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ORIGINAL RESEARCH

Sugammadex vs Neostigmine for Reversal of Neuromuscular Blockade and Association with Postoperative Atelectasis After Video-Assisted Thoracoscopic Surgery: A Propensity Score-Matched Cohort Study

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Purpose: Postoperative atelectasis remains a significant concern after video-assisted thoracoscopic surgery (VATS). This study aimed to evaluate the association between sugammadex use and postoperative atelectasis in patients who underwent VATS.

Patients and methods: From the TriNetX Global Collaborative Network (2016–2024), adults undergoing elective VATS who received rocuronium reversed with either sugammadex or neostigmine were identified. The primary outcome was atelectasis within 30 days, identified using the administrative ICD diagnostic codes recorded in the TriNetX database. The secondary outcomes included pneumonia, acute respiratory failure, pneumothorax, sepsis, and major adverse cardiovascular events (MACEs). Outcomes were additionally assessed at 7-day and 90-day intervals.

Results: After propensity score matching (1:1), 7345 patients were analyzed per group. Sugammadex exposure was associated with lower odds of atelectasis at 30 days (odds ratio [OR], 0.79; 95% confidence interval [CI], 0.72–0.86; $P < 0.001$), corresponding to an absolute risk reduction of 3.3% (15.3% vs 18.6%). The association remained consistent at 7-day (OR, 0.75) and 90-day (OR, 0.81) follow-ups. Time-to-event analysis demonstrated a lower hazard of atelectasis (hazard ratio, 0.82; 95% CI, 0.76–0.88). Sugammadex was also associated with reduced pneumothorax (OR, 0.90) and MACEs (OR, 0.75), but not with pneumonia, respiratory failure, or sepsis. Subgroup analyses revealed significant interactions between sex ($P = 0.003$) and obesity status ($P = 0.047$), with more pronounced associations in males and non-obese patients.

Conclusion: Sugammadex use was associated with a reduced postoperative atelectasis risk in patients undergoing VATS. Prospective randomized trials are warranted to confirm these findings and establish causality.

Keywords: sugammadex, neostigmine, atelectasis, video-assisted thoracoscopic surgery, neuromuscular blockade, postoperative pulmonary complications

Introduction

Video-assisted thoracoscopic surgery (VATS) has become the preferred approach for pulmonary and pleural procedures owing to its minimally invasive nature and favorable recovery profile.[1–3] VATS requires one-lung ventilation, which reduces functional residual capacity and alters ventilation–perfusion matching, predisposing patients to atelectasis. Consequently, postoperative pulmonary complications remain a major concern after thoracic surgery, with atelectasis being one of the most common and earliest events.[4,5] Reported rates of postoperative atelectasis in thoracic surgery generally range from

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approximately 5% to 20%, depending on the patient population and diagnostic criteria used.[6–8] Importantly, atelectasis is not merely a transient finding but often serves as a precursor to more severe complications; retained secretions in collapsed lung segments promote bacterial proliferation and substantially increase the risk of subsequent pneumonia, which may ultimately progress to respiratory failure if inadequately managed.[4,9,10] However, pneumonia is a multifactorial complication influenced by host immunity, microbial exposure, perioperative ventilatory management, and postoperative care. Therefore, a reduction in atelectasis does not necessarily translate into a measurable reduction in pneumonia. Nevertheless, interventions that effectively reduce early postoperative atelectasis may still confer clinically meaningful benefits by improving early respiratory mechanics and mitigating downstream pulmonary risks.

The administration of neuromuscular blocking agents during general anesthesia is essential for optimizing surgical conditions during VATS procedures. Nevertheless, incomplete reversal of neuromuscular blockade at the conclusion of surgery can lead to postoperative residual curarization, which compromises respiratory muscle function and increases susceptibility to pulmonary complications.[11–13] Sugammadex, a modified gamma-cyclodextrin that selectively encapsulates steroidal neuromuscular blocking agents, enables rapid and complete reversal of rocuronium-induced blockade and has been associated with reduced postoperative pulmonary complications.[14–18] In contrast to traditional acetylcholinesterase inhibitors, such as neostigmine, sugammadex achieves neuromuscular recovery without the muscarinic side effects associated with anticholinergic co-administration. Although several meta-analyses have examined the relationship between sugammadex exposure and postoperative pulmonary complications, evidence specifically regarding atelectasis remains inconclusive.[19–22] However, existing studies included in these meta-analyses[19–22] have been limited by small sample sizes, typically enrolling fewer than 100 patients, which restricts the statistical power for detecting clinically meaningful differences. Furthermore, the heterogeneity of surgical populations across prior studies has precluded definitive conclusions regarding the efficacy of sugammadex in reducing atelectasis risk, specifically among patients undergoing VATS procedures.

We hypothesized that sugammadex exposure for neuromuscular blockade reversal would be associated with a lower incidence of postoperative atelectasis than neostigmine exposure in patients undergoing VATS. To test this hypothesis, we conducted a large-scale retrospective matched cohort study to assess the association between reversal agent selection and the risk of pulmonary atelectasis.

