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Early deep sedation was associated with post-hospital one-year mortality in critically ill surgical patients: a propensity-matched retrospective cohort study

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Abstract

Objective Sedation is a crucial issue in critical care, but the impact of early deep sedation on post-hospital mortality in critically ill surgical patients remains unclear.

Methods We linked the 2015–2020 critical care database at Taichung Veterans General Hospital with the nationwide death registration in Taiwan. Log-rank test was used to estimate survival curves between patients with and without deep sedation, defined by the average Richmond Agitation-Sedation Scale (RASS) level within the first 3 days equal to or lower than − 3. A multivariable Cox proportional hazards regression model was used to determine hazard ratios (HR) and 95% confidence intervals (CI). Furthermore, we used propensity score-matching (PSM) analysis to validate the association.

Results A total of 7,135 critically ill surgical patients were enrolled, and 13.7% of them experienced early deep sedation. Independent predictors for post-hospital one-year mortality included old age, male, more comorbidities, high acute physiology and chronic health evaluation (APACHE) II score, and low body mass index. We noted that receiving midazolam (aHR 1.368, 95% CI 1.052–1.780) or propofol (aHR 1.459, 95% CI 1.136–1.874) was associated with increased mortality compared with dexmedetomidine. Early deep sedation was independently associated with post-hospital mortality after adjusting for covariates (aHR 1.216, 95% CI 1.019–1.452), and the association remained robust in the PSM analysis (aHR 1.313, 95% CI 1.054–1.636).

Conclusion We identified the association between early deep sedation and post-hospital mortality, a modifiable factor, in critically ill surgical patients. Further prospective studies are warranted to confirm our findings.

Keywords Deep sedation, Critical illness, Long-term outcome, Post-hospital mortality, Surgery

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Background

Sedation is one of the key managements used to facilitate compliance with mechanical ventilation and to mitigate deleterious effects resulting from agitation in patients who were admitted to the intensive care unit (ICU) [1]. Early deep sedation has been found to be associated with not only short-term but also long-term outcomes in critically ill patients, including those with coronavirus disease-19 (COVID-19) [2–4].

Due to the steady increase in the number of critically ill survivors, the long-term outcome has been attributed as a research priority in critical care [5, 6]. Previous studies, including our research, have explored the early predictors for long-term mortality in critically ill patients, but studies focusing on critically ill surgical patients remain sparse [7–10]. Moreover, conducting long-term outcome-relevant studies is challenging due to the high attrition rate after the discharge from the ICU and the difficulty in delineating the short- and long-term impacts of ICU-associated variables [11]. An in-depth analysis of post-hospital long-term mortality by excluding in-hospital mortality should enable us to explore the prolonged post-hospital mortality impact of ICU-relevant factors in critically ill surgical patients [12].

In the present study, we aimed to determine the association between early deep sedation and post-hospital one-year mortality in critically ill surgical patients. We linked the critical care database at Taichung Veterans General Hospital (TCVGH) and Taiwan's national death registry database to explore the prevalence of early deep sedation and to assess the independent predictors for post-hospital mortality in critically ill surgical patients.

Methods

Ethical approval

This study was approved by the Institutional Review Board of the Taichung Veterans General Hospital (TCVGH: SE20249B#1). The requirement for informed consent was waived as all of the analyzed data were de-identified.

Data source and study population

We used the critical care database at TCVGH for demographic data and relevant critical care covariates, as well as the death registration profile of the National Health Insurance Research Database (NHIRD) in Taiwan, to ascertain the date of death among enrolled subjects. The primary outcome of interest was post-hospital overall mortality. Taiwan established the National Health Insurance program in 1995, and the coverage of the population was up to 99.9% in 2019; therefore, the date of death in this study should be highly reliable [13, 14]. This cohort study retrospectively enrolled consecutive patients who were admitted to surgical ICUs at TCVGH, a tertiary referral center with approximately 1,600 beds and three surgical ICUs in central Taiwan, between 2015 and 2020. We used the first ICU admission among patients with more than one ICU admission.

Assessment of sedation

The primary interest of exposure was the early sedation status in critically ill surgical patients.

We used the average Richmond Agitation-Sedation Scale (RASS) within the first three days of ICU admission to represent the sedation status of enrolled subjects, and RASS equal to or lower than − 3 was defined as deep sedation in accordance with previous studies [15, 16]. In the study hospital, the depth of sedation was measured and recorded by the nurse using RASS every four hours [17].

