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Etomidate is Associated with a Reduced Incidence of Systemic Inflammatory Response Syndrome after Thoracoscopic Lung Resection: A Retrospective Analysis

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Abstract

Pulmonary complications remain frequent and are a major source of morbidity after thoracic surgery. In this study, we retrospectively examined whether the choice of intravenous general anesthetic—etomidate versus propofol—is associated with the postoperative incidence of systemic inflammatory response syndrome (SIRS) after thoracoscopic lung resection. Patients who underwent thoracoscopic lung resection between February 2022 and May 2024 were included in the analysis. The participants were categorized into two groups based on the intravenous general anesthetic agent administered: etomidate or propofol. Propensity score matching (1:2) was employed to balance baseline characteristics, including age, body mass index, operation duration, and anesthesia duration, between the etomidate group and the propofol group. SIRS occurred in 29.2% (66/226) of patients in the etomidate group compared to 38.7% (175/452) in the propofol group, indicating a significantly higher incidence in the propofol cohort ($p < 0.05$). Furthermore, respiratory failure was more prevalent among patients receiving propofol than among those receiving etomidate (18.6% vs. 12.4%; $p < 0.05$). Compared with the propofol group, the etomidate group exhibited significantly lower postoperative systemic immune-inflammation index, and the propofol group demonstrated a higher incidence of intraoperative hypotension. However, no significant differences

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were observed between the two groups regarding respiratory infections, occurrences of pneumothorax, the proportion of patients requiring vasoactive agents, time to extubation, duration of stay in the post-anesthesia care unit, and the length of hospital stay. In conclusion, compared with propofol, etomidate was associated with a lower incidence of SIRS and a reduced risk of respiratory failure. These findings suggest that etomidate may offer advantages in mitigating inflammatory responses in patients undergoing thoracoscopic lung resection.

***Keywords*:** Thoracoscopic lung resection; Etomidate; Propofol; Systemic inflammatory response syndrome

INTRODUCTION

Systemic inflammatory response syndrome (SIRS) remains associated with substantial mortality, with reported rates ranging from 25% to 60% among critically ill patients.[1] The incidence of SIRS significantly increases following thoracoscopic lung resection.[2] Moreover, emerging evidence suggests that the severity of SIRS may correlate with the extent of postoperative complications. One-lung ventilation during anesthesia induces significant physiological disturbances, including intrapulmonary shunting, ventilation-perfusion mismatch, elevated peak airway pressures, and lung ischemia-reperfusion injury. These alterations provoke a pronounced systemic stress response, stimulating the release of stress hormones. Consequently, this cascade can trigger SIRS, ultimately contributing to a spectrum of postoperative pulmonary complications (PPCs). In thoracic surgery, PPCs remain a leading cause of morbidity and mortality, significantly affecting patient outcomes.[3]

Anesthesia may influence oxidative stress and inflammatory responses in patients. Emerging evidence suggests that the choice of anesthetic technique during lung adenocarcinoma surgery can significantly modulate postoperative inflammatory profiles.[4] Different anesthetic regimens may elicit distinct immunological and inflammatory responses in surgical patients, potentially influencing postoperative outcomes.[5] Clinical studies have demonstrated comparable mortality rates between etomidate and alternative induction agents across diverse high-risk populations, including trauma patients,[6] cardiac surgery patients, and critical illness patients.[7] In elderly surgical patients, continuous etomidate infusion demonstrated in-hospital morbidity rates comparable to those of propofol infusion.[8] A comparative analysis showed that propofol exhibited more potent antioxidant effects and more effectively reduced SIRS in pediatric patients with congenital cyanotic heart disease undergoing cardiac surgery, compared to sevoflurane anesthesia.[9] Etomidate mitigates ischemia-reperfusion injury in a rat ovarian torsion-detorsion model by inhibiting the expression of pro-inflammatory cytokines, including interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α).[10] However, there is a lack of data regarding the effects of continuous etomidate infusion for anesthesia maintenance on the incidence of SIRS in thoracic surgery compared with propofol. Hence, this study compares the effects of continuous infusions of propofol versus etomidate on the incidence of SIRS following thoracoscopic lung resection.

