Journal of Anesthesia (2019) 33:230–237
https://doi.org/10.1007/s00540-018-2602-9

ORIGINAL ARTICLE

Prophylactic sivelestat for esophagectomy and in-hospital mortality: a propensity score-matched analysis of claims database

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Received: 25 June 2018 / Accepted: 19 December 2018 / Published online: 5 January 2019

Abstract

Purpose Transthoracic esophagectomy is an invasive surgery, and the excessive surgical stress produces inflammatory cytokines, which provoke acute respiratory distress syndrome (ARDS). Sivelestat sodium hydrate—a selective neutrophil elastase inhibitor—is used to treat or prevent ARDS in patients undergoing esophagectomy, although clear evidence is lacking. We investigated the benefits and risk of prophylactic sivelestat.

Methods This retrospective study used an administrative claims database in Japan. Adult patients who underwent transthoracic esophagectomy from 2010 to 2016 were identified and divided into a prophylactic sivelestat use group and a non-prophylactic use group that included both non-users and therapeutic users. The primary outcome was all-cause in-hospital mortality, and a secondary outcome included the proportion of ARDS. We used 1:1 propensity score matching. For sensitivity analyses, we conducted a 1:2 propensity score matching analysis and several analyses with various patient inclusion criteria.

Results Of the 3391 patients with esophagectomy, 621 received prophylactic sivelestat. On unadjusted analysis, the sivelestat group had a higher proportion of in-hospital mortality (5.3% vs. 2.9%) compared with the control group. We created a matched cohort of 615 pairs, whose baseline characteristics were well balanced. On adjusted analysis using propensity score matching, prophylactic sivelestat administration was not associated with decreased in-hospital mortality [adjusted odds ratio (aOR) 1.65; 95% confidence interval (CI) 0.95–2.88], ARDS rate (aOR 1.25; 95% CI 0.49–3.17). The findings were also consistent with other sensitivity analyses.

Conclusion Because mortality and postoperative complications were similar, our findings do not support prophylactic sivelestat administration for patients undergoing esophagectomy.

Keywords Esophagectomy · Sivelestat · Mortality · Propensity score · Administrative claims

Introduction

Transthoracic esophagectomy for esophageal cancer is one of the most invasive procedures in gastrointestinal surgery [1]. Although there have been significant improvements in perioperative care and advancements in surgical technologies and techniques, in-hospital mortality following esophagectomy remains prevalent, and pulmonary complications are one of the most frequent events [2, 3]. Excessive surgical stress produces inflammatory cytokines and often induces systemic inflammatory response syndrome. This excess production of cytokines can trigger organ dysfunction, such as acute respiratory distress syndrome (ARDS). Therefore, perioperative management to suppress excess cytokines might improve short-term outcomes in patients undergoing esophagectomy [4, 5].

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00540-018-2602-9) contains supplementary material, which is available to authorized users.

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Sivelestat sodium hydrate is a selective neutrophil elastase inhibitor that controls neutrophil function and relieves the systemic inflammatory response [6]. In Japan, after a phase III trial [6], sivelestat was approved for the treatment of acute lung injury with systematic inflammatory response syndrome. Several studies have examined the efficacy of this drug, but the results are conflicting because of different study designs, patient profiles, and outcomes used in each study [7–9].

Sivelestat is also used for prophylaxis, even for highly intricate surgery such as esophagectomy. Several small studies from Japan indicated that perioperative sivelestat administration might improve the postoperative clinical course—increased ventilator-free days—following transthoracic esophagectomy [10–15]. Despite the lack of sufficient evidence, prophylactic sivelestat is often used for esophagectomy in Japan, only where sivelestat is approved by the regulatory agency.

In this retrospective study, we first determined the prevalence of the use of prophylactic sivelestat for transthoracic esophagectomy in Japan, using a claims database. Further, we investigated whether prophylactic sivelestat administration improved perioperative outcomes among patients with esophagectomy.

Methods

The Kyoto University Graduate School and the Faculty of Medicine Ethics Committee (Kyoto, Japan, R0703) approved the study protocol. The requirement for informed consent was waived because of the anonymous nature of the data and retrospective study design.