Statistical analyses

We presented the descriptive data as means ± standard deviation or number (percentages). Kaplan-Meier analysis was used to show the association between post-hospital mortality and sedation-associated variables. We included variables as candidates for the multivariable regression if the associated univariable p-value was lower than 0.20, and the measurement of the variance inflation factor (VIF) was used to determine the collinearity among variables [18]. A Cox proportional hazards model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for post-hospital mortality after adjustment for age, sex, comorbidity, the severity of critical illness, and potential cofounders. In addition, we used propensity score matching (PSM) to validate the association between early deep sedation and the post-hospital one-year overall mortality. The propensity scores were estimated through using a logistic regression model. The dependent variable was the early deep sedation, and the independent variables were the aforementioned covariates. The optimal nearest neighbor matching algorithm was used in PSM, and the caliper distance of the standard mean difference was set at 0.10 [19, 20]. The statistical analyses were conducted using R 3.6.0, and the level of significance was set at 0.05.

Results

Baseline characteristics of the study participants

A total of 9,109 critically ill surgical patients were identified, and we excluded those whose ICU admission was less than 24 h ($n = 1,057$), given that the sedation status assessment duration was short. We also excluded patients who did not survive during the index ICU admission ($n = 917$) to focus on the long-term post-hospital mortality (Fig. 1). Table 1 summarizes the baseline characteristics of enrolled subjects. The post-hospital one-year overall mortality was 14.4% (1,031/7,135). Among the

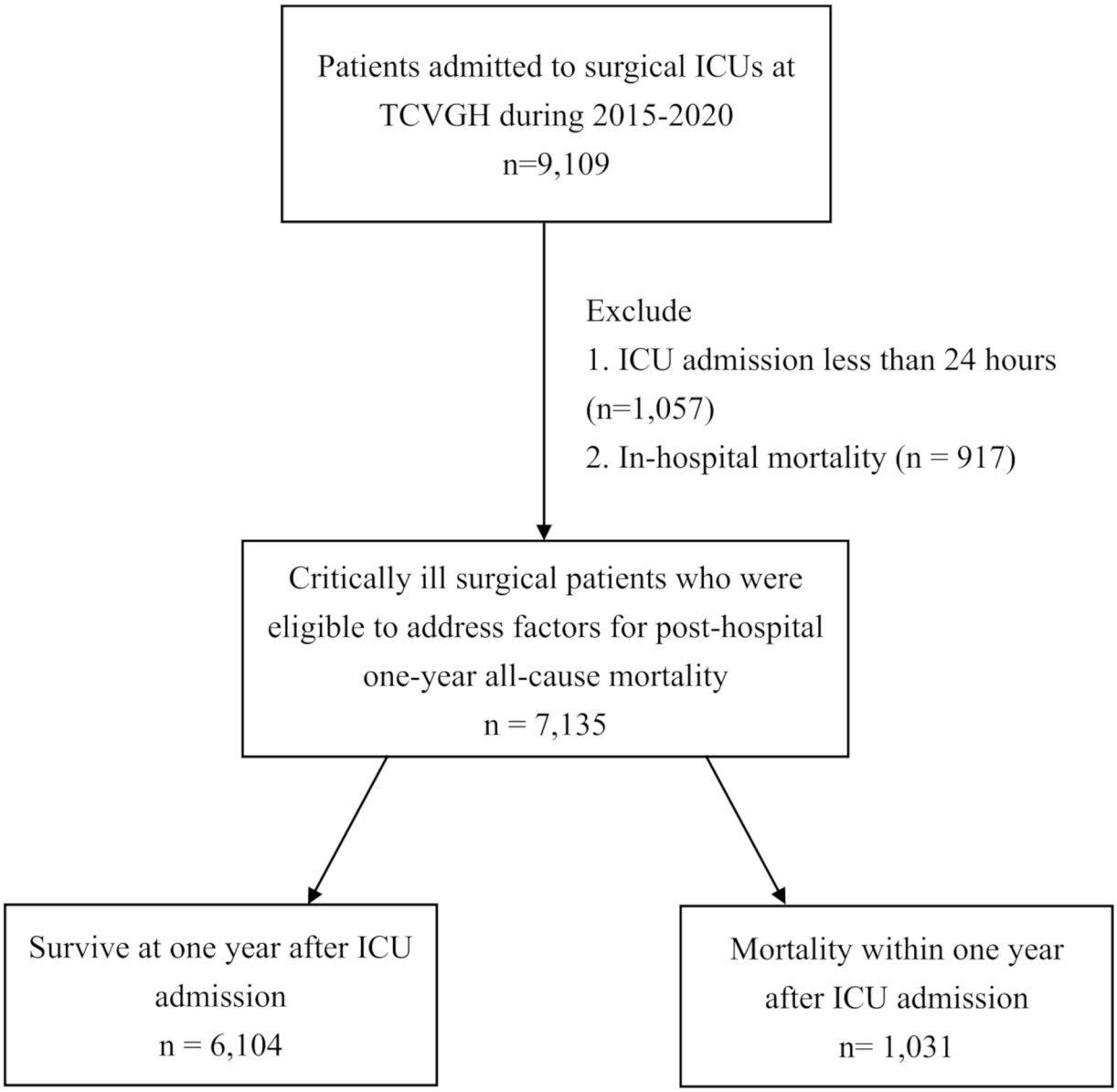

Fig. 1 Flowchart of subject enrollment. Abbreviations: ICU, intensive care unit; TCVGH, Taichung Veterans General Hospital