Methods

Study Design and Data Source

This study employed a retrospective matched cohort design, drawing upon electronic health records from the TriNetX Global Collaborative Network. This federated research platform integrates de-identified patient data from 169 healthcare institutions, spanning academic medical centers and community-based facilities worldwide. The database captures comprehensive clinical information, including patient demographics, diagnostic codes, procedural records, pharmaceutical exposure, and laboratory measurements. Because TriNetX operates through a federated architecture, individual patient records remain at their source institutions, while aggregate analyses can be performed across the network, thereby maintaining patient confidentiality. Ethical approval was obtained from the Institutional Review Board of Chi Mei Medical Center (approval no. 11403-E03), which waived the requirement for informed consent given the retrospective and de-identified nature of the data. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Study Population

We identified adults aged ≥ 18 years who underwent elective video-assisted thoracoscopic procedures involving pulmonary or pleural structures. The analysis encompassed records from January 2016 to December 2024, with the study period commencing after the United States Food and Drug Administration granted approval for sugammadex in late 2015. Given that the TriNetX database predominantly comprises healthcare organizations within the United States, our study population primarily reflects American clinical practice patterns. The date of surgical intervention was defined as each patient's index date for cohort entry.

The patients were stratified according to their neuromuscular blockade reversal approach. The exposure cohort comprised individuals who received rocuronium with subsequent reversal using sugammadex, whereas the control cohort included individuals who received rocuronium reversed with neostigmine and had no documented sugammadex exposure. To prevent misclassification between the groups, we excluded any patients who received both reversal agents.

Exclusion Criteria

We applied several exclusion criteria to establish a clinically homogeneous study population suitable for comparative analysis. Patients presenting with acute kidney injury, sepsis, acute respiratory failure, COVID-19 infection, or those requiring critical care interventions during the 30 days preceding their surgical procedures were excluded. Individuals with advanced renal impairment (chronic kidney disease stages 4 and 5) or end-stage renal disease were also excluded, as altered drug pharmacokinetics in this population could confound the exposure-outcome relationship. To minimize outcome misclassification, we excluded patients with documented pulmonary collapse, pneumothorax, or pneumonia before index surgery. Patients with neuromuscular junction disorders or primary myopathies were excluded because such conditions alter the pharmacodynamic response to neuromuscular blocking agents. Finally, we restricted our analysis to elective procedures by excluding emergency surgical cases, thereby ensuring uniform perioperative management protocols across the study population.

Propensity Score Matching

We estimated propensity scores through multivariable logistic regression, incorporating baseline covariates documented within the three-year period preceding each patient's index date. The matching algorithm incorporated demographic variables (age, sex, and race), relevant comorbid conditions, and the most recent laboratory values available before surgery. We implemented a 1:1 greedy nearest-neighbor matching algorithm without replacement, applying a caliper width equivalent to 0.1 standard deviations of the logit-transformed propensity score. Adequate covariate balance was confirmed when the standardized mean differences fell below the conventional threshold of 0.1. Additionally, we verified sufficient overlap between cohorts through visual examination of the propensity score density distributions. Supplemental Table 1 provides a complete list of the variables and outcome definitions.

Outcome Assessment

The primary endpoint was the occurrence of atelectasis within 30 days of the index surgical date. Secondary endpoints included pneumonia, acute respiratory failure, sepsis, pneumothorax, and major adverse cardiovascular events (MACEs) (defined as the composite of cardiac arrest, myocardial infarction, and stroke). To evaluate the temporal consistency of our findings, we additionally assessed all outcomes at the 7-day and 90-day follow-up intervals. Atelectasis was identified using ICD diagnostic codes recorded within 30 days of surgery. The TriNetX platform does not provide access to individual imaging reports; therefore, radiographic confirmation (eg, chest radiography or computed tomography) cannot be independently verified. In routine clinical practice, such codes are typically assigned following imaging evaluation and clinical documentation and thus likely represent clinically recognized cases. We selected atelectasis as the primary outcome because it is an early and mechanistically plausible manifestation of residual neuromuscular weakness after thoracic surgery that may precede downstream pulmonary complications.

Sensitivity Analyses

Three sensitivity analyses were conducted to evaluate the stability of the primary findings under alternative analytical conditions. Model I restricted the analysis to patients whose procedures were performed at academic medical centers, thereby evaluating whether institutional setting influenced outcomes. Model II excluded patients who received intraoperative blood transfusions because transfusion requirements may indicate more complex surgical procedures or greater intraoperative blood loss that could independently affect pulmonary outcomes. Model III excluded patients admitted directly to the intensive care unit following surgery, removing a subset of patients whose clinical trajectory may differ substantially from those following routine postoperative care pathways.

Subgroup Analyses

Pre-specified subgroup analyses were used to examine whether the association between sugammadex exposure and outcomes differed across the clinically relevant patient subpopulations. We stratified the patients by sex, age category (18–65 years versus > 65 years), presence of lung malignancy, nicotine dependence, chronic obstructive pulmonary disease, obstructive sleep apnea, and obesity. These stratification variables were selected based on their established or potential influence on pulmonary function and postoperative respiratory complications.[6]

Statistical Analysis

Continuous variables were expressed as means with standard deviations, while categorical variables were reported as frequencies with corresponding percentages. We applied an available-case approach within the TriNetX analytical platform. The TriNetX environment provides access to aggregated analyses but does not permit extraction of individual-level raw data or implementation of custom multiple imputation procedures. Therefore, missing values were handled according to the platform's default complete-case strategy for each variable included in the propensity score model. Odds ratios (OR) with 95% confidence intervals (CI) were calculated to quantify the association between sugammadex exposure and each outcome. For the primary endpoint, we further characterized the temporal pattern of atelectasis occurrence by constructing cumulative incidence curves over the 90-day follow-up period. Statistical significance was established at a two-sided alpha level of 0.05 for all outcomes. To quantify the potential influence of unmeasured confounding on our primary findings, we calculated E-values, which represent the minimum strength of association that an unmeasured confounder would need to have with both exposure and outcome to fully explain the observed association. All statistical procedures were performed using an integrated analytical platform within the TriNetX environment.