Data source

This was a retrospective cohort study using an administrative claims database. We used data from the database accumulated by the database vendor, Medical Data Vision (MDV) Co., Ltd. (Tokyo, Japan). The database from MDV contains claims data from hospitals participating in the Diagnostic Procedure Combination (DPC) system in Japan [16, 17]. In September 2016, the MDV database had collected approximately 17 million patients' inpatient and claims data from 284 DPC hospitals, representing approximately 18% of all DPC hospitals throughout Japan. The DPC is a Japanese case-mix payment system for inpatient care launched in 2002 by the Ministry of Health, Labor, and Welfare, which is similar to the diagnosis-related groups in the US Medicare program. In 2015, about 75% of acute-care beds in Japan participated in the DPC. The MDV database contains not only administrative claims, but also detailed patient data, including an anonymized patient identifier, age, sex, self-reported smoking history, diagnosis codes, prescriptions, and medical procedures, such as surgical operations, dates of admission and discharge, and outcomes at the discharging hospital. Prescriptions and medical procedures were coded using original Japanese K codes with the dates of administration and execution. The primary diagnosis, comorbidities on admission, and complications after hospitalization were specified using the International Classification of Diseases, 10th version (ICD-10) codes. This MDV's database has been used in multiple epidemiological studies [18, 19].

Study population

Using the DPC database, we selected patients aged 20 years or older who were diagnosed with esophageal cancer (ICD-10 code C15) and underwent esophagectomy (K codes K527 and K529) between April 1, 2010 and September 30, 2016. We excluded patients who underwent a two-stage esophagectomy. Patients who underwent abdominal esophagectomy (K code K5293) were excluded. We also excluded patients whose admission and discharge dates or baseline characteristic factors were missing.

The exposure variable of interest was whether patients received prophylactic administration of sivelestat sodium hydrate. Prophylactic use was defined as starting administration of sivelestat on the same day of esophagectomy, and both non-users and patients receiving sivelestat after the second day of surgery constituted the control group.

Patient characteristics

Baseline characteristics of patients in the database included the following: demographic factors (age, sex, body mass index, smoking history); use of induction chemotherapy and radiation; fiscal year of surgery; preoperative risk factors including major comorbidities coded using the ICD-10 codes; hospital factors (volume of esophagectomy, teaching hospital); and surgical factors including thoracoscope thoracoscope, differential lung ventilation, anesthesia time, and transfusion. The hospital volume of patients with esophagectomy was defined as the average number of esophagectomies performed in each hospital annually. Hospitals were divided into three categories according to their number of esophagectomies per year: low (<5), middle (5–30), and high volume (>30). Designation as a teaching hospital indicates a hospital that offers a residency training program. The Quan modification of the Charlson Comorbidity Index (CCI) (scores ranging from 0 to 33) was calculated. The CCI score is a validated measure of comorbidities in large administrative databases in Japan [20].

Outcomes

We analyzed the association between prophylactic sivelestat and the primary outcome of in-hospital mortality rate. Secondary outcomes included the following: the proportion of incident cases of ARDS, other respiratory complications, sepsis, and postoperative hospital stays. The incidence of any complication was defined using diagnosis codes between postoperative day 1 and day of discharge during hospitalization (Supplemental Table 1).

Statistical analysis

Distributed continuous variables are presented as means with standard deviation (SD) and medians with the interquartile range (25th, 75th percentiles). Categorical variables are presented as counts and proportions (%). Pearson's Chi squared test was performed for categorical dichotomous outcomes; a *t* test was performed for continuous outcomes.

To control for confounding factors between patients who did and did not receive prophylactic administration of sivelestat, propensity score (PS) matching was conducted using nearest neighbor matching without replacement. A caliper was fixed at 10% of the SD of the logit of the propensity scores. The confounding factors included in the propensity score model were as follows: demographic factors (age, sex, body mass index), preoperative factors (smoking history, preoperative chemotherapy, preoperative radiotherapy), hospital factors (volume of esophagectomy, teaching hospital), perioperative factors (thoracoscope, differential lung ventilation, anesthesia time, and transfusion), and the CCI score. Differences in covariates between the prophylactic sivelestat group and control group were assessed using the standardized difference, whereby an absolute standardized difference above 10% represents a meaningful imbalance [21]. We assessed model performance to discriminate between the prophylactic sivelestat group and control group using the *C* statistic. Conditional logistic regression was performed to compare in-hospital mortality rates and the rate of ARDS, other respiratory complications, and sepsis between the matched groups. We also used a paired *t* test to compare continuous secondary outcomes between them. The adjusted odds ratio (aOR) and 95% confidence interval (CI) are reported, along with the *P* values for the difference in mortality rates and proportion of complications. The adjusted differences and 95% CIs of postoperative hospital stays, as well as the *P* values, were also calculated.

Three sensitivity analyses were performed to check the robustness of our results. First, for the purpose of checking whether the result was the same regardless of sample size, 1:2 matching was performed as sensitivity analysis. Second, we excluded patients with a diagnosis of ARDS on the same day of the esophagectomy. This is because the indication for sivelestat (i.e., either receiving prophylaxis or not) was not provided in the claims data, and sivelestat might have been used therapeutically for these patients. Third, we carefully considered the duration of sivelestat administration. Therefore, we limited the sivelestat group to those who had received the drug for less than 5 days in this sensitivity analysis.