7,135 patients who were eligible for analyses, the mean age was 60.4 ± 15.9 years, and 4,439 patients (62.2%) were male. With regards to the main surgical divisions, the proportion of patients admitted for neurosurgery, cardiovascular surgery and major abdominal surgery were 51.3%, 20.5% and 11.5%, respectively. Patients in the non-survivor group were more likely to receive midazolam (21.0% vs. 10.7%, $p < 0.01$), or propofol (31.1% vs. 24.6%, $p < 0.01$) and were less likely to be administered with dexmedetomidine (8.5% vs. 15.5%, $p < 0.01$) than those in the survivor group. Furthermore, we found that the non-survivor group had a higher proportion of receiving deep sedation within the first three days of ICU admission compared with those in the survivor group (18.3% vs. 12.9%, $p < 0.01$).

Predictors for post-hospital mortality in critically ill surgical patients

We used Kaplan-Meier analyses to illustrate the correlation between distinct sedation status as well as medications for sedation and post-hospital one-year mortality (Fig. 2 and Supplemental Fig. 1). We then used a multivariable Cox proportional hazards model to determine independent risk and protective factors for post-hospital

Table 1 Patient characteristics categorized by the post-hospital one-year all-cause mortality

	All *n* = 7,135	Survivors *n* = 6,104	Non-survivors *n* = 1,031	*p* value
Basic characteristics				
Age, years	60.4 ± 15.9	59.2 ± 15.9	67.1 ± 14.7	< 0.01
Male	4,439 (62.2%)	3721 (61%)	718 (69.6%)	< 0.01
Body mass index	24.2 ± 4.5	24.5 ± 4.5	22.7 ± 4.3	< 0.01
Charlson Comorbidity Index	1.6 ± 1.4	1.5 ± 1.4	2.2 ± 1.5	< 0.01
Severity of critical illness				
APACHE II score	19.7 ± 6.7	19.4 ± 6.7	21.8 ± 6.3	< 0.01
Presence of shock	2,118 (29.7%)	1,747 (28.6%)	371 (36%)	< 0.01
Scheduled surgery	4,108 (57.6%)	3,565 (58.4%)	543 (52.7%)	< 0.01
Surgical divisions				< 0.01
Neurosurgery	3,657 (51.3%)	3,287 (53.8%)	370 (35.9%)	
Cardiovascular surgery	1,464 (20.5%)	1,360 (22.3%)	104 (10.1%)	
Major abdomen surgery	819 (11.5%)	586 (9.6%)	233 (22.6%)	
Others	1,195 (16.7%)	871 (14.3%)	324 (31.4%)	
Laboratory data				
White blood cell count (x 10^3 count/μL)	10.3 ± 2.8	10.3 ± 2.7	10.2 ± 3.1	0.15
Haemoglobin (g/dL)	11.8 ± 1.2	11.8 ± 1.19	11.6 ± 1.0	< 0.01
Platelet (10^3/μL)	228.3 ± 45.0	228.5 ± 44.7	226.6 ± 46.4	0.20
Albumin (g/dL)	3.0 ± 0.4	3.0 ± 0.4	2.9 ± 0.4	< 0.01
Creatinine (mg/dL)	0.8 ± 0.3	0.8 ± 0.3	0.9 ± 0.4	< 0.01
Sedative agents				
Opioid-alone	3,406 (47.7%)	3,000 (49.1%)	406 (39.4%)	< 0.01
Dexmedetomidine	1,035 (14.5%)	947 (15.5%)	88 (8.5%)	< 0.01
Propofol	1,824 (25.6%)	1,503 (24.6%)	321 (31.1%)	< 0.01
Midazolam	870 (12.2%)	654 (10.7%)	216 (21%)	< 0.01
Deep sedation	974 (13.7%)	785 (12.9%)	189 (18.3%)	< 0.01
NMBA	285 (4.0%)	211 (3.5%)	74 (7.2%)	< 0.01
Outcomes				
ICU length of stay, days	8.4 ± 7.9	8.0 ± 7.6	10.8 ± 8.7	< 0.01
Hospital length of stay, days	18.7 ± 8.9	18.0 ± 8.8	22.6 ± 8.1	< 0.01