METHODS

Ethics

Ethics approval was obtained from the Ethics Committee of The First People's Hospital of Foshan (2024139).

Study procedures

This single-center retrospective cohort study was conducted at The First People's Hospital of Foshan. Data were collected from patients who underwent thoracoscopic lung resection between February 2022 and May 2024. Thoracoscopic lung resection primarily includes thoracoscopic wedge resection of the lung, segmentectomy, and lobectomy. Routinely collected clinical data were obtained from the hospital's electronic health records. All personal identifiers were removed, and case-specific numbers were omitted. The Institutional Review Board waived the requirement for individual informed consent for this study.

Patient selection

From February 2022 to May 2024, 3,692 patients underwent thoracic surgery. We excluded surgeries involving maintenance with more than one intravenous anesthetic agent, repeat surgeries, and non-lung surgeries. A total of 1,172 patients aged 18 years or older who underwent thoracoscopic lung resection were identified.

Outcomes

The primary outcome was the incidence of SIRS three days after surgery. SIRS was defined according to the American College of Chest Physicians/Society of Critical Care Medicine consensus criteria, with the presence of at least two of the following four conditions: (i) core body temperature > 38 °C or <36 °C; (ii) heart rate > 90 beats/minute; (iii) respiratory rate > 20 breaths/minute or arterial partial pressure of carbon dioxide < 32 mm Hg; and (iv) white blood cell count > 12,000/mm^3, <4,000/mm^3, or >10% immature (band) forms.

Secondary outcomes included systemic immune-inflammation index (SII), incidence of hypotension, proportion of patients requiring vasoactive agents, duration of stay in the post-anesthesia care unit (PACU), the length of hospital

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stay, and presence of PPCs within seven days postoperatively (including respiratory failure, contralateral pneumothorax, respiratory infection, pleural effusion, atelectasis, and bronchospasm).

Statistical analysis

Statistical analysis was performed using R software (version 4.3.1). Categorical variables are presented as numbers (percentages). Group differences were assessed using Fisher's exact test or the chi-square test, as appropriate. Continuous variables are expressed as mean ± standard deviation or median (interquartile range [IQR]), and differences were assessed using the Student's *t*-test or Mann–Whitney U test, based on distribution normality assessed by the Shapiro–Wilk test and Levene's test for equality of variances. For the comparison of event rates between groups, Fisher's exact test was the primary method due to the low frequency of events. To adjust for potential confounders, propensity score matching was conducted using a logistic regression model that included age, body mass index (BMI), operation duration, and anesthesia duration. Standardized mean differences were computed to evaluate covariate balance, with a threshold of <0.1 indicating adequate balance. A *p*-value of less than 0.05 was considered statistically significant.

RESULTS

Patient characteristics and matching

Patients who underwent thoracic surgery at the center during the study period were screened for eligibility (n = 3,692). After selection based on the inclusion and exclusion criteria, 1,172 unmatched patients were identified (**Figure 1**). We excluded seven patients who underwent emergency surgery, and nine other patients who had pre-existing sepsis or were on chronic steroid therapy, resulting in a final sample of 1,156 patients. Among the included patients, 226 received continuous infusion of etomidate for anesthesia maintenance during thoracoscopic lung resection. Patients in the propofol group (Group P) had longer operation durations (etomidate: 92.5 hours [77–117] vs. propofol: 120 hours [90–160]; $p = 0.001$) and longer anesthesia durations (etomidate: 136 hours [111–170] vs. propofol: 170 hours [135–217]; $p = 0.001$). Before matching, the groups differed significantly in age and BMI (**Table 1**). Using 1:2 propensity score matching, Group P was matched to the etomidate group (Group E) based on age, BMI, operation duration, and anesthesia duration. Finally, a total of 678 matched patients (238 males and 440 females) met the inclusion criteria, with 452 patients assigned to Group P and 226 to Group E. The subjects were matched using a caliper propensity-score approach, with a default caliper width of 0.2 standard deviations.