All reported probability values were two-sided, and we considered $P < 0.05$ to exhibit statistical significance. An academic researcher was in charge of data handling and statistical analyses. All statistical analyses were performed using SAS version 9.4 for Windows (SAS Institute Inc.; Cary, NC, USA).

Results

Study cohort

A flow diagram for identification of the cohort is shown in Fig. 1. During the study period, we identified 3568 esophageal cancer patients who underwent esophagectomy. Of these, 3391 were identified as the full study cohort, based on the predetermined inclusion and exclusion criteria. A total of 177 candidate patients were excluded for the following reasons: underwent abdominal esophagectomy (102 patients), underwent second-time esophagectomy (11 patients), and missing data (64 patients).

Patient characteristics and crude outcome

Of the full study cohort, 621 (18.3%) patients received prophylactic sivelestat. The baseline characteristics of these patients are presented in Table 1. Patients who received prophylactic sivelestat were less likely to undergo surgery at a high-volume surgery hospital. Among the full study cohort, the crude in-hospital mortality rate was 3.3% (114/3391) and significantly differed between the prophylactic sivelestat group and the control group according to the unadjusted analysis [5.3% (33/621) vs. 2.9% (81/2770); $P = 0.0028$]. The proportion of respiratory complications differed significantly, but the proportion of ARDS and sepsis did not differ significantly, and postoperative hospital stays were significantly longer (Table 2).

Propensity-matched analysis

PS matching created 615 pairs. The established model for estimating propensity scores had a *C* statistic of 0.756. Standardized differences were under 10% for all variables, indicating that patients' baseline characteristics were well balanced between the two groups after PS matching.

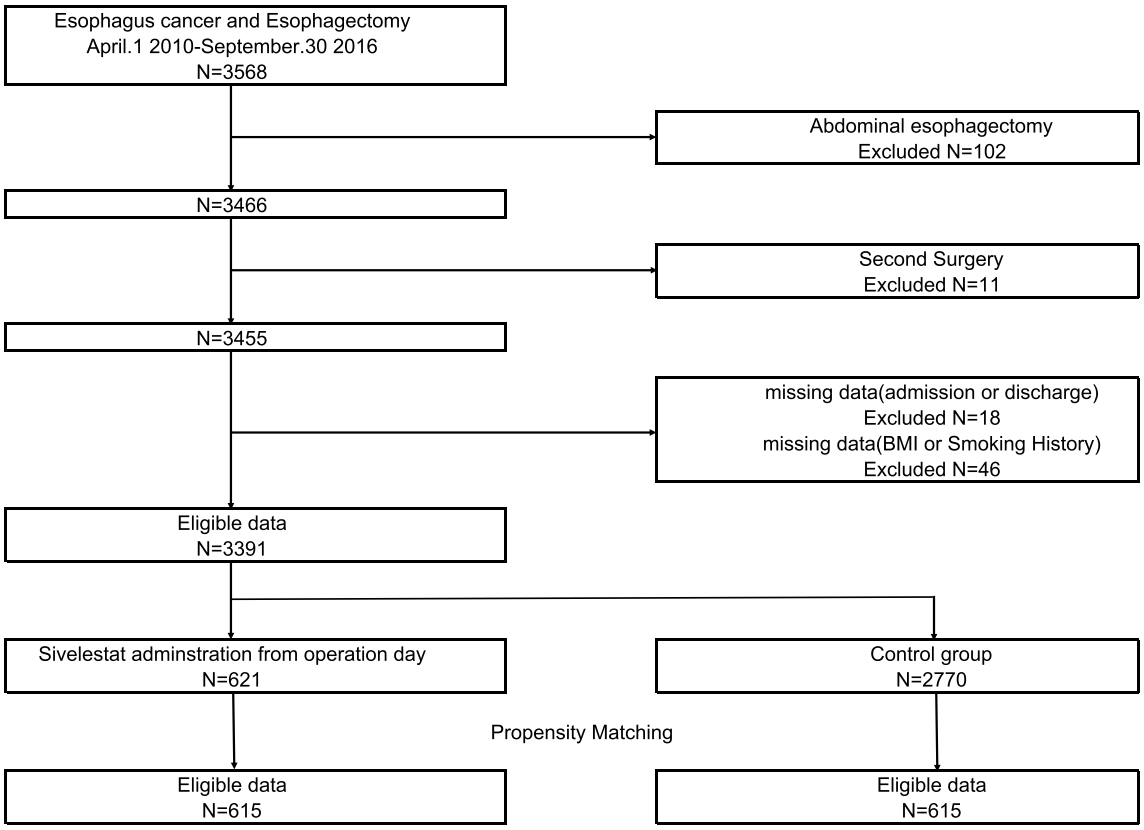

Fig. 1 Study flow diagram. The values indicate the number of all the eligible patients during the study period