Abbreviations: APACHE II, acute physiology and chronic health evaluation; ICU, intensive care unit; NMBA, neuromuscular blocking agent

mortality in critically ill surgical patients (Table 2). We found that a high age (aHR 1.018, 95% CI 1.013–1.022), male (aHR 1.235, 1.074–1.420), high Charlson comorbidity index (CCI) (aHR 1.231, 95% 1.186–1.279), acute physiology and chronic health evaluation (APACHE) II score (aHR 1.020, 95% CI 1.010–1.030), underwent neurosurgery (aHR 1.457, 95% CI 1.136–1.867) or major abdominal surgery (aHR 2.716, 95% CI 2.112–3.494) compared with cardiovascular surgery were associated with increased post-hospital mortality, whereas high BMI appeared to be a protective factor (aHR 0.926, 95% CI 0.911–0.941). We further noted that receiving midazolam (aHR 1.368, 95% CI 1.052–1.780) or propofol (aHR 1.459, 95% CI 1.136–1.874) was associated with increased mortality compared with dexmedetomidine. Notably, early deep sedation was independently associated with an increased risk of post-hospital mortality after adjusting for the aforementioned covariates (aHR 1.216, 95% CI 1.019–1.452).

PSM analysis

A total of 1,848 patients were eligible for the PSM analysis after matching demographics, comorbidities, surgical divisions, types of surgery, severities of critical illness, and laboratory data (Fig. 3). The low standardized mean difference (SMD) measurement of variables between the two groups demonstrated the high matching quality in this study (Table 3 and Supplemental Fig. 2). Table 4 reveals the consistent association between early deep sedation and the risk for one-year post-hospital mortality in the PSM population, with an adjusted HR of 1.313 (95% CI 1.054–1.636) (Table 4).

Discussion

Light sedation is a crucial issue in critical care, but the prolonged impact of early deep sedation in critically ill surgical patients remains unclear. We found that old age, male, low BMI, more comorbidities, high APACHE II score, underwent neurosurgery/major abdominal surgery compared with cardiovascular surgery, receiving midazolam/propofol compared with dexmedetomidine, and early deep sedation were independent risk factors for post-hospital mortality. These findings provide crucial evidence for risk stratification, and the avoidance of deep sedation might serve as a modifiable factor to improve long-term survival in critically ill surgical patients.

Given the advances in critical care and improvement of hospital survival, there is a steadily increasing number of patients who survive critical illness worldwide [5]. Therefore, identifying predictors, particularly modifiable factors, for long-term outcomes in critically ill patients is currently one of the research priorities in critical care medicine [6]. Recent studies, including our own research, have found that pre-existing comorbidities, positive fluid balance and culture positivity were associated with increased long-term mortality in critically ill patients [7–9]. Indeed, we have examined the association between early deep sedation and ICU mortality, and the adjHR was high (4.373, 95% CI 3.576–5.283)