Results

Patient Selection and Baseline Characteristics

Figure 1 illustrates the patient selection process. After applying the exclusion criteria, 27,305 patients received sugammadex for neuromuscular blockade reversal, while 7349 patients received neostigmine. Propensity score matching yielded 7345 patients per cohort for the primary analysis. Before matching, the sugammadex group was older and demonstrated a higher prevalence of several comorbidities, including neoplasms, hypertension, and COVID-19 infection. After propensity score matching, all baseline characteristics achieved adequate balance, with standardized mean differences below 0.1 for all covariates (Table 1). The propensity score density plots confirmed a substantial distributional overlap between cohorts following the matching procedure (Figure 2). The proportion of patients with available preoperative laboratory and physiological data is summarized in Supplemental Table S2.

Association Between Sugammadex Exposure and 30-Day Outcomes

Sugammadex exposure was associated with a lower likelihood of atelectasis at the 30-day follow-up than neostigmine exposure (OR, 0.79; 95% CI, 0.72–0.86; $P < 0.001$) (Table 2). An E-value of 1.50 suggests that a confounder with modest associations with both exposure and outcome could plausibly explain the observed association. Among secondary outcomes, sugammadex exposure was also associated with lower odds of pneumothorax (OR, 0.90; 95% CI, 0.84–0.97; $P = 0.008$) and MACEs (OR, 0.75; 95% CI, 0.57–0.99; $P = 0.040$). No statistically significant differences were observed between the groups for pneumonia, acute respiratory failure, or sepsis at the 30-day assessment.

Association Between Sugammadex Exposure and 7-Day and 90-Day Outcomes

The association between sugammadex exposure and atelectasis remained consistent across the alternative follow-up intervals (Table 3). At the 7-day follow-up, the OR for atelectasis was 0.75 (95% CI, 0.67–0.82; $P < 0.001$). At the 90-day follow-up, sugammadex exposure continued to demonstrate an association with lower atelectasis risk (OR, 0.81; 95% CI, 0.74–0.88; $P < 0.001$). Time-to-event analysis using Cox proportional hazards regression yielded consistent findings, with sugammadex exposure associated with a lower hazard of atelectasis over the 90-day follow-up period (hazard ratio,

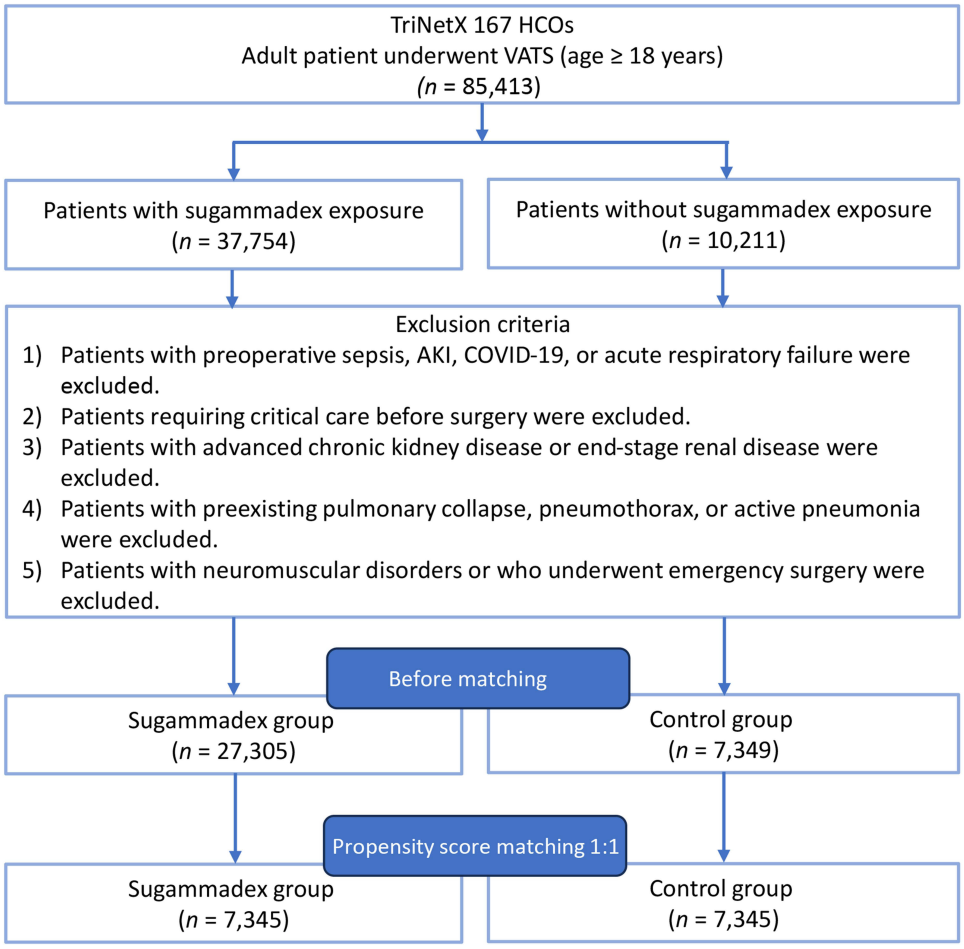

Figure 1 Patient selection flowchart. Patients undergoing video-assisted thoracoscopic surgery (VATS) were identified from the TriNetX Global Collaborative Network and stratified according to the neuromuscular blockade reversal strategy. After applying the exclusion criteria and propensity score matching, 7345 patients remained in each cohort.
Abbreviations: VATS, video-assisted thoracoscopic surgery; AKI, acute kidney injury; HCOs: Healthcare Organizations.