We found that prophylactic sivelestat administration was not significantly associated with mortality rate (aOR 1.65; 95% CI 0.95–2.88; $P=0.0772$), ARDS (aOR 1.25; 95% CI 0.49–3.17; $P=0.6380$), respiratory complications (aOR 1.24; 95% CI 0.91–1.67; $P=0.1682$), and sepsis (aOR 1.15; 95% CI 0.68–1.95; $P=0.5933$) based on conditional logistic regression modeling after PS matching. We also found that prophylactic sivelestat administration was not associated with postoperative hospital stay (2.5 days; 95% CI −2.3 to 7.2; $P=0.3065$) (Table 2).

Sensitivity analyses

We examined three sensitivity analyses (Table 3). The first sensitivity analysis used 1:2 propensity matching, and the estimated aOR for in-hospital mortality did not change (primary analysis, aOR 1.65; sensitivity analysis, aOR 1.59; 95% CI 0.99–2.58). In the second sensitivity analysis excluding patients with a recorded diagnosis of ARDS on the day of surgery, 599 patient pairs were matched (aOR 1.24; 95% CI 0.73–2.10). In this sensitivity analysis to alleviate indication bias, we also found that prophylactic sivelestat administration was not significantly associated with mortality rate. In the third sensitivity analysis, we considered prophylaxis duration, with patients who received sivelestat for ≤ 5 days constituting the prophylactic cohort. We further found that prophylactic sivelestat administration was not significantly associated with mortality rates for 574 patient pairs (aOR 1.38; 95% CI 0.72–2.62).

Discussion

In this nationwide retrospective cohort study among acute hospitals in Japan, we investigated the association between perioperative prophylactic sivelestat therapy and mortality in patients who underwent radical esophagectomy. The primary finding was that the proportion of in-hospital mortality was similar among patients who received prophylactic sivelestat, as compared with those who did not (aOR 1.65; 95% CI 0.95–2.88). As for the pre-specified secondary outcomes, we also found no benefits of prophylactic sivelestat use.

Pulmonary complications are frequent following esophageal resection and reconstruction, and these complications account for more than half of the mortality related to esophageal resection [2, 22]. Pneumonia, ARDS, respiratory failure, pulmonary edema, and empyema are among those complications, and the preventive or therapeutic strategy of these

Table 1 Demographic and hospital characteristics of patients receiving esophagectomy before and after propensity matching

