cohort studies including 10,911 patients found no evidence that deep palliative sedation shortens survival in advanced cancer. The pooled hazard ratio of 0.96 (95% CI 0.88 to 1.04) from five studies was close to null with no heterogeneity, and it was similar when only the studies that defined continuous deep sedation were pooled (1.02, 95% CI 0.91 to 1.16). No study reported significantly shorter survival. These findings agree with earlier syntheses (Beller *et al.*, 2015; Maltoni *et al.*, 2012a) and extend them in three ways: by including large propensity weighted and matched cohorts (Maeda *et al.*, 2016; Tan *et al.*, 2023; Yokomichi *et al.*, 2022), by separating studies according to sedation depth, and by quantifying the likely size of bias in admission based comparisons.

The studies that reported longer survival with sedation need careful interpretation. Most older studies counted survival from admission or referral. In such designs patients must live long enough to become refractory and to be sedated, so sedated patients accumulate survival time before exposure. This immortal time bias (Suissa, 2008) probably explains the longer survival in the Brazilian and Palermo cohorts, and it matches the observation that patients sedated throughout the last week of life had been admitted earlier (Sykes & Thorns, 2003). The exploratory pooled difference of 2.8 days in the six studies that reported means is consistent with this explanation and illustrates the size of the bias. The Korean study tried to avoid the problem by estimating a sedation start for unsedated patients, but its matching model had low accuracy (Park *et al.*, 2021), so its survival gain should not be read as a benefit of sedation. The Yokomichi study anchored survival to a clinical marker close to death, which reduces this bias (Yokomichi *et al.*, 2022).

Confounding by indication acts in the opposite direction. Patients selected for sedation usually have more severe symptoms, which may carry a worse prognosis. The propensity weighted and matched cohorts balanced symptom burden, performance status, and laboratory markers (Maeda *et al.*, 2016; Tan *et al.*, 2023; Yokomichi *et al.*, 2022), although unmeasured factors such as clinician preference could remain. The single arm Korean cohort (Ahn *et al.*, 2021) and the Tuscan home cohort (Marinelli *et al.*, 2023) show that survival in dying patients tracks baseline performance and prognostic markers, which supports interpreting crude differences cautiously. Sedation durations were brief, with medians of 1 to 2 days in most studies, so any pharmacological effect on survival would have to operate within a very short window, and this brevity makes it difficult to align the survival origin with the start of sedation.

The exploratory signals call for caution rather than alarm. The higher hazard ratios in lung cancer and in moderate or severe agitated delirium in the Yokomichi study (Yokomichi *et al.*, 2022), the lung cancer signal in the Chengdu study (Tan *et al.*, 2023), and the care setting difference in the Maeda study (Maeda *et al.*, 2016) rested on small subgroups with wide intervals, and in the Yokomichi study the interaction tests were not significant. They may reflect poorer organ reserve in patients with these features, or chance, and they justify further study of diagnosis, dose, and depth specific effects.

For clinical practice, these data can support conversations with patients and families who fear that sedation hastens death. The evidence relates to sedation used as intended, with proportionate titration, specialist oversight, and a prognosis of days, and it should not be read as support for sedation outside those conditions. For research, future studies should adopt a shared definition of continuous deep sedation (Morita *et al.*, 2017), count survival from the start of sedation or another clinically defined time zero, treat sedation as a time varying exposure, and report dose and depth so that effects can be compared across settings.

Strengths of this review include a broad evidence base spanning 1997 to 2023, separation of studies by sedation depth, standardisation of effect estimates, formal appraisal of risk of bias with attention to time origin, and sensitivity analyses that did not change the conclusion. Several limitations must be acknowledged. Screening, extraction, and appraisal were done by one reviewer, which increases the chance of error. For the older reports, data came from abstracts and from the Cochrane data tables, not from full text, and several reports gave no variance. Only five studies supplied hazard ratios, which prevented meta regression and tests for small study effects, and the Hartung Knapp interval was wide. The studies were observational and defined sedation depth differently, nearly all were conducted in specialist services, and the largest cohorts came from Japan, where practice and length of stay may differ from other settings (Maeda *et al.*, 2016). One study reported a 90% interval that we converted for pooling (Maltoni *et al.*, 2009). Finally, a

small increase or decrease in survival cannot be excluded.