0.82; 95% CI, 0.76–0.88; log-rank P < 0.001) (Figure 3). The association between pneumothorax and MACEs persisted at the 90-day follow-up, while no significant between-group differences emerged for pneumonia, acute respiratory failure, or sepsis at either time point.

Table 1 Baseline Characteristics of Patients Before and After Propensity Score Matching

Variables	Before Matching			After Matching		
	Sugammadex Group (n = 27,305)	Control Group (n = 7349)	SMD†	Sugammadex Group (n = 7345)	Control Group (n = 7345)	SMD†
Patient characteristics						
Age at index (years)	62.7±14.6	59.9±16.8	0.179	59.8±16.3	59.9±16.8	0.010
Female	14401 (52.7)	3840 (52.3)	0.010	3874 (52.7)	3837 (52.2)	0.010
BMI≥30 kg/m^2	8514 (31.2)	2502 (34.0)	0.061	2457 (33.5)	2498 (34.0)	0.012
White	21699 (79.5)	5935 (80.8)	0.032	5982 (81.4)	5932 (80.8)	0.017
Black or African American	2684 (9.8)	796 (10.8)	0.033	753 (10.3)	795 (10.8)	0.019
Other Race	803 (2.9)	236 (3.2)	0.016	236 (3.2)	236 (3.2)	0.000
Asian	1008 (3.7)	200 (2.7)	0.055	191 (2.6)	200 (2.7)	0.008

(*Continued*)

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Table 1 (Continued).

Variables	Before Matching			After Matching		
	Sugammadex Group (n = 27,305)	Control Group (n = 7349)	SMD†	Sugammadex Group (n = 7345)	Control Group (n = 7345)	SMD†
Comorbidities						
Neoplasms	22000 (80.6)	5515 (75.0)	0.133	5494 (74.8)	5513 (75.1)	0.006
Essential (primary) hypertension	15656 (57.3)	3831 (52.1)	0.105	3735 (50.9)	3829 (52.1)	0.026
Malignant neoplasm of bronchus and lung	14543 (53.3)	3551 (48.3)	0.099	3534 (48.1)	3549 (48.3)	0.004
Nicotine dependence	7357 (26.9)	1902 (25.9)	0.024	1843 (25.1)	1900 (25.9)	0.018
COPD	6653 (24.4)	1831 (24.9)	0.013	1729 (23.5)	1829 (24.9)	0.032
Ischemic heart diseases	7143 (26.2)	1612 (21.9)	0.099	1593 (21.7)	1611 (21.9)	0.006
Diabetes mellitus	5585 (20.5)	1366 (18.6)	0.047	1312 (17.9)	1363 (18.6)	0.018
Obstructive sleep apnea	4500 (16.5)	983 (13.4)	0.087	925 (12.6)	983 (13.4)	0.023
Other anemias	3799 (13.9)	874 (11.9)	0.060	828 (11.3)	874 (11.9)	0.020
Diseases of liver	3264 (12.0)	793 (10.8)	0.037	763 (10.4)	793 (10.8)	0.013
Chronic kidney disease	2957 (10.8)	598 (8.1)	0.092	605 (8.2)	598 (8.1)	0.003
Cerebrovascular diseases	2373 (8.7)	586 (8.0)	0.026	573 (7.8)	585 (8.0)	0.006
Heart failure	1955 (7.2)	449 (6.1)	0.042	442 (6.0)	449 (6.1)	0.004
Alcohol related disorders	1441 (5.3)	358 (4.9)	0.018	344 (4.7)	358 (4.9)	0.009
COVID-19	1318 (4.8)	131 (1.8)	0.171	131 (1.8)	131 (1.8)	0.000
Unspecified dementia	205 (0.8)	35 (0.5)	0.035	39 (0.5)	35 (0.5)	0.008
Laboratory data						
Albumin g/dL (<3.5 g/dL)	4945 (18.1)	1233 (16.8)	0.035	1210 (16.5)	1233 (16.8)	0.008
Hemoglobin <12 g/dL	9337 (34.2)	2497 (34.0)	0.005	2402 (32.7)	2495 (34.0)	0.027
eGFR <60 mL/min/1.73m^2	7504 (27.5)	1820 (24.8)	0.062	1772 (24.1)	1820 (24.8)	0.015
Hemoglobin A1c ≥9%	487 (1.8)	143 (1.9)	0.012	148 (2.0)	140 (1.9)	0.008
C-reactive protein ≥10 mg/L	1295 (4.7)	361 (4.9)	0.008	356 (4.8)	360 (4.9)	0.003
FEV1/FVC<70%	928 (3.4)	294 (4.0)	0.032	288 (3.9)	294 (4.0)	0.004
Medication						
Insulins and analogues	6765 (24.8)	1746 (23.8)	0.024	1649 (22.5)	1743 (23.7)	0.030
ACE inhibitors	4460 (16.3)	1053 (14.3)	0.056	984 (13.4)	1052 (14.3)	0.027
Angiotensin II inhibitor	4246 (15.6)	766 (10.4)	0.153	734 (10.0)	766 (10.4)	0.014
SGLT2 inhibitors	622 (2.3)	66 (0.9)	0.111	88 (1.2)	66 (0.9)	0.029
GLP-1 analogues	645 (2.4)	65 (0.9)	0.117	68 (0.9)	65 (0.9)	0.004

Notes: †SMD values <0.1 indicate adequate balance between groups after matching.