Total	Before propensity score matching			After propensity score matching		
	Sivelestat $n=621$	Control $n=2770$	Standardized difference (%)	Sivelestat $n=615$	Control $n=615$	Standardized difference (%)
Age (years), mean (SD)	66.7 (8.4)	65.8 (8.6)	10.3	66.7 (8.4)	66.9 (8.5)	2.1
Age (years), median (IQR)	67.0 (11.0)	66.0 (11.0)		67.0 (11.0)	67.0 (12.0)	
Male sex	525 (84.5)	2317 (83.6)	2.4	519 (84.4)	512 (83.3)	3.1
BMI (kg/m^2), mean (SD)	21.5 (3.3)	21.5 (4.1)	1.0	21.5 (3.3)	21.4 (3.2)	1.7
Smoking	441 (71.0)	2072 (74.8)	8.5	437 (71.1)	443 (72.0)	2.2
Comorbidities						
Charlson comorbidity index score (SD)	4.2 (2.7)	4.1 (2.6)	6.5	4.2 (2.7)	4.3 (2.6)	2.7
Myocardial infarction	11 (1.8)	39 (1.4)	2.9	11 (1.8)	12 (2.0)	1.2
Any heart disease	81 (13.0)	232 (8.4)	15.1	79 (12.8)	82 (13.3)	1.4
Peripheral vascular disease	27 (4.3)	70 (2.5)	10.0	26 (4.2)	18 (2.9)	7.0
Cerebrovascular disease	44 (7.1)	187 (6.8)	1.3	44 (7.2)	42 (6.8)	1.3
Chronic pulmonary disease	122 (19.6)	469 (16.9)	7.0	121 (19.7)	129 (21.0)	3.2
Chronic renal disease	15 (2.4)	42 (1.5)	6.5	14 (2.3)	17 (2.8)	3.1
Liver disease	22 (3.5)	69 (2.5)	6.2	22 (3.6)	19 (3.1)	2.7
Diabetes mellitus	3 (0.5)	5 (0.2)	5.3	3 (0.5)	3 (0.5)	0.0
Difficulty in anesthesia	66 (10.6)	228 (8.2)	8.2	64 (10.4)	59 (9.6)	2.7
Preoperative therapy						
Chemotherapy	210 (33.8)	1347 (48.6)	30.4	209 (34.0)	204 (33.2)	1.7
Radiotherapy	31 (5.0)	142 (5.1)	0.6	31 (5.0)	31 (5.0)	0.0
Perioperative factors						
Operation time (min) (SD)	615 (151.2)	580 (161.8)	22.4	615 (151.4)	618 (183.7)	1.5
Thoracoscope	163 (26.2)	717 (25.9)	0.8	160 (26.0)	169 (27.5)	3.3
Differential ventilation	503 (81.0)	2432 (87.8)	18.8	503 (81.8)	503 (81.8)	0.0
Transfusion	100 (16.1)	333 (12.0)	11.8	99 (16.1)	105 (17.1)	2.6
Corticosteroid	471 (75.8)	1857 (67.0)	19.6	465 (75.6)	460 (74.8)	1.9
Hospital information						
Surgical volume						
Low volume (< 5)	130 (20.9)	670 (24.2)	7.8	130 (21.1)	136 (22.1)	2.4
Middle volume (5–30)	466 (75.0)	1213 (43.8)	67.1	460 (74.8)	456 (74.1)	1.5
High volume (> 30)	25 (4.0)	887 (32.0)	78.2	25 (4.1)	23 (3.7)	1.7
Teaching hospital	448 (72.1)	1707 (61.6)	22.5	442 (71.9)	436 (70.9)	2.2
Fiscal year						
2010	36 (5.8)	114 (4.1)	7.8	35 (5.7)	37 (6.0)	1.4
2011	42 (6.8)	209 (7.5)	3.0	42 (6.8)	41 (6.7)	0.6
2012	68 (11.0)	320 (11.6)	1.9	68 (11.1)	61 (9.9)	3.7
2013	111 (17.9)	499 (18.0)	0.4	109 (17.7)	106 (17.2)	1.3
2014	186 (30.0)	698 (25.2)	10.7	183 (29.8)	189 (30.7)	2.1
2015	149 (24.0)	773 (27.9)	8.9	149 (24.2)	151 (24.6)	0.8
2016	29 (4.7)	157 (5.7)	4.5	29 (4.7)	30 (4.9)	0.8

All data are described as number (%), except for age, BMI, Charlson Comorbidity Index score, and operation time

BMI body mass index, *IQR* interquartile range, *SD* standard deviation

pulmonary complications is further warranted. In Japan, some surgeons and anesthesiologists administer sivelestat prophylactically for esophagectomy based on the protective drug effects suggested by small clinical trials [10–14]. In this study, however, we did not observe any beneficial effect regarding all outcomes between patients with esophagectomy receiving prophylactic sivelestat and the matched cohort without prophylaxis. As for the secondary outcomes,

Table 2 Outcomes after propensity score adjustment

	Sivelestat	Control	Unadjusted analysis				Propensity score-adjusted analysis			
	$n = 621$	$n = 2770$	OR	95% CI	*P* value		aOR	95% CI		*P* value
Hospital mortality	33 (5.3)	81 (2.9)	1.86	1.23–2.82	0.0028		1.65	0.95–2.88		0.0772
ARDS	10 (1.6)	30 (1.1)	1.49	0.73–3.07	0.2714		1.25	0.49–3.17		0.6380
Respiratory complication	114 (18.4)	366 (13.2)	1.48	1.17–1.86	0.0009		1.24	0.91–1.67		0.1682
Sepsis	31 (5.0)	95 (3.4)	1.48	0.98–2.24	0.0628		1.15	0.68–1.95		0.5933
	Means	± SE	Means	± SE		Difference	± SE	*P* value	Difference	± SE	*P* value
Postoperative length of hospital stay	45.0	± 1.9	37.0	± 0.7		8.1	± 4.0	< 0.0001	2.5	± 4.7	0.3065

aOR adjusted odds ratio, *ARDS* acute respiratory distress syndrome, *CI* confidential interval, *SE* standard error

there were no differences in the proportion of incident cases of ARDS, respiratory complications, and sepsis, or in postoperative hospital stays between the two groups. All these results indicate that prophylactic use of sivelestat does not offer a short-term clinical benefit for patients undergoing esophagectomy, consistent with the results from the main analysis.

We further confirmed our findings through three sensitivity analyses (Table 3), wherein we (1) analyzed data using different PS methods, (2) excluded patients with a diagnosis of ARDS on the same day of surgery, and (3) used different inclusion criteria for the prophylaxis group. We conducted these analyses to observe the impact of bias inherent to retrospective observational studies. In all sensitivity analyses, prophylactic sivelestat therapy did not result in favorable outcomes for patients who underwent esophagectomy.