The basic patient characteristics of the matched and unmatched cohorts are presented in **Table 1**. After matching, there were no statistically significant differences between the two groups in terms of gender, American Society of Anesthesiologists grade, operation modes, operation site, intraoperative blood loss, fluid input, history of chronic obstructive pulmonary disease, history of smoking, and preoperative complications (arterial hypertension, coronary heart disease, and diabetes mellitus) (**Table 2**).

Primary outcome

Regression analyses, both univariate and multivariate, demonstrated that the occurrence of postoperative SIRS was significantly associated with the group allocation (**Table 3**). The incidence of SIRS three days after surgery was significantly higher in Group P compared to Group E (38.7% vs. 29.2%; $p < 0.05$) (**Table 4**).

Secondary outcomes

Postoperative SII was significantly lower in Group E than in Group P. The

Table 1. Basic characteristics of matched and unmatched cohorts

Characteristics	Unmatched				Matched				
	All (n = 1,156)	Group E (n = 226)	Group P (n = 930)	p	All (n = 678)	Group E (n = 226)	Group P (n = 452)	p	SMD
Age (years)	59 (19)	56 (22)	60 (18)	0.006	57 (19)	56 (22)	57 (19)	0.44	0.02
BMI (kg/m^2)	22.9 (4.5)	22.5 (5)	22.9 (4.3)	0.02	22.9 (4)	22.9 (4.3)	22.9 (3.6)	0.35	0.08
Operation duration (hours)	110 (70)	92.5 (40)	120 (70)	0.001	95 (43.8)	92.5 (40)	95 (44.2)	0.53	0.02
Anesthesia duration (hours)	162 (75)	136 (59)	170 (82)	0.001	140 (52)	136 (58)	141 (51)	0.32	0.04

Note: Data presented as median (interquartile range).
Abbreviation: SMD: Standardized mean difference.

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Table 2. Comparison of demographic and control parameters in matched groups

Variable	Group E (*n* = 226)	Group P (*n* = 452)	*p*-value	SMD
Gender			0.62	0.046
Male	76 (33.6%)	162 (35.8%)		
Female	150 (66.4%)	290 (64.2%)		
ASA grade			1	0.001
I	32 (14.2%)	64 (14.2%)		
II	171 (75.7%)	342 (75.7%)		
III	23 (10.2%)	46 (10.2%)		
Operation modes			0.43	0.03
Pulmonary wedge resection	162 (71.6%)	353 (78.1%)		
Pulmonary segmentectomy	18 (7.9%)	17 (3.7%)		
Pulmonary lobectomy	46 (20.3%)	92 (20.3%)		
Operation site			0.89	0.02
Left	96 (42.5%)	196 (43.4%)		
Right	130 (57.5%)	256 (56.6%)		
History of COPD	3 (1.3%)	7 (1.5%)	0.82	0.003
History of smoking	44 (19.4%)	81 (17.9%)	0.62	0.04
Diabetes mellitus	18 (7.96%)	22 (4.93%)	0.16	0.08
Arterial hypertension	49 (21.7%)	112 (25.1%)	0.37	0.09
Coronary heart disease	2 (0.88%)	4 (0.90%)	1	0.001
Blood loss (mL), median (IQR)	10 (15)	10 (15)	0.82	0.06
Fluid input (mL), median (IQR)	500 (0)	500 (0)	0.33	0.08

Note: Data presented as *n* (%), unless stated otherwise.
Abbreviations: ASA: American Society of Anesthesiologists; COPD: Chronic obstructive pulmonary disease; SD: Standard deviation; SMD: Standardized mean difference.