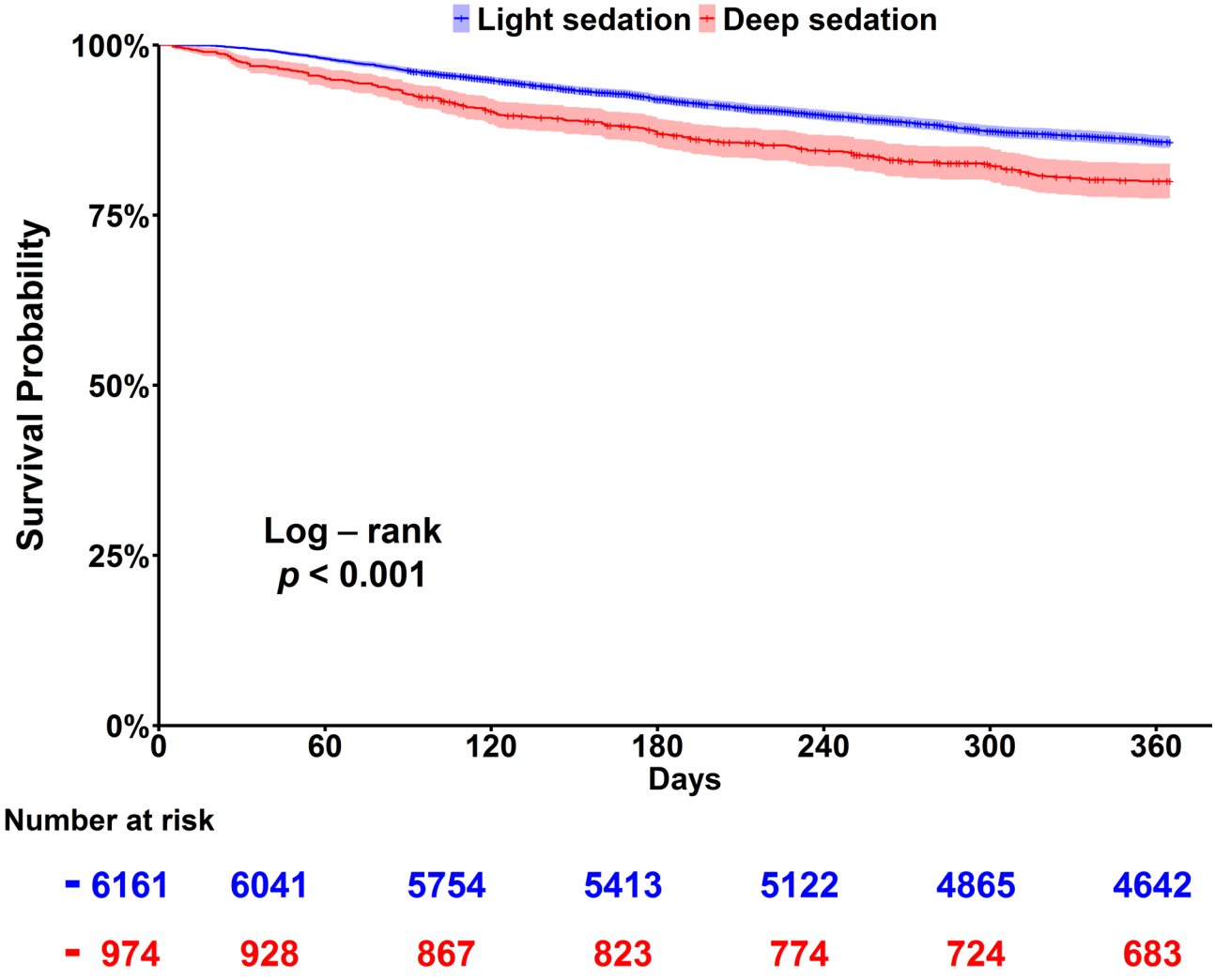

Fig. 2 Kaplan-Meier survival curves for patients with and without early deep sedation

(Supplemental Table 1). Recently, one phase-3 study (Sevoflurane for Sedation in Acute Respiratory Distress Syndrome (SESAR)) compared the effect of inhaled sevoflurane and propofol in patients with moderate to severe acute respiratory distress syndrome (PaO2/FiO2 < 150) and found similar 28-day mortality (44.1% vs. 38.8%) but higher 90-day mortality (52.9% vs. 44.3%) in patients receiving sevoflurane than those receiving propofol [21]. However, delineating the short- and long-term impact of ICU-relevant variables is somehow difficult, and excluding in-hospital mortality, as we have shown in the present study, may enable us to address the long-term impact of ICU-associated factors through focusing on post-hospital mortality. Using an approach similar to ours, aiming to explore post-hospital mortality, Manu Shankar-Hari et al.., analyzing 43 studies, reported post-acute mortality in patients with sepsis, reported that the one-year post-acute mortality was 16.1% (95% CI 14.1–18.1%) [12]. Currently, the majority of studies regarding long-term outcomes in critically ill patients were conducted in medical or mixed ICUs, whereas studies focusing on long-term outcomes in patients admitted to surgical ICUs are sparse. Therefore, there appears to be a knowledge gap in critical care with respect to ICU-associated risks for post-hospital mortality in critically ill surgical patients [22]. In the present study, we excluded in-hospital mortality in critically ill patients and focused on addressing factors associated with one-year post-hospital mortality (14.4%, 1,031/7,135). We found that more comorbidities, higher severity and early deep sedation, which might be a modifiable factor in critical care, were independently associated with increased post-hospital mortality in critically ill surgical patients. In univariate analysis, shock, high serum creatinine, and scheduled surgery were significantly associated with the outcome; however, in multivariate analysis, these variables were no longer statistically significant, although their directions of association remained consistent. The attenuation in

Table 2 Cox proportional hazards regression for post-hospital mortality in critically ill surgical patients

Characteristics	Univariable		Multivariable	
	HR (95% C.I.)	*p* value	HR (95% C.I.)	*p* value
Basic characteristics				
Age, per 1 year increment	1.033 (1.028–1.037)	< 0.001	1.018 (1.013–1.022)	< 0.001
Male	1.423 (1.246–1.625)	< 0.001	1.235 (1.074–1.420)	0.003
Body mass index, pre 1 increment	0.907 (0.893–0.922)	< 0.001	0.926 (0.911–0.941)	< 0.001
CCI, per 1 increment	1.351 (1.304-1.400)	< 0.001	1.231 (1.186–1.279)	< 0.001
Disease severity				
APACHE II score, per 1 increment	1.052 (1.042–1.061)	< 0.001	1.020 (1.010–1.030)	< 0.001
Presence of shock	1.386 (1.220–1.574)	< 0.001	0.987 (0.857–1.137)	0.855
Scheduled surgery	0.786 (0.696–0.889)	< 0.001	0.883 (0.773–1.008)	0.066
Types of surgery				
Cardiovascular surgery	Reference		Reference	
Neurosurgery	1.438 (1.111–3.272)	0.001	1.457 (1.136–1.867)	0.003
Major abdominal surgery	4.552 (1.118–12.848)	< 0.001	2.716 (2.112–3.494)	< 0.001
Laboratory data				
White blood cell count (x 10^3 count/μL)	0.986 (0.964–1.008)	0.204	1.012 (0.990–1.035)	0.288
Haemoglobin (g/dL)	0.796 (0.749–0.846)	< 0.001	0.917 (0.860–0.977)	0.007
Platelet (10^3/μL)	0.999 (0.998–1.001)	0.221	0.999 (0.998-1.000)	0.108
Albumin (g/dL)	0.462 (0.395–0.540)	< 0.001	0.661 (0.565–0.774)	< 0.001
Creatinine (mg/dL)	1.785 (1.483–2.149)	< 0.001	1.183 (0.964–1.452)	0.107
Sedative agent				
Dexmedetomidine	Reference		Reference	
Midazolam	3.006 (0.127–8.703)	< 0.001	1.368 (1.052–1.780)	0.019
Propofol	2.084 (0.120–6.104) 1.368 (0.118–2.662)	< 0.001 0.008	1.459 (1.136–1.874)	0.003
Early deep sedation	1.482 (1.266–1.736)	< 0.001	1.216 (1.019–1.452)	0.030