Our results are different from findings of previous studies [10–14], which showed a benefit of prophylactic sivelestat administration after esophagectomy. One possible reason for the difference between the results of previous studies and the current study may be differences in the outcome definition. Earlier studies found that prophylactic sivelestat was related to a reduction in inflammatory markers, improved pulmonary function, and longer ventilator-free days, all of which are so-called "surrogate" end points. In contrast, the present study assessed mortality, which is a patient-centered outcome rather than a surrogate outcome.

A strength of the present study was the use of a large dataset collected from approximately 300 hospitals accounting for approximately 20% of inpatients admitted to acute care hospitals in Japan. Moreover, this study design was set in a pragmatic context, based on a real-world clinical setting. Because of the large sample size, we were able to investigate a lower frequency event, such as mortality. Additionally, previous studies investigated several surrogate outcomes, as described above; however, they failed to evaluate mortality rates because of their small sample sizes.

A previous multinational randomized control trial, the STRIVE trial [9], showed that administration of sivelestat had no significant benefit on either 28-day mortality rate or ventilator-free days in patients with ARDS, and the 180-day mortality rate was significantly higher in the sivelestat group than in the placebo group. Thus, the STRIVE trial was stopped early because of the increase in 180-day mortality rate. In response to the unsuccessful results of this trial, most countries have not approved sivelestat, and sivelestat is not used for the treatment of ARDS except in Japan. Furthermore, the recent "Guidelines for treatment of ARDS 2016" [23], established by the Japanese Respiratory Society, do not suggest the use of neutrophil elastase inhibitors in adult patients with ARDS. Despite this clinical context, in Japan, sivelestat is used as prophylaxis for highly intensive surgery, such as esophagectomy, as well as the treatment of

Table 3 Outcomes after propensity score adjustment

Sensitivity analysis 1	Propensity score-adjusted analysis		
	aOR	95% CI	*P* value
In-hospital mortality	1.59	0.99–2.58	0.0578
ARDS	1.65	0.70–3.91	0.2561
Respiratory complications	1.24	0.96–1.61	0.1064
Sepsis	1.28	0.79–2.07	0.3167
	Difference	±SE	*P* value
Postoperative length of hospital stay	3.1	±3.4	0.0769
Sensitivity analysis 2	aOR	95% CI	*P* value
In-hospital mortality	1.24	0.73–2.10	0.4236
ARDS	2.67	0.71–10.1	0.1474
Respiratory complications	1.28	0.95–1.73	0.1092
Sepsis	1.53	0.80–2.94	0.1978
	Difference	±SE	*P* value
Postoperative length of hospital stay	5.1	±4.7	0.0348
Sensitivity analysis 3	aOR	95% CI	*P* value
In-hospital mortality	1.38	0.72–2.62	0.3324
ARDS	1.17	0.39–3.47	0.7817
Respiratory complications	1.32	0.95–1.83	0.0989
Sepsis	1.32	0.73–2.39	0.3672
	Difference	±SE	*P* value
Postoperative length of hospital stay	0.4	±4.2	0.8674

ARDS acute respiratory distress syndrome, *aOR* adjusted odds ratio, *CI* confidential interval, *SE* standard error

ARDS. The effectiveness of prophylactic sivelestat is worth reevaluation because there are no preventive strategies for respiratory complications among patients with esophagectomy. However, this is feasible only in Japan because this drug is not available elsewhere. The current results did not indicate any efficacy of sivelestat and suggest reconsidering the use of sivelestat.

We acknowledge that our study has some limitations. Firstly, the present study was a retrospective observational study using an administrative database. In this study, it was difficult to distinguish between prophylactic and therapeutic administration. It is impossible to establish causality because this study was observational rather than a randomized controlled trial. Although PS matching minimized bias relevant to indication of sivelestat, there could be a residual bias. For example, there was a substantial imbalance regarding the severity between the sivelestat and non-prophylaxis groups: patients in the sivelestat group had lower physical status, received invasive procedures more often, and had higher odds of in-hospital death in unadjusted analysis. We acknowledge that severe patients had a high likelihood of receiving prophylactic sivelestat—a bias referred to as indication bias. If the indication bias was not removed by PS matching, the beneficial effect of sivelestat could be underestimated. We confirmed that the imbalance was reduced after PS matching, with respect to the factors potentially related to prophylactic use of sivelestat (Table 1). In addition, the results were unchanged in several sensitivity analyses (Table 3). Nevertheless, the possibility remains that residual indication bias affected our results. We did not conduct instrumental variable analysis, which may be useful in case of unmeasured confounders, if a valid instrumental variable is available [24, 25]. Commonly used instrumental variables include the distance between patients' home (using zip code) and the hospital and hospitals' prescription preferences. These data were not available to us for our study and the hospital-related factors in Table 1 cannot be used as instrumental variables, since they were correlated with the hospital itself. Secondly, the database lacked information concerning several possible confounding factors; for example, short-term drug adverse events, the PaO_2/FiO_2 ratio, and severity indices such as the Acute Physiology and Chronic Health Evaluation (APACHE) II score. We were unable to determine surgery-related information, such as blood loss, surgical time, and tumor size. To partially overcome these issues, blood product use (e.g., transfusion) and anesthetic time were used as proxies for severe blood loss and surgical time to adjust for severity between groups. This allowed us to estimate the severity of surgical invasion. Thirdly, because the data source was restricted to Japan, our findings have a limitation in the extent to which they can be generalized to clinical settings outside Japan. Finally, there were sources of bias specific to research using administrative data, such as coding errors. Nonetheless, the proportion of respiratory complications in this study was 14.2% (480/3391), which is similar to the proportion of respiratory complications in a recent study from Japan on pneumonia [26].