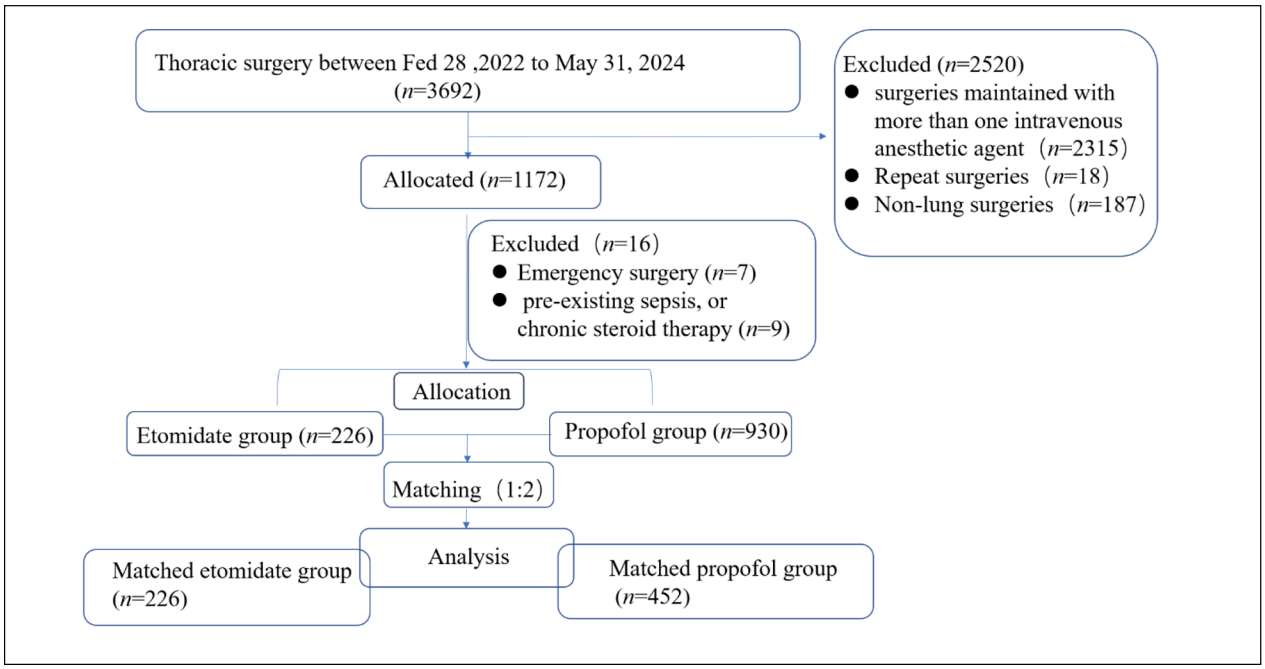

Figure 1. Study flow chart

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Table 3. Univariate and multivariate regression analysis of systemic inflammatory response syndrome

Variables	Univariate logistic regression		Multivariate logistic regression	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Group (E/P)	0.65 (0.46, 0.91)	0.013	0.69 (0.48, 0.98)	0.038
Age	1 (0.99, 1.01)	0.607		
Body mass index	1.05 (0.99, 1.1)	0.095		
Gender	0.87 (0.63, 1.21)	0.423		
ASA grade	1.22 (0.77, 1.95)	0.394		
Anesthesia duration (hours)	1.01 (1, 1.01)	<0.001	1 (0.99, 1.01)	0.901
Operation duration (hours)	1.01 (1.01, 1.01)	<0.001	1.01 (1, 1.02)	0.033
Blood loss (mL)	1 (1, 1.01)	0.252		
Fluid input (mL)	1 (1, 1)	0.103		
Preoperative SII	1 (1, 1)	0.404		

Abbreviations: ASA: American Society of Anesthesiologists; CI: Confidence interval; OR: Odds ratio; SII: Systemic immune-inflammation index.