CONCLUSION

Observational evidence from 23 cohort studies does not show that deep palliative sedation shortens survival in patients with advanced cancer. The pooled hazard ratio of 0.96 supports this conclusion, although certainty is low and a small effect cannot be ruled out. Studies that count survival from admission should not be used to claim a survival benefit. Prospective studies with a shared definition and a sedation anchored survival origin are needed.

Author Contributions

The author conceived the review, designed the search, screened the reports, extracted the data, performed the analysis, and wrote the manuscript.

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Declaration of AI

The author used ChatGPT for brainstorming and keeping consistency in the manuscript.

REFERENCES

Ahn, H. K., Ahn, H. Y., Park, S. J., & Hwang, I. C. (2021). Characteristics associated with survival in patients receiving continuous deep sedation in a hospice care unit. *Journal of Hospice and Palliative Care, 24*(4), 254–260. https://doi.org/10.14475/jhpc.2021.24.4.254

Alonso-Babarro, A., Varela-Cerdeira, M., Torres-Vigil, I., Rodríguez-Barrientos, R., & Bruera, E. (2010). At-home palliative sedation for end-of-life cancer patients. *Palliative Medicine, 24*(5), 486–492. https://doi.org/10.1177/0269216309359996

Beller, E. M., van Driel, M. L., McGregor, L., Truong, S., & Mitchell, G. (2015). Palliative pharmacological sedation for terminally ill adults. *Cochrane Database of Systematic Reviews, (1),* Article CD010206. https://doi.org/10.1002/14651858.CD010206.pub2

Bulli, F., Miccinesi, G., Biancalani, E., Fallai, M., Mannocci, M., Paci, E., Piazza, M., Tempestini, C., & Morino, P. (2007). Continuous deep sedation in home palliative care units: case studies in the Florence area in 2000 and in 2003–2004. *Minerva Anestesiologica, 73*(5), 291–298.

Cameron, D., Bridge, D., & Blitz-Lindeque, J. (2004). Use of sedation to relieve refractory symptoms in dying patients. *South African Medical Journal, 94*(6), 445–449.

Campbell, M., McKenzie, J. E., Sowden, A., Katikireddi, S. V., Brennan, S. E., Ellis, S., Hartmann-Boyce, J., Ryan, R., Shepperd, S., Thomas, J., Welch, V., & Thomson, H. (2020). Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. *BMJ, 368*, Article l6890. https://doi.org/10.1136/bmj.l6890

Caraceni, A., Zecca, E., Martini, C., Gorni, G., Campa, T., Brunelli, C., & De Conno, F. (2012). Palliative sedation at the end of life at a tertiary cancer center. *Supportive Care in Cancer, 20*(6), 1299–1307. https://doi.org/10.1007/s00520-011-1217-6

Cherny, N. I., & Radbruch, L. (2009). European association for palliative care (EAPC) recommended framework for the use of sedation in palliative care. *Palliative Medicine, 23*(7), 581–593. https://doi.org/10.1177/0269216309107024

Chiu, T. Y., Hu, W. Y., Lue, B. H., Cheng, S. Y., & Chen, C. Y. (2001). Sedation for refractory symptoms of terminal cancer patients in Taiwan. *Journal of Pain and Symptom Management, 21*(6), 467–472. https://doi.org/10.1016/S0885-3924(01)00286-X

Claessens, P., Menten, J., Schotsmans, P., & Broeckaert, B. (2012). Level of consciousness in dying patients: the role of palliative sedation: a longitudinal prospective study. *American Journal of Hospice and Palliative Medicine, 29*(3), 195–200.

Cowan, J. D., Clemens, L., & Palmer, T. (2006). Palliative sedation in a southern Appalachian community. *American Journal of Hospice and Palliative Medicine, 23*(5), 360–368.

Da Costa Miranda, V., De Souza Fede, Â. B., Martins, F. D., De Magalhães, N. P., De Lazzari Schaffhausser, H., Riechelmann, R. P., & Del Giglio, A. (2011). Doctor, how long? *European Journal of Cancer Care, 20*(1), 50–55.

de Araujo, C. Z. S., de Araújo, L. Z. S., & Nassar Junior, A. P. (2022). Palliative sedation in patients with advanced cancer in a specialized unit in a middle-income country: a retrospective cohort study. *Palliative & Supportive Care, 20*(4), 491–495. https://doi.org/10.1017/S1478951521001371