Conclusions

We performed a propensity-matched analysis using a cohort derived from an administrative database. We found that perioperative prophylactic use of sivelestat was not related to a significant decrease in in-hospital mortality, ARDS, and respiratory complications for patients who underwent transthoracic esophagectomy in Japan. Our findings suggest that prophylactic sivelestat is not recommended for patients with esophagectomy, keeping in line with the "Less is More" initiative [27].

Acknowledgements We acknowledge Professor Kazuhiko Fukuda, M.D., Ph.D. (affiliated with Department of Anesthesia, Graduate School of Medicine, Kyoto University, Kyoto, Japan) for his valuable comments on the study. We also thank Mr. Masaki Nakamura and staff

at Medical Data Vision, Co, Ltd. (Tokyo, Japan) for data preparation assistance. We also thank Editage (http://www.editage.jp) for English language editing.

References

1. Haga Y, Beppu T, Doi K, Nozawa F, Mugita N, Ikei S, Ogawa M. Systemic inflammatory response syndrome and organ dysfunction following gastrointestinal surgery. Crit Care Med. 1997;25:1994–2000.
2. Avendano CE, Flume PA, Silvestri GA, King LB, Reed CE. Pulmonary complications after esophagectomy. Ann Thorac Surg. 2002;73:922–6.
3. Bailey SH, Bull DA, Harpole DH, Rentz JJ, Neumayer LA, Pappas TN, Daley J, Henderson WG, Krasnicka B, Khuri SF. Outcomes after esophagectomy: a ten-year prospective cohort. Ann Thorac Surg. 2003;75:217–22.
4. Bhatia M, Moochhala S. Role of inflammatory mediators in the pathophysiology of acute respiratory distress syndrome. J Pathol. 2004;202:145–56.
5. Morita M, Yoshida R, Ikeda K, Egashira A, Oki E, Sadanaga N, Kakeji Y, Ichiki Y, Sugio K, Yasumoto K, Maehara Y. Acute lung injury following an esophagectomy for esophageal cancer, with special reference to the clinical factors and cytokine levels of peripheral blood and pleural drainage fluid. Dis Esophagus. 2008;21:30–6.
6. Tamakuma S, Ogawa M, Aikawa N, Kubota T, Hirasawa H, Ishizaka A, Taenaka N, Hamada C, Matsuoka S, Abiru T. Relationship between neutrophil elastase and acute lung injury in humans. Pulmon Pharmacol Ther. 2004;17:271–9.
7. Aikawa N, Ishizaka A, Hirasawa H, Shimazaki S, Yamamoto Y, Sugimoto H, Shinozaki M, Taenaka N, Endo S, Ikeda T, Kawasaki Y. Reevaluation of the efficacy and safety of the neutrophil elastase inhibitor, Sivelestat, for the treatment of acute lung injury associated with systemic inflammatory response syndrome; a phase IV study. Pulmon Pharmacol Ther. 2011;24:549–54.
8. Hayakawa M, Katabami K, Wada T, Sugano M, Hoshino H, Sawamura A, Gando S. Sivelestat (selective neutrophil elastase inhibitor) improves the mortality rate of sepsis associated with both acute respiratory distress syndrome and disseminated intravascular coagulation patients. Shock. 2010;33:14–8.
9. Zeiher BG, Artigas A, Vincent J-L, Dmitrienko A, Jackson K, Thompson BT, Bernard G. Neutrophil elastase inhibition in acute lung injury: results of the STRIVE study. Crit Care Med. 2004;32:1695–702.
10. Iwahashi M, Nakamori M, Nakamura M, Ojima T, Naka T, Yamaue H. Optimal period for the prophylactic administration of neutrophil elastase inhibitor for patients with esophageal cancer undergoing esophagectomy. World J Surg. 2011;35:1573–9.
11. Kawahara Y, Ninomiya I, Fujimura T, Funaki H, Nakagawara H, Takamura H, Oyama K, Tajima H, Fushida S, Inaba H, Kayahara M. Prospective randomized controlled study on the effects of perioperative administration of a neutrophil elastase inhibitor to patients undergoing video-assisted thoracoscopic surgery for thoracic esophageal cancer. Dis Esophagus. 2010;23:329–39.