Table 4. Primary outcome

	Group E (*n* = 226)	Group P (*n* = 452)	*p*-value
SIRS incidence rate	66 (29.2%)	175 (38.7%)	0.01

Note: Data presented as *n* (%).

incidence of intraoperative hypotension was higher in Group P compared to Group E (Table 5). There were no statistically significant differences between the two groups in preoperative SII, time to extubation, duration of stay in PACU, and length of hospital stay or the proportion of patients requiring vasoactive agents (Table 5).

There was no significant difference in the incidence of PPCs within seven days after the operation between the two groups. However, respiratory failure occurred more frequently in Group P than Group E (Table 6). The rates of respiratory infection, pleural effusion, bronchospasm, pneumothorax, and atelectasis did not differ significantly between the two groups.

DISCUSSION

In our study, we found a significantly lower incidence rate of SIRS in Group E compared to Group P after thoracoscopic lung resection. While surgical trauma inevitably triggers inflammation and associated immune responses, our findings suggest that despite propofol's known anti-inflammatory properties,[11] etomidate may provide superior modulation of the systemic inflammatory response in this surgical context. Etomidate has been shown to possess certain anti-inflammatory effects.[12] Experimental studies in septic rat models have demonstrated that intravenous etomidate anesthesia significantly reduces serum TNF-α levels.[13,14] TNF-α and IL-6 are key mediators involved in the cyto-

Table 5. Secondary outcomes

Parameters	Group E (*n* = 226)	Group P (*n* = 452)	*p*-value
Postoperative SII	1,687 (663)	2,213 (739)	0.02*
Preoperative SII	496 (132)	444 (133)	0.55
Time to extubation (hours)	37.5 (22.9)	37.5 (25)	0.36
Duration of stay in PACU (hours)	81 (43.2)	78 (46)	0.16
Length of hospital stay (days)	12 (5)	13 (5)	0.63
Incidence of hypotension, *n* (%)	55 (24.3%)	160 (35.4%)	0.04*
The proportion of patients requiring vasoactive agents, *n* (%)	16 (7.1%)	44 (9.7%)	0.31

Abbreviations: PACU: Post-anesthesia care unit; SII: systemic immune-inflammation index.
Note: Data presented as median (interquartile range), unless stated otherwise. *Statistical significance at $p < 0.05$.

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Table 6. Postoperative pulmonary complications

Complications	Group E (*n* = 226)	Group P (*n* = 452)	*p*-value
Postoperative pulmonary complications	79 (35%)	176 (38.9%)	0.36
Respiratory failure	28 (12.4%)	84 (18.6%)	0.05
Respiratory infection	14 (6.2%)	25 (5.5%)	0.86
Atelectasis	22 (9.7%)	48 (10.6%)	0.79
Bronchospasm	3 (1.3%)	8 (1.7%)	0.76
Pleural effusion	10 (4.4%)	31 (6.8%)	0.28
Pneumothorax	49 (21.7%)	77 (17%)	0.17

Note: Data presented as *n* (%).

kine storm within the immune system.[15] The significant decrease in TNF-α and IL-6 levels observed following etomidate administration suggests that this agent may mitigate systemic inflammation by suppressing key pro-inflammatory cytokines. Zheng *et al*.[4] demonstrated etomidate's superior anti-inflammatory properties in patients undergoing thoracic surgery, showing significantly lower IL-6 levels at 6, 12, and 24 h postoperatively compared to propofol ($p < 0.05$ at all time points). Their findings further revealed a significant reduction in C-reactive protein levels at 24 h in Group E, supporting its enhanced systemic anti-inflammatory effects.[4] Animal studies evidence demonstrated that intraoperative administration of etomidate for sedation maintenance significantly increased serum superoxide dismutase levels and reduced the release of inflammatory factors, such as TNF-α, IL-1, and IL-6, following ischemia-reperfusion injury.[16] Propofol exerts vasodilatory effects either directly on vascular smooth muscle or indirectly by reducing sympathetic nervous activity, which can result in hypotension. In contrast, etomidate does not significantly suppress sympathetic tone or myocardial function, thereby maintaining greater cardiovascular and hemodynamic stability. We found that the incidence of intraoperative hypotension was higher in Group P than in Group E. This may explain the lower incidence of SIRS observed with etomidate.