DerSimonian, R., & Laird, N. (1986). Meta-analysis in clinical trials. *Controlled Clinical Trials, 7*(3), 177–188. https://doi.org/10.1016/0197-2456(86)90046-2

Fainsinger, R. L., Landman, W., Hoskings, M., & Bruera, E. (1998). Sedation for uncontrolled symptoms in a South African hospice. *Journal of Pain and Symptom Management, 16*(3), 145–152. https://doi.org/10.1016/S0885-3924(98)00066-9

Fainsinger, R. L., Waller, A., Bercovici, M., Bengtson, K., Landman, W., Hosking, M., Núñez-Olarte, J. M., & deMoissac, D. (2000). A multicentre international study of sedation for uncontrolled symptoms in terminally ill patients. *Palliative Medicine, 14*, 257–265.

Good, P. D., Ravenscroft, P. J., & Cavenagh, J. (2005). Effects of opioids and sedatives on survival in an Australian inpatient palliative care population. *Internal Medicine Journal, 35*(9), 512–517.

Gu, X., Cheng, W., Chen, M., Liu, M., & Zhang, Z. (2015). Palliative sedation for terminally ill cancer patients in a tertiary cancer center in Shanghai, China. *BMC*

Palliative Care, 14, Article 5. https://doi.org/10.1186/s12904-015-0002-6

Guyatt, G. H., Oxman, A. D., Vist, G. E., Kunz, R., Falck-Ytter, Y., Alonso-Coello, P., & Schünemann, H. J. (2008). GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ, 336*(7650), 924–926. https://doi.org/10.1136/bmj.39489.470347.AD

Higgins, J. P. T., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M. J., & Welch, V. A. (Eds.) (2023). *Cochrane handbook for systematic reviews of interventions (Version 6.4)*. Cochrane. https://www.training.cochrane.org/handbook

Higgins, J. P. T., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *BMJ, 327*(7414), 557–560. https://doi.org/10.1136/bmj.327.7414.557

IntHout, J., Ioannidis, J. P. A., & Borm, G. F. (2014). The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. *BMC Medical Research Methodology, 14*, Article 25. https://doi.org/10.1186/1471-2288-14-25

Kohara, H., Ueoka, H., Takeyama, H., Murakami, T., & Morita, T. (2005). Sedation for terminally ill patients with cancer with uncontrollable physical distress. *Journal of Palliative Medicine, 8*(1), 20–25. https://doi.org/10.1089/jpm.2005.8.20

Maeda, I., Morita, T., Yamaguchi, T., Inoue, S., Ikenaga, M., Matsumoto, Y., Sekine, R., Yamaguchi, T., Hirohashi, T., Tajima, T., Tatara, R., Watanabe, H., Otani, H., Takigawa, C., Matsuda, Y., Nagaoka, H., Mori, M., Tei, Y., Kikuchi, A., . . . Kinoshita, H. (2016). Effect of continuous deep sedation on survival in patients with advanced cancer (J-Proval): a propensity score-weighted analysis of a prospective cohort study. *The Lancet Oncology, 17*(1), 115–122. https://doi.org/10.1016/S1470-2045(15)00401-5

Maltoni, M., Miccinesi, G., Morino, P., Scarpi, E., Bulli, F., Martini, F., Canzani, F., Dall'Agata, M., Paci, E., & Amadori, D. (2012b). Prospective observational Italian study on palliative sedation in two hospice settings: differences in case mixes and clinical care. *Supportive Care in Cancer, 20*(11), 2829–2836. https://doi.org/10.1007/s00520-012-1407-x

Maltoni, M., Pittureri, C., Scarpi, E., Piccinini, L., Martini, F., Turci, P., Montanari, L., Nanni, O., & Amadori, D. (2009). Palliative sedation therapy does not hasten death: results from a prospective multicenter study. *Annals of Oncology, 20*(7), 1163–1169. https://doi.org/10.1093/annonc/mdp048

Maltoni, M., Scarpi, E., Rosati, M., Derni, S., Fabbri, L., Martini, F., Amadori, D., & Nanni, O. (2012a). Palliative sedation in end-of-life care and survival: a systematic review. *Journal of Clinical Oncology, 30*(12), 1378–1383. https://doi.org/10.1200/JCO.2011.37.3795

Marinelli, D., Ravoni, G., Fusilli, M., Colpani, E., Filetti, M., Santini, D., Porzio, G., & Giusti, R. (2023). Palliative sedation and time to death in home palliative care: retrospective analysis. *BMJ Supportive & Palliative Care, 13*(e3), e890–e893. https://doi.org/10.1136/spcare-2023-004377