12. Makino H, Kunisaki C, Kosaka T, Akiyama H, Morita S, Endo I. Perioperative use of a neutrophil elastase inhibitor in video-assisted thoracoscopic oesophagectomy for cancer. Br J Surg. 2011;98:975–82.
13. Nagai Y, Watanabe M, Baba Y, Iwatsuki M, Hirashima K, Karashima R, Kurashige J, Kinoshita K, Baba H. Preventive effect of sivelestat on postoperative respiratory disorders after thoracic esophagectomy. Surg Today. 2013;43:361–6.
14. Nishiyama J, Matsuda M, Ando S, Hirasawa M, Suzuki T, Makuuchi H. The effects of the early administration of sivelestat sodium, a selective neutrophil elastase inhibitor, on the postoperative course after radical surgery for esophageal cancer. Surg Today. 2012;42:659–65.
15. Wang ZQ, Chen LQ, Yuan Y, Wang WP, Niu ZX, Yang YS, Cai J. Effects of neutrophil elastase inhibitor in patients undergoing esophagectomy: a systematic review and meta-analysis. World J Gastroenterol. 2015;21:3720–30.
16. Ishii M. DRG/PPS and DPC/PDPS as Prospective Payment Systems. Jpn Med Assoc J. 2012;55:279–91.
17. Tanaka S, Seto K, Kawakami K. Pharmacoepidemiology in Japan: medical databases and research achievements. J Pharmaceut Health Care Sci. 2015;1:16.
18. Fuji T, Akagi M, Abe Y, Oda E, Matsubayashi D, Ota K, Kobayashi M, Matsushita Y, Kaburagi J, Ibusuki K, Takita A, Iwashita M, Yamaguchi T. Incidence of venous thromboembolism and bleeding events in patients with lower extremity orthopedic surgery: a retrospective analysis of a Japanese healthcare database. J Orthopaed Surg Res. 2017;12:55.
19. Kanazawa Y, Takeuchi M, Tateya I, Omori K, Kawakami K. Clinical epidemiology of tracheal invasion from thyroid cancer in Japanese population: functional outcomes and effect of aging. Cancer Epidemiol. 2017;50:107–12.
20. Yamana H, Moriwaki M, Horiguchi H, Kodan M, Fushimi K, Yasunaga H. Validity of diagnoses, procedures, and laboratory data in Japanese administrative data. J Epidemiol. 2017;27:476–82.
21. Austin PC. Propensity-score matching in the cardiovascular surgery literature from 2004 to 2006: a systematic review and suggestions for improvement. J Thorac Cardiovasc Surg. 2007;134:1128–35.
22. Law S, Wong KH, Kwok KF, Chu KM, Wong J. Predictive factors for postoperative pulmonary complications and mortality after esophagectomy for cancer. Ann Surg. 2004;240:791–800.
23. Hashimoto S, Sanui M, Egi M, Ohshimo S, Shiotsuka J, Seo R, Tanaka R, Tanaka Y, Norisue Y, Hayashi Y, Nango E. The clinical practice guideline for the management of ARDS in Japan. J Intensive Care. 2017;5:50.
24. Tagami T, Matsui H, Ishinokami S, Oyanagi M, Kitahashi A, Fukuda R, Unemoto K, Fushimi K, Yasunaga H. Amiodarone or nifekalant upon hospital arrival for refractory ventricular fibrillation after out-of-hospital cardiac arrest. Resuscitation. 2016;109:127–32.
25. Tagami T, Matsui H, Fushimi K, Yasunaga H. Supplemental dose of antithrombin use in disseminated intravascular coagulation patients after abdominal sepsis. Thromb Haemost. 2015;114:537–45.
26. Takeuchi H, Miyata H, Gotoh M, Kitagawa Y, Baba H, Kimura W, Tomita N, Nakagoe T, Shimada M, Sugihara K, Mori M. A risk model for esophagectomy using data of 5354 patients included in a Japanese nationwide web-based database. Ann Surg. 2014;260:259–66.
27. Malhotra A, Maughan D, Ansell J, Lehman R, Henderson A, Gray M, Stephenson T, Bailey S. Choosing Wisely in the UK: the Academy of Medical Royal Colleges' initiative to reduce the harms of too much medicine. Br Med J. 2015;350:h2308.