HR: hazard ratio; C.I.: confidence interval; CCI, Charlson comorbidity index; APACHE: acute physiology and chronic health evaluation

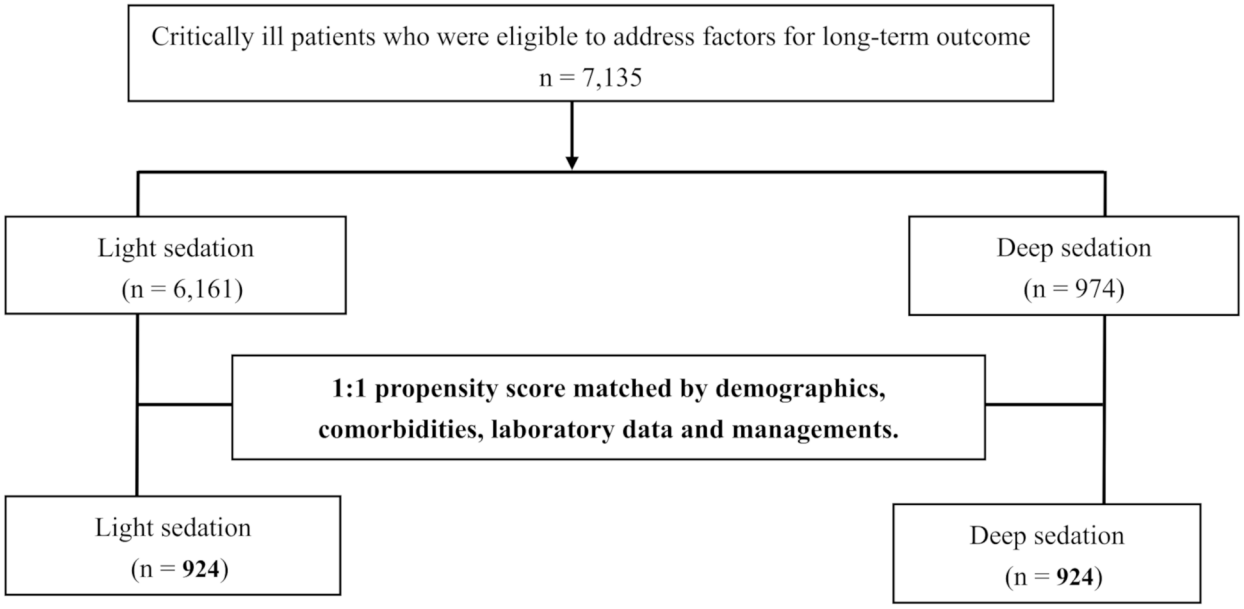

Fig. 3 Flowchart of subject enrollment in the propensity score-matched patients

Table 3 Characteristics between the patients categorized by sedation in the primary cohort and propensity score-matched cohort