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; GLP-1, glucagon-like peptide-1; SGLT2, sodium-glucose cotransporter-2; SMD, standardized mean difference.

Sensitivity Analyses

Sensitivity analyses confirmed the robustness of the primary findings across various analytical scenarios (Table 4). When restricted to procedures performed at academic medical centers (Model I), sugammadex exposure remained associated with lower odds of atelectasis (OR, 0.71, p<0.001). Similar associations were observed after excluding patients who received intraoperative blood transfusions (Model II: OR, 0.75; p<0.001) and those admitted to the intensive care unit immediately after surgery (Model III: OR, 0.78; p<0.001). The association between sugammadex exposure and pneumothorax remained consistent across all sensitivity models, whereas the association with MACEs was attenuated and no longer statistically significant in Models II and III.

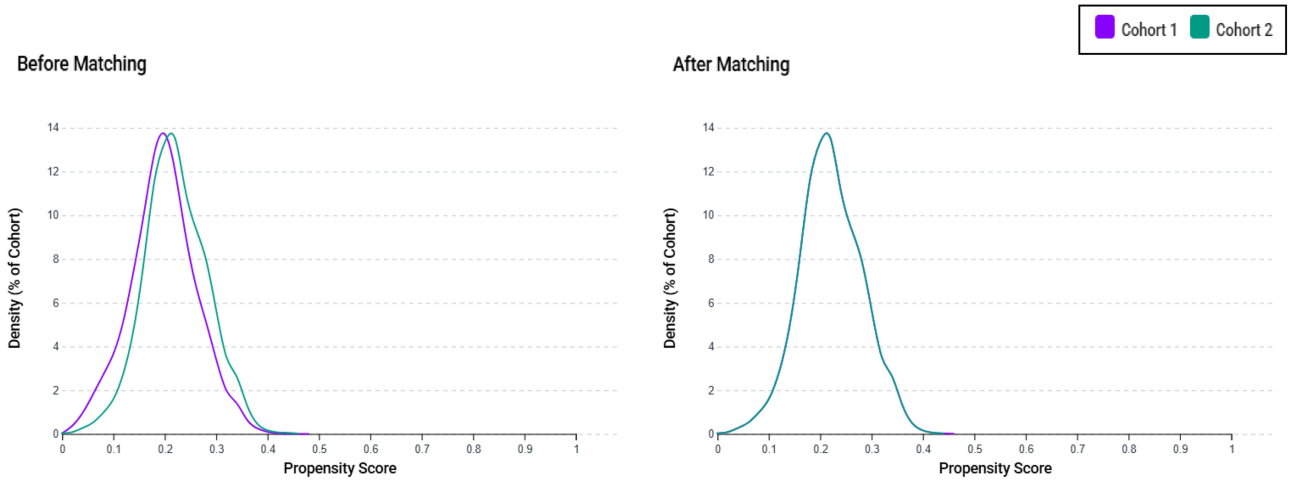

Figure 2 Propensity score distribution before and after matching. Density plots illustrate the distribution of propensity scores in the sugammadex (Cohort 1) and control (Cohort 2) groups before (left panel) and after matching (right panel). The substantial overlap observed after matching supports the validity of the propensity score matching procedure.

Subgroup Analyses

Subgroup analyses explored potential effect modifications across prespecified patient characteristics (Table 5). An association between sugammadex exposure and atelectasis was observed across most subgroups examined. A statistically significant interaction was detected for sex (P for interaction = 0.003), with a more pronounced association observed among male patients (OR, 0.67) than among female patients (OR, 0.87). A significant interaction was also identified for obesity status (P for

Table 2 Association Between Sugammadex Exposure and 30-Day Outcomes

Outcomes	Sugammadex Group‡ Events (%)	Control Group‡ Events (%)	OR (95% CI)	P-Value	Absolute Risk Difference†
Atelectasis	1123 (15.3%)	1368 (18.6%)	0.79 (0.72–0.86)	<0.001	−3.3%
Pneumonia	232 (3.2%)	229 (3.1%)	1.01 (0.84–1.22)	0.887	+0.1%
Acute respiratory failure	177 (2.4%)	164 (2.2%)	1.08 (0.87–1.34)	0.476	+0.25%
Pneumothorax	1745 (23.8%)	1883 (25.6%)	0.90 (0.84–0.97)	0.008	−1.8%
Sepsis	77 (1.0%)	80 (1.1%)	0.96 (0.70–1.32)	0.810	−0.1%
MACEs	87 (1.2%)	116 (1.6%)	0.75 (0.57–0.99)	0.040	−0.4%

Notes: ‡N = 7345 in each group. OR, odds ratio; CI, confidence interval; MACEs, major adverse cardiovascular events (composite of cardiac arrest, myocardial infarction, and stroke); †Absolute risk difference calculated as sugammadex group minus control group.

Table 3 Association Between Sugammadex Exposure and Outcomes at 7-Day and 90-Day Follow-Up

Outcomes	7-Day		90-Day	
	OR (95% CI)	P-Value	OR (95% CI)	P-Value
Atelectasis	0.75 (0.67–0.82)	<0.001	0.81 (0.74–0.88)	<0.001
Pneumonia	1.06 (0.79–1.41)	0.711	1.02 (0.87–1.19)	0.812
Acute respiratory failure	1.04 (0.79–1.36)	0.782	1.00 (0.83–1.21)	1.000
Pneumothorax	0.95 (0.87–1.03)	0.187	0.91 (0.85–0.98)	0.016
Sepsis	0.81 (0.48–1.37)	0.422	0.94 (0.74–1.20)	0.617
MACEs	0.91 (0.59–1.40)	0.662	0.74 (0.59–0.93)	0.008

Abbreviations: OR, odds ratio; CI, confidence interval; MACEs, major adverse cardiovascular events (composite of cardiac arrest, myocardial infarction, and stroke).