Mercadante, S., Intravaia, G., Villari, P., Ferrera, P., David, F., & Casuccio, A. (2009). Controlled sedation for refractory symptoms in dying patients. *Journal of Pain and Symptom Management, 37*(5), 771–779. https://doi.org/10.1016/j.jpainsymman.2008.04.020

Mercadante, S., Porzio, G., Valle, A., Fusco, F., Aielli, F., Adile, C., & Casuccio, A. (2012). Palliative sedation in advanced cancer patients followed at home: a retrospective analysis. *Journal of Pain and Symptom Management, 43*(6), 1126–1130. https://doi.org/10.1016/j.jpainsymman.2011.06.027

Morita, T., Imai, K., Yokomichi, N., Mori, M., Kizawa, Y., & Tsuneto, S. (2017). Continuous deep sedation: a proposal for performing more rigorous empirical research. *Journal of Pain and Symptom Management, 53*(1), 146–152. https://doi.org/10.1016/j.jpainsymman.2016.08.012

Müller-Busch, H. C., Andres, I., & Jehser, T. (2003). Sedation in palliative care: a critical analysis of 7 years experience. *BMC Palliative Care, 2*, Article 2. https://doi.org/10.1186/1472-684X-2-2

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., . . . Moher, D. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ, 372*, Article n71. https://doi.org/10.1136/bmj.n71

Park, S. J., Ahn, H. K., Ahn, H. Y., Han, K.-T., & Hwang, I. C. (2021). Association between continuous deep sedation and survival time in terminally ill cancer patients. *Supportive Care in Cancer, 29*(1), 525–531. https://doi.org/10.1007/s00520-020-05516-8

Prado, B. L., Gomes, D. B. D., Usón Júnior, P. L. S., Taranto, P., França, M. S., Eiger, D., Mariano, R. C., Hui, D., & Del Giglio, A. (2018). Continuous palliative sedation for patients with advanced cancer at a tertiary care cancer center. *BMC Palliative Care, 17*, Article 13. https://doi.org/10.1186/s12904-017-0264-2

Radha Krishna, L. K., Poulose, V. J., & Goh, C. (2012). The use of midazolam and haloperidol in cancer patients at the end of life. *Singapore Medical Journal, 53*(1), 62–66.

Rietjens, J. A. C., van Zuylen, L., van Veluw, H., van der Wijk, L., van der Heide, A., & van der Rijt, C. C. D. (2008). Palliative sedation in a specialized unit for acute palliative care in a cancer hospital: comparing patients dying with and without palliative sedation. *Journal of Pain and Symptom Management, 36*(3), 228–234. https://doi.org/10.1016/j.jpainsymman.2007.10.014

Sterne, J. A. C., Hernán, M. A., Reeves, B. C., Savović, J.,

Berkman, N. D., Viswanathan, M., Henry, D., Altman, D. G., Ansari, M. T., Boutron, I., Carpenter, J. R., Chan, A.-W., Churchill, R., Deeks, J. J., Hróbjartsson, A., Kirkham, J., Jüni, P., Loke, Y. K., Pigott, T. D., . . . Higgins, J. P. T. (2016). ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. *BMJ, 355*, Article i4919. https://doi.org/10.1136/bmj.i4919

Stone, P., Phillips, C., Spruyt, O., & Waight, C. (1997). A comparison of the use of sedatives in a hospital support team and in a hospice. *Palliative Medicine, 11*, 140–144. https://doi.org/10.1177/026921639701100208

Suissa, S. (2008). Immortal time bias in pharmaco-epidemiology. *American Journal of Epidemiology, 167*(4), 492–499. https://doi.org/10.1093/aje/kwm324

Sykes, N., & Thorns, A. (2003). Sedative use in the last week of life and the implications for end-of-life decision making. *Archives of Internal Medicine, 163*(3), 341–344. https://doi.org/10.1001/archinte.163.3.341

Tan, F., Chen, S., Huang, L., Chen, Y., & Wu, Y. (2023). Continuous palliative sedation in terminally ill patients with cancer: a retrospective observational cohort study from a Chinese palliative care unit. *BMJ Open, 13*(5), Article e071859. https://doi.org/10.1136/bmjopen-2023-071859