	Before PSM			1:1 PSM		
	Light sedation	Deep sedation	SMD	Light sedation	Deep sedation	SMD
	(*n* = 6,161)	(*n* = 974)		(*n* = 924)	(*n* = 924)	
Basic characteristics						
Age	60.4 ± 15.8	60.4 ± 16.8	0.001	59.6 ± 16.6	60.4 ± 16.7	0.049
Sex (male)	3848 (62.5%)	591 (60.7%)	0.037	566 (61.3%)	566 (61.3%)	< 0.001
Body mass index	24.2 ± 4.5	24.2 ± 4.6	0.019	24.3 ± 4.7	24.1 ± 4.5	0.037
CCI	1.6 ± 1.4	1.6 ± 1.4	0.061	1.5 ± 1.4	1.6 ± 1.4	0.091
Disease severity						
APACHE II score ≥ 23	1,872 (30.4%)	579 (59.4%)	0.611	542 (58.7%)	542 (58.7%)	< 0.001
Surgical divisions						
Cardiovascular surgery	1,424 (23.1%)	40 (4.1%)	0.657	36 (3.9%)	36 (3.9%)	< 0.001
Neurosurgery	2,943 (47.8%)	714 (73.3%)		675 (73.1%)	675 (73.1%)	
Major abdominal surgery	732 (11.9%)	87 (8.9%)		82 (8.9%)	82 (8.9%)	
Laboratory data						
Hemoglobin (g/dL)	11.8 ± 1.2	11.7 ± 1.0	0.113	11.7 ± 1.0	11.7 ± 1.0	0.001
Albumin (g/dL)	3.0 ± 0.4	3.0 ± 0.4	0.045	3.0 ± 0.4	3.0 ± 0.4	0.025
Sedative agent						
Opioid-alone	644 (10.5%)	226 (23.2%)	1.075	191 (20.7%)	191 (20.7%)	< 0.001
Dexmedetomidine	1023 (16.6%)	12 (1.2%)		12 (1.3%)	12 (1.3%)	
Midazolam	1299 (21.1%)	525 (53.9%)		510 (55.2%)	510 (55.2%)	
Propofol	3195 (51.9%)	211 (21.7%)		211 (22.8%)	211 (22.8%)	

Abbreviations: CCI, Charlson comorbidity index; APACHE: acute physiology and chronic health evaluation

Table 4 Estimation of the association between early deep sedation and one-year post-hospital mortality in 1,848 propensity score-matched critically ill surgical patients

	Adjusted HR (95% CI)	*p* value
Model 1	1.346 (1.081–1.676)	0.008
Model 2	1.323 (1.062–1.647)	0.013
Model 3	1.313 (1.054–1.636)	0.015

Model 1. Unadjusted

Model 2. Adjusted for demographic data, comorbidities, BMI, disease severity and surgical divisions

Model 3. Adjusted for variables in model 2 and Laboratory data and Sedative agent

Abbreviations: HR, hazard ratio; CI, confidence interval

multivariable analysis suggests the effects were explained by the other covariates, such as APACHE II and CCI, which already incorporate mean arterial pressure and creatinine. However, despite of that early deep sedation is modifiable, the association with higher severities of critical illness necessitates cautious interpretation, as residual confounding by disease severity cannot be fully excluded. To further clarify the confounding effects of the disease severity of critical illness and comorbidities, we used a propensity score matching approach to show the robust association between early deep sedation and post-hospital mortality. These findings provide clinical evidence for the risk stratification of post-hospital mortality and risk reduction through measures focusing on modifiable factors in the near future among critically ill surgical patients.

Balzer et al. retrospectively enrolled 1,884 patients admitted to one mixed ICU between 2007 and 2012 in Germany and found that 27.2% (513/1,884) of them experienced early deep sedation, which correlated with two-year mortality [3]. Given that our study was conducted in the surgical ICU during 2015–2020 and the evolving concept with regard to light sedation in the past decade, the overall proportion of patients who experienced deep sedation was relatively low (13.8%, 863/6,243). Similarly, in a study by Shehabi Y et al., which enrolled 703 patients among 42 mixed ICUs in Australia and New Zealand (*n* = 251), Malaysia (*n* = 259), and Singapore (*n* = 193), it was found that high sedation intensity in the first 48 h following mechanical ventilation was associated with an increased risk of death on day 180 (HR, 1.29; 95% CI 1.15–1.46) [23].

In the present study, we not only focused on critically ill surgical patients but also clarified the prolonged impact on post-hospital mortality of early deep sedation. Notably, early deep sedation appeared to be a crucial issue during the COVID-19 pandemic. Stephens RJ et al., enrolling 391 critically ill ventilated patients at Barnes-Jewish Hospital and the University of Iowa Hospital during the COVID-19 pandemic, reported a high proportion (72.4%, 283/391) of patients experienced early deep sedation, which was highly associated with increased in-hospital mortality (aOR 3.44; 95% CI 1.65–7.17) [4]. Stephens RJ et al.. further conducted subgroup analyses and found that patients with COVID-19 infection (*n* = 203) experienced deep sedation more frequently

early and throughout the first week of ICU admission [4]. Given that the study period of this Taiwanese study was 2015–2020, with few patients with COVID-19 infection in Taiwan during the study period [23, 24], we think COVID-19 should not confound the findings of the present study.

Intriguingly, we found that in patients who received midazolam.m or propofol, there tended to be an association with higher post-hospital mortality compared with those receiving dexmedetomidine. One recent meta-analysis, analyzing 252 randomized trials comprising 30,757 patients, reported that propofol may be associated with reduced survival in perioperative and critically ill patients [24]. Compared with midazolam/propofol, dexmedetomidine has analgesic actions, which is an essential issue in critically ill surgical patients [25]. Previous studies have found that dexmedetomidine improved patients' ability to communicate pain compared with midazolam and propofol in patients requiring mechanical ventilation [26, 27]. Lewis K et al. recently conducted a meta-analysis of 77 randomized trials and reported that using dexmedetomidine compared with other sedatives resulted in a lower risk of delirium, ventilator day, and ICU length of stay [28]. The Sedation Practice in Intensive Care Evaluation (SPICE) III trial has demonstrated that early dexmedetomidine use in critically ill patients was associated with reduced 90-day mortality in those aged > 65 years and surgical subgroups, though the long-term survival impact remained undetermined [29, 30]. This study evaluates post-hospitalization one-year mortality in a surgical cohort (mean age 60.5 ± 12.1 years), providing evidence on the long-term impact of dexmedetomidine. Given the nature of the retrospective study, we think it would be imprudent to conclude the association between the use of dexmedetomidine and post-hospital mortality, and more studies are required to validate this finding.

The long-term effects of early deep sedation may result from a number of sedation-associated deleterious effects, including delirium, prolonged use of mechanical ventilation, delayed mobilization, and prolonged impairment of cognitive function [15, 16, 31, 32]. Intriguingly, deep sedation might also be implicated in ICU-acquired weakness, which may lead to impaired long-term outcomes [33]. However, the association between sedation and weakness may be indirect and may exert deleterious impacts through sedation-induced immobility or concomitant use of neuromuscular blocking agents [34, 35]. Notably, unlike unmodifiable risk factors such as age, comorbidities, and severity of critical illness, early deep sedation should be considered a modifiable factor, given that various strategies have been proposed to improve sedation practices in critically ill ventilated patients [36, 37]. Future studies are warranted to explore the impact of intervention with avoidance of early deep sedation on long-term outcomes in critically ill surgical patients.

In this study, we used not only the Cox regression model but also PSM to address the association between early deep sedation and long-term mortality. We noted that the use of the neuromuscular blocking agent (NMBA) was highly associated with the depth of sedation and, therefore, led to a collinearity with high VIF (Supplemental Table 2). Therefore, we did not include the NMBA as the adjusted covariate. However, the application of PSM mitigates the confounding effect but removes subjects in the matching process. Therefore, we transformed the APACHE II score from a continuous variable to a categorical variable in PSM to include the majority (95.0%, 924/974) of subjects with deep sedation.

Delirium is an essential issue among critically ill patients and has been found to be associated with sedation [31]. However, to accurately identify patients with delirium, particularly in the retrospective study, is somehow difficult, and a number of studies have found that delirium is often under-recognized given that the majority of delirium appears to be the hypoactive form, which might not be recorded [38, 39]. Notably, sedation depth and choice of agents play a critical role in delirium pathogenesis; for example, benzodiazepine use has been independently associated with higher delirium risk compared to dexmedetomidine [31, 40]. Moreover, studies have demonstrated that lighter sedation strategies reduce the incidence of delirium and improve patient-centered outcomes in critically ill populations [41]. Intriguingly, Long et al., analyzing 18 studies with 8001 mechanically ventilated patients, reported that sedation depth was not associated with the occurrence of delirium [42]. Therefore, future prospective research incorporating validated delirium assessments is warranted to clarify the mediating role of delirium in the relationship between sedation and long-term outcomes in surgical ICU patients.

Limitations

There are limitations in this study. First, the retrospective design limits the causal inference; therefore, we claimed an association, instead of a causal effect, between early deep sedation and post-hospital mortality. Second, the single-hospital study, despite the number of enrolled subjects was high. Third, the decision on sedation agents and targeted depth were made by individual physicians, but the administration of intensivists in Taiwan could at least partly mitigate this concern. Fourth, this study cannot assess the potential existence of unmeasured confounding factors, including delirium and the cause of death.

Conclusions

Sedation is one of the crucial managements in critical care, but the long-term impact of early deep sedation in critically ill surgical patients remains a research niche. In the present study, we identified a number of risk factors for post-hospital mortality, and these data may be helpful for risk stratification of post-hospital mortality in patients discharged from surgical ICUs. We also found that early deep sedation, which is a modifiable factor, was independently associated with increased one-year post-hospital mortality in critically ill surgical patients. Our data highlights the critical role of light sedation in critically ill surgical patients. Further prospective studies are warranted to validate our findings and to elucidate the underlying mechanisms.

Supplementary Information

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Supplementary Material 1

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Author contributions
Study concept and design: PYW, SYL, and WCC. Acquisition of data: LTW and WCC. Analysis and interpretation of data: PYW, SYL, and WCC. Drafting the manuscript: PYW, SYL and WCC. All authors agree and are responsible for the content of the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study was performed in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of the Taichung Veterans General Hospital TCVGH: SE20249B#1). All the data were anonymised data, and informed consent was waived by the Institutional Review Board of Taichung Veterans General Hospital.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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