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ORIGINAL ARTICLE

Sivelestat sodium and mortality in pneumonia patients requiring mechanical ventilation: propensity score analysis of a Japanese nationwide database

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Abstract
Purpose Sivelestat is widely used in Japan for the treatment of acute respiratory distress syndrome caused by pneumonia. Although the efficacy of sivelestat was reported in several Japanese studies in the early 2000 s, a multinational randomized control trial did not support these findings. We therefore conducted the present study to examine the association between the use of sivelestat and mortality in pneumonia patients requiring mechanical ventilation.
Methods We conducted a retrospective observational study using the Diagnosis Procedure Combination database, a national inpatient database in Japan. We identified pneumonia patients requiring mechanical ventilation who were hospitalized between April 2012 and March 2014. Propensity score matching was performed to compare 7- and 30-day mortality between patients with and without sivelestat use.
Results The eligible patients (n = 16,471) were categorized into the sivelestat (n = 1707) and control (n = 14,764) groups. The unmatched comparison showed significant differences between the sivelestat and control groups in both 7-day mortality (11.0 vs. 7.6%, $p < 0.001$) and 30-day mortality (29.9 vs. 19.7%, $p < 0.001$). In the 1516 pairs of propensity-matched patients, there were no significant differences in 7-day mortality (sivelestat vs. control: 10.2 vs. 10.9%, $p = 0.516$) and 30-day mortality (sivelestat vs. control 29.0 vs. 29.0%, $p = 1.000$).
Conclusions The propensity-matched analyses revealed that the use of sivelestat was not associated with decreased mortality for pneumonia patients requiring mechanical ventilation.

Keywords Acute respiratory distress syndrome · Outcomes assessment · Pneumonia · Propensity score matching · Sivelestat

Introduction

Sivelestat sodium is a neutrophil elastase inhibitor. Based on the favorable results of a clinical trial reported in 1998, sivelestat sodium has been widely used for the treatment of acute respiratory distress syndrome (ARDS) in Japan [1]. As pneumonia is reported to be the most frequent cause of ARDS [2, 3], sivelestat is administered to severe pneumonia patients, most of whom have ARDS as a complication. Since the 1998 trial, the efficacy of sivelestat has been reported in several Japanese studies [1, 4–7], most of which only showed short-term improvement of oxygenation.

It remains controversial as to whether sivelestat is effective in decreasing mortality. Several randomized controlled trials (RCTs) in Japan showed that the use of sivelestat for ARDS patients was not associated with either increased or decreased mortality. A meta-analysis of eight RCTs

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reported that sivelestat use improved short-term PaO_2/FiO_2 (P/F) ratio, but was not associated with mortality in patients with acute lung injury (ALI) [8] or ARDS, while a non-randomized trial [4] showed decreased 180-day mortality in the sivelestat group. Several Japanese studies have also suggested that early sivelestat use could reduce mortality in ARDS patients [9]. However, a previous multinational RCT showed no significant differences in 28-day mortality or ventilator free days in ALI patients requiring mechanical ventilation between the sivelestat and control groups [10].

All of the RCTs for sivelestat were conducted in the early 2000s, and we believe a reevaluation of this drug is essential in light of recent advances in intensive care medicine.

We therefore conducted the present study using a national inpatient database in Japan to examine the association between sivelestat use and decreased mortality in pneumonia patients requiring mechanical ventilation.

Methods

The present study was approved by the Institutional Review Board of The University of Tokyo. The requirement for informed consent from the patients was waived because of the anonymous nature of the data.

Sivelestat use and ARDS diagnosis in Japan

Sivelestat is administered to ARDS patients who satisfy the following criteria for both systemic inflammatory response syndrome (SIRS) [11] and ALI [12]. The diagnostic criteria of SIRS are as follows: (1) body temperature of >38 or <36 °C, (2) heart rate of >90/min (3) respiratory rate of >20/min or $PaCO_2$ of <32 mmHg, and (4) WBC of >12,000/μl or <4000/μl or band cells of >10%. The diagnostic criteria of ALI included: (1) decreased pulmonary function (PaO_2/FiO_2 ≤300 mmHg under control of mechanical ventilation, (2) chest X-ray showing bilateral infiltrative shadow, (3) pulmonary arterial wedge pressure of ≤18 mmHg when it is measured, or no clinical finding of increased left arterial pressure when it is not measured. The use of sivelestat is approved by the Japanese Ministry of Health, Labour and Welfare, when two or more of the criteria for SIRS and all of the criteria for ALI are met. The daily dose of sivelestat sodium is 4.8 mg/kg with a continuous infusion for 24 h (0.2 mg/kg/h). The maximum infusion period for sivelestat is 14 days.

Data source

The Diagnosis Procedure Combination (DPC) database is a national administrative claims and discharge abstract database of acute-care inpatients in Japan [13]. The database includes data on approximately 7 million inpatients from more than 1000 participating hospitals, which covers more than 50% of acute-care hospitalizations in Japan. The database includes information on age; sex; primary diagnosis; comorbidities at admission and complications after admission; medical procedures (including surgery, which is coded with original Japanese codes); daily records of drug administration and treatments; date of admission and discharge; and Japan Coma Scale (JCS) at admission. A JCS score of 0 indicates alert consciousness, scores of 1–3 indicate wakefulness without any stimuli, scores of 10