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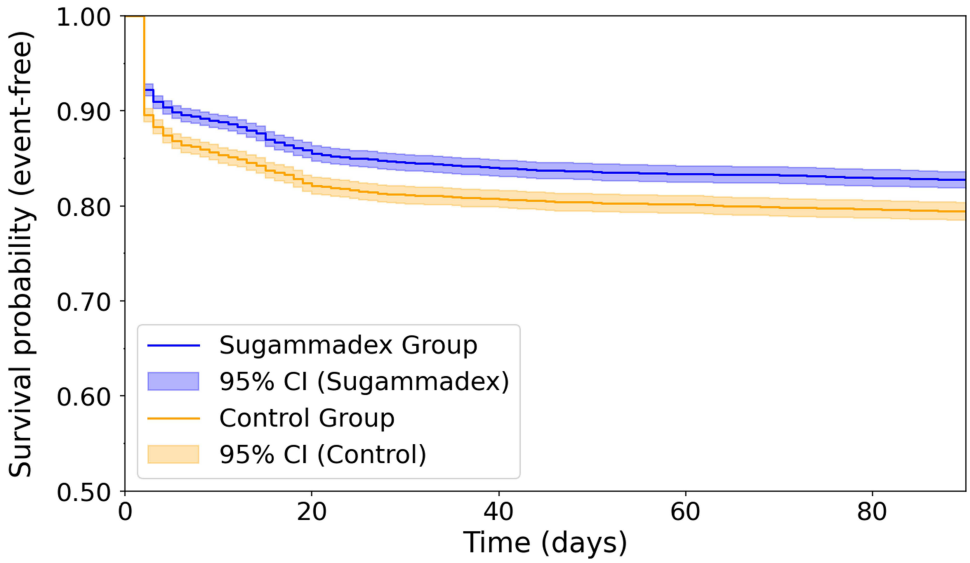

Figure 3 Kaplan-Meier curves for atelectasis-free survival over the 90-day follow-up period. The sugammadex group (blue) demonstrated a consistently higher atelectasis-free survival probability than the control group (Orange) throughout the observation period. The shaded areas represent 95% confidence intervals. The between-group difference was statistically significant (hazard ratio, 0.82; 95% confidence interval, 0.76–0.88; log-rank P < 0.001).

interaction = 0.047), whereby the association was evident among non-obese patients (OR, 0.75) but attenuated and not statistically significant among obese patients (OR, 0.96). No significant effect modification was observed according to age, lung cancer status, nicotine dependence, chronic obstructive pulmonary disease, or obstructive sleep apnea.

Table 4 Sensitivity Analyses for the Association Between Sugammadex Exposure and 30-Day Outcomes

Outcomes	Model I		Model II		Model III	
	OR (95% CI)	p-Value	OR (95% CI)	p-Value	OR (95% CI)	p-Value
Atelectasis	0.71 (0.65–0.79)	<0.001	0.75 (0.69–0.82)	<0.001	0.78 (0.71–0.85)	<0.001
Pneumonia	0.80 (0.63–1.00)	0.053	0.93 (0.77–1.13)	0.468	0.84 (0.69–1.03)	0.096
Acute respiratory failure	1.15 (0.86–1.53)	0.343	0.92 (0.73–1.15)	0.453	0.84 (0.65–1.08)	0.169
Pneumothorax	0.85 (0.78–0.93)	<0.001	0.91 (0.84–0.98)	0.013	0.90 (0.83–0.97)	0.005
Sepsis	0.69 (0.46–1.05)	0.080	0.79 (0.56–1.10)	0.153	0.91 (0.65–1.29)	0.597
MACEs	0.69 (0.49–0.96)	0.025	0.83 (0.63–1.09)	0.186	0.95 (0.72–1.26)	0.720

Notes: Model I restricted to patients undergoing surgery at academic medical centers (n = 5543 per group). Model II excluded patients who received intraoperative blood transfusion (n = 7297 per group). Model III excluded patients admitted to the intensive care unit immediately after surgery (n = 7036 per group).
Abbreviations: OR, odds ratio; CI, confidence interval; MACEs, major adverse cardiovascular events (composite of cardiac arrest, myocardial infarction, and stroke).

Table 5 Subgroup Analyses for the Association Between Sugammadex Exposure and 30-Day Atelectasis Risk

Variables	OR (95% CI)	P-Value	P for Interaction
Male	0.67 (0.59–0.75)	<0.001	Ref
Female	0.87 (0.77–0.98)	0.021	0.003
Age 18–65	0.73 (0.62–0.85)	<0.001	Ref
Age>65	0.77 (0.69–0.85)	<0.001	0.578
Lung cancer (Yes)	0.67 (0.58–0.76)	< 0.001	Ref
Lung cancer (No)	0.79 (0.71–0.89)	< 0.001	0.065

(*Continued*)

Table 5 (Continued).

Variables	OR (95% CI)	P-Value	P for Interaction
Nicotine (Yes)	0.72 (0.61–0.84)	< 0.001	Ref
Nicotine (No)	0.78 (0.70–0.86)	< 0.001	0.401
COPD (Yes)	0.81 (0.68–0.97)	0.023	Ref
COPD (No)	0.68 (0.61–0.75)	< 0.001	0.114
OSA (Yes)	0.78 (0.59–1.04)	0.087	Ref
OSA (No)	0.74 (0.68–0.81)	< 0.001	0.738
Obesity (Yes)	0.96 (0.79–1.18)	0.715	Ref
Obesity (No)	0.75 (0.68–0.82)	< 0.001	0.047

Notes: P for interaction assesses the heterogeneity of treatment association across subgroups.
Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; OR, odds ratio; OSA, obstructive sleep apnea.