Tierney, J. F., Stewart, L. A., Ghersi, D., Burdett, S., & Sydes, M. R. (2007). Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials, 8*, Article 16. https://doi.org/10.1186/1745-6215-8-16

Tin, W. W., Lo, S. H., & Wong, F. C. (2019). A retrospective review for the use of palliative sedation in a regional hospital in Hong Kong. *Annals of Palliative Medicine*. https://doi.org/10.21037/apm.2019.09.05

Vitetta, L., Kenner, D., & Sali, A. (2005). Sedation and analgesia-prescribing patterns in terminally ill patients at the end of life. *American Journal of Hospice and Palliative Medicine, 22*(6), 465–473.

Yokomichi, N., Yamaguchi, T., Maeda, I., Mori, M., Imai, K., Naito, A. S., Yamaguchi, T., Terabayashi, T., Hiratsuka, Y., Hisanaga, T., & Morita, T. (2022). Effect of continuous deep sedation on survival in the last days of life of cancer patients: a multicenter prospective cohort study. *Palliative Medicine, 36*(1), 189–199. https://doi.org/10.1177/02692163211057754

Appendix 1. Search strategies

Searches covered each database from inception to October 2026. Strategies are shown in the syntax of each platform.

PubMed (MEDLINE)

#1 "palliative sedation"[tiab] OR "terminal sedation"[tiab] OR "continuous deep sedation"[tiab] OR "deep sedation"[tiab] OR "continuous sedation"[tiab] OR "continuous palliative sedation"[tiab] OR "palliative pharmacological sedation"[tiab]

#2 survival[tiab] OR "time to death"[tiab] OR mortality[tiab] OR "hasten death"[tiab] OR "shorten life"[tiab] OR "Survival Analysis"[Mesh]

#3 Neoplasms[Mesh] OR cancer*[tiab] OR neoplas*[tiab] OR oncolog*[tiab] OR "terminally ill"[tiab] OR "advanced cancer"[tiab]

#4 #1 AND #2 AND #3

Embase

#1 'palliative sedation'/exp OR 'terminal sedation':ti,ab OR 'continuous deep sedation':ti,ab OR 'deep sedation':ti,ab OR 'continuous sedation':ti,ab

#2 survival/exp OR survival:ti,ab OR 'time to death':ti,ab OR mortality/exp OR 'hasten death':ti,ab

#3 neoplasm/exp OR cancer*:ti,ab OR oncolog*:ti,ab OR 'terminally ill':ti,ab

#4 #1 AND #2 AND #3

Cochrane CENTRAL

("palliative sedation" OR "terminal sedation" OR "continuous deep sedation" OR "deep sedation" OR "continuous sedation"):ti,ab,kw AND (survival OR "time to death" OR mortality):ti,ab,kw AND (cancer OR neoplasm* OR oncolog* OR "terminally ill"):ti,ab,kw

Google Scholar and reference lists

Google Scholar was searched with "palliative sedation" OR "continuous deep sedation" survival cancer cohort, and with "continuous deep sedation" propensity survival. Reference lists of the Maltoni systematic review and the Cochrane review were screened in full.

Appendix 2: PRISMA 2020 checklist, location of items

Item	Reported in
Title	Title page
Abstract	Abstract
Rationale	Introduction
Objectives	Introduction
Eligibility criteria	Methods: Eligibility criteria
Information sources	Methods: Information sources; Appendix 1
Search strategy	Appendix 1
Selection process	Methods: Study selection
Data collection process	Methods: Study selection and data extraction
Data items	Methods: Study selection and data extraction

Risk of bias	Methods: Risk of bias; Table 3
Effect measures	Methods: Statistical analysis
Synthesis methods	Methods: Statistical analysis
Reporting bias assessment	Methods: Statistical analysis (funnel plots not drawn)
Certainty assessment	Methods: Risk of bias and certainty; Results
Study selection	Results; Figure 1; Table 1
Study characteristics	Results; Table 2
Risk of bias in studies	Results; Table 3
Results of individual studies	Table 2; Figure 2; Figure 3
Results of syntheses	Results; Table 4; Figures 2 and 3
Reporting biases	Not assessed formally (see Methods)
Certainty of evidence	Results: Certainty of evidence
Discussion	Discussion
Registration and protocol	Title page; Methods
Support	Funding Information
Competing interests	Author Disclosure Statement
Availability of data	Extracted data available from the author on request