Our comparative analysis revealed no statistically significant differences ($p > 0.05$) in PPCs between patients undergoing thoracoscopic lung resection who received etomidate versus propofol for general anesthesia maintenance. Group E demonstrated a reduction in the incidence of respiratory failure compared to Group P. Our study observed a PPC rate of 37.6% (95% confidence interval [CI]: 34.2–41.0), which aligns with the established benchmark of 38% (95% CI: 35–41.2) reported in prior multicenter studies.[17] The incidence of PPCs following video-assisted thoracoscopic lung resection remains clinically significant. This is attributable to physiological challenges, such as one-lung ventilation-induced ischemia-reperfusion injury, surgical manipulation of pulmonary tissue, and systemic inflammatory responses,[18] pre-existing lung conditions in patients,[19] elevated intraoperative oxygen inhalation levels, and both acute and chronic pain. SIRS serves as a critical pathophysiological factor in the development of PPCs. Clinical evidence demonstrated a significant association between SIRS and respiratory failure, with inflammatory mediators such as TNF-α, IL-6 exacerbating alveolar-capillary membrane injury and impairing gas exchange.[20-22] This may explain the lower incidence of respiratory failure in Group E compared to Group P.

However, we found no clinically relevant differences in respiratory infection rates. While Weiss *et al*.[23] reported higher respiratory infection rates with etomidate in cardiac surgery, our thoracic surgery data showed no such association. Our results differ from the findings of Lu *et al*.,[8] who reported higher postoperative pneumonia rates with etomidate compared to propofol in abdominal surgery (23.1% vs. 16.4%, $p = 0.03$). This discrepancy may be explained by several key factors: the abdominal–pulmonary axis of inflammation may differentially modulate etomidate's immunomodulatory effects; thoracic procedures inherently reduce aspiration risk compared to upper abdominal surgery; and our lung-protective ventilation protocol may have mitigated the risk of secondary infection.

The SII has emerged as a significant prognostic biomarker in pulmonary medicine, demonstrating clinical utility in both diagnostic evaluation and outcome prediction across multiple lung pathologies.[23] Early alterations in neutrophil, platelet, and lymphocyte counts serve as predictive hematological markers for PPCs and surgical site infections.[24] SII demonstrated significant predictive value for PPCs in elderly patients (≥65 years) undergoing laparoscopic abdominal surgery.[25] Patients receiving etomidate exhibited significantly lower SII values compared to those in Group P. This relative reduction in SII suggests that etomidate may more effectively attenuate the surgical stress response.

In this study, there were no statistically significant differences in the proportion of patients requiring vasoactive agents, time to extubation, duration of stay in PACU, and the length of hospital stay between the two groups. These results are consistent with previous studies.[8]

Nevertheless, there are some limitations in this study. First, this is a retrospective study. Although matching was employed, the selection of anesthetic drugs was based on the preferences of anesthesiologists, which may introduce some bias. Prospective studies are needed to provide further confirmation. Second, the observation time for SIRS and postoperative pulmonary complica-

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tions in this study was short; this study did not evaluate the longer-term impact of SIRS on prognosis, which warrants further study. Third, the mechanisms underlying the effects of etomidate and propofol on SIRS, oxygenation, and lung-related outcomes remain unclear, necessitating further *in vitro* and animal experiments.

CONCLUSION

Compared with propofol, etomidate was associated with a reduced incidence of SIRS after thoracoscopic lung resection. Patients receiving etomidate exhibited lower rates of respiratory failure than those receiving propofol. However, PPCs did not differ significantly between the two groups.

AUTHORS' DISCLOSURE

No funding was received for conducting this study. Ethics approval was provided by the Ethics Committee of The First People's Hospital of Foshan (2024139). The Institutional Review Board (IRB) waived the requirement for individual informed consent for this study.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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