Discussion

This propensity score-matched cohort study of 14,690 patients undergoing VATS demonstrated that sugammadex exposure for neuromuscular blockade reversal was associated with a 21% lower likelihood of postoperative atelectasis than neostigmine exposure at the 30-day follow-up. This association persisted across multiple time points, with risk reductions evident at both the 7-day and 90-day intervals. Sugammadex exposure was also associated with reduced odds of pneumothorax and MACEs; however, no significant differences were observed for pneumonia, acute respiratory failure, or sepsis. Sensitivity analyses across various clinical scenarios consistently supported these associations.

The relationship between sugammadex use and postoperative atelectasis has been examined in several meta-analyses, although the findings have remained inconsistent. Liu et al[19] conducted a systematic review with trial sequential analysis suggesting a potential benefit of sugammadex in reducing overall pulmonary complications; however, atelectasis-specific findings were limited by heterogeneous surgical populations and small individual trial sizes. Similarly, Wang et al[20] and Yang et al[21] reported trends toward fewer pulmonary complications with sugammadex; however, the inclusion of non-thoracic procedures in their pooled analyses may have attenuated the relevance of these findings to populations undergoing thoracic surgery. Differences between our findings and prior studies may reflect variation in surgical populations, outcome definitions, and perioperative management practices, particularly with respect to thoracic versus non-thoracic procedures. More recently, Liu et al[22] focused specifically on patients undergoing thoracic surgery and demonstrated that sugammadex was associated with reduced risks of atelectasis (relative risk = 0.61) and pneumonia (relative risk = 0.64), although no significant difference was observed for pneumothorax. However, this meta-analysis[22] included only 1445 subjects from 11 studies and did not include extended follow-up beyond the immediate postoperative period. These limitations underscore the need for larger cohort studies with longer observation periods to better characterize the temporal dynamics of this association.

Our findings align with and extend previous meta-analytic evidence[19,21,22] suggesting an association between sugammadex exposure and a reduced risk of atelectasis. While prior systematic reviews reported pooled estimates favoring sugammadex for various respiratory outcomes, our study is the first large-scale analysis specifically examining this association in a well-defined cohort of patients undergoing VATS. The observed 21% lower odds of atelectasis at 30 days, along with consistent associations at 7-day (OR 0.75) and 90-day (OR 0.81) follow-up, strengthens the evidence base by demonstrating the temporal consistency of this relationship. Several methodological features distinguish our investigation from previous studies. First, our matched cohort of 14,690 patients substantially exceeded the sample sizes of individual studies included in prior meta-analyses,[19,21,22] thereby providing greater statistical precision. Second, extending the follow-up period to 90 days and incorporating time-to-event analyses allowed characterization of the temporal pattern of atelectasis occurrence. These analyses revealed an early divergence in cumulative incidence (Figure 3), which may reflect more rapid restoration of diaphragmatic function and expiratory muscle strength with sugammadex in the immediate postoperative period.[23,24] These findings suggest that the association between sugammadex and reduced atelectasis risk is not transient but sustained over the postoperative course.

The absolute risk reduction for atelectasis at 30 days was 3.3%, corresponding to a number needed to treat (NNT) of approximately 30 patients to prevent one episode of postoperative atelectasis. Although this magnitude may appear modest, atelectasis is common after thoracic surgery and may contribute to prolonged recovery or downstream pulmonary complications. However, given the substantially higher acquisition cost of sugammadex compared with neostigmine, the clinical benefit should be interpreted in the context of resource utilization and institutional cost considerations. Formal cost-effectiveness analyses were beyond the scope of this study but warrant further investigation. In contrast, MACEs were infrequent events, and the corresponding absolute risk difference was small (0.4%); therefore, the observed association with MACEs should be interpreted cautiously and considered exploratory.

An additional contribution of our study is the identification of potential effect modifications across patient subgroups. This sex-based heterogeneity may reflect differences in neuromuscular pharmacology and body composition. Males generally have greater lean body mass affecting rocuronium distribution and may experience different patterns of residual curarization that render them more susceptible to incomplete reversal with neostigmine compared with sugammadex.[25,26] An interaction with obesity status was also observed (P = 0.047), with the association apparent in non-obese patients (OR 0.75), but attenuated and not statistically significant in obese patients (OR 0.96). This finding may be attributed to multiple interacting factors. First, obese patients have markedly reduced functional residual capacity and elevated baseline compression atelectasis due to increased intra-abdominal pressure and cephalad diaphragmatic displacement,[27,28] potentially creating a ceiling effect that limits the detectable benefit of any intervention. Second, mechanical constraints, including reduced chest wall compliance, persist regardless of neuromuscular recovery. Third, higher inspired oxygen concentrations required to maintain adequate oxygenation may promote absorption atelectasis through nitrogen washout.[29,30] However, the observed effect modification by sex and obesity status should be interpreted as exploratory and hypothesis-generating, because subgroup analyses were not powered to establish definitive interaction effects. These findings should not be overinterpreted and require validation in adequately powered prospective and mechanistic studies.

Evidence from large observational studies regarding the association between sugammadex exposure and postoperative pneumonia or respiratory failure remains inconsistent. A STRONGER multicenter analysis by Kheterpal et al[31] reported substantially lower odds of pneumonia and acute respiratory failure among patients receiving sugammadex. In contrast, Li et al[32] observed no difference in postoperative pulmonary complications between neuromuscular reversal agents in a single-center cohort, and the European POPULAR study[33] found no association between sugammadex exposure and suspected postoperative pulmonary infection. Consistent with these latter findings, our study demonstrated no statistically significant association between sugammadex exposure and pneumonia or acute respiratory failure across all follow-up intervals. The lack of a significant association may partly reflect the selection of a relatively low-risk population due to the stringent exclusion of patients with recent critical illness, resulting in a floor effect that limited detectable between-group differences. In addition, the use of electronic health record–based outcome ascertainment may have led to the undercapture of milder or transient respiratory events that did not prompt formal diagnostic coding.

In the current study, the persistence of the association between sugammadex exposure and pneumothorax across sensitivity analyses, despite attenuation of associations for pneumonia and MACEs, may suggest a mechanism more closely related to perioperative respiratory mechanics rather than a broader systemic medication effect. Regarding cardiovascular outcomes, the inverse association between sugammadex exposure and major adverse cardiovascular events may be partially mediated by the pulmonary effects observed in this study. Atelectasis can impair ventilation–perfusion matching and lead to hypoxemia, which may contribute to myocardial oxygen supply-demand imbalance and subsequent cardiac events. Accordingly, a reduction in atelectasis may be associated with downstream cardiovascular benefits. However, this finding should be interpreted cautiously, as the association was attenuated after excluding patients with intraoperative transfusion or immediate ICU admission, suggesting residual confounding related to surgical complexity or patient acuity. Further studies are required to clarify the relationship between neuromuscular reversal, postoperative pulmonary function, and cardiovascular outcome.

To assess the potential impact of unmeasured confounding, we calculated the E-value for the primary association (OR 0.79), which was 1.50 for the point estimate and 1.37 for the lower confidence limit. The E-value represents the minimum strength of association that an unmeasured confounder would need to have with both the exposure and outcome, beyond the measured covariates, to fully account for the observed association. Although

VanderWeele and Ding introduced the E-value as a quantitative measure of robustness,[34] no formal scale has been proposed. Subsequent reports suggest that values between 1.0 and 1.5 reflect limited robustness, whereas values between 2 and 3 are more consistent with moderate robustness.[35,36] Our results indicate that a confounder of modest magnitude (approximately 1.4–1.5 for its associations with both exposure and outcome) could explain the association. Potential candidates include the duration of one-lung ventilation and surgical complexity,[7] which are variables not captured in the TriNetX database. Accordingly, these findings should be interpreted as associative rather than causal.

Several limitations warrant consideration when interpreting our findings. First, as an observational study, our investigation could not establish causality, and unmeasured confounding factors may persist despite rigorous propensity score matching. Detailed perioperative variables, including the duration of one-lung ventilation, surgical complexity, specific VATS procedure type (eg, lobectomy versus wedge resection), intraoperative ventilatory strategies, and postoperative respiratory physiotherapy, were not available in the TriNetX database. These unmeasured factors may influence both reversal agent selection and pulmonary outcomes, potentially introducing residual confounding and affecting internal validity. Second, intraoperative neuromuscular monitoring parameters (eg, train-of-four monitoring) and the precise timing of reversal agent administration were not available in the TriNetX database. Therefore, differences in monitoring practices and reversal timing, which may independently influence residual neuromuscular blockade and postoperative pulmonary complications, could not be accounted for in our analysis. Third, the TriNetX database relies on administrative diagnostic codes, which may underascertain mild atelectasis cases or introduce outcome misclassifications. Mild or transient radiographic atelectasis that did not result in formal diagnostic coding may have been underascertained, potentially leading to an underestimation of the true incidence of postoperative atelectasis. Nonetheless, clinically documented events are likely to capture moderate-to-severe cases of the greatest relevance to patient outcomes. Fourth, the predominance of United States–based healthcare organizations within the database may constrain the external validity of the findings, as reversal agent availability and perioperative practice patterns vary across healthcare systems and geographic regions. Finally, we could not assess cost-effectiveness, which is relevant given the higher acquisition cost of sugammadex compared to neostigmine, although potential reductions in complications might offset these expenses.

In conclusion, this large-scale retrospective matched cohort study demonstrated that sugammadex exposure is associated with reduced odds of postoperative atelectasis in patients undergoing VATS, with consistent associations observed across multiple time points and most patient subgroups. These findings suggest a potential clinical benefit of sugammadex compared to neostigmine; however, given the observational design and possibility of residual confounding, the results should not be interpreted as definitive practice recommendations. The subgroup findings, including those related to sex and obesity status, were exploratory in nature and were not adjusted for multiple testing; therefore, they should be interpreted cautiously and require confirmation in prospective studies. Prospective randomized controlled trials and mechanistic investigations are warranted to validate the observed subgroup interactions and clarify the underlying physiological pathways.

Data Sharing Statement

The data used in this study were obtained from the TriNetX Research Network under collaborative agreement and are not publicly available. However, de-identified data may be accessed upon reasonable request from the author (I-Wen Chen) with permission from TriNetX and subject to a data-sharing agreement or network membership.

Ethics Approval Statement

The study protocol was approved by the Institutional Review Board of Chi Mei Medical Center, which waived the requirement for informed consent in accordance with the regulations for observational research (IRB No. 11403-E03).

Patient Consent Statement

Informed consent was not required for this retrospective study, as it involved secondary analysis of pre-existing data without any interventions or direct participant interaction.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no conflicts of interest in this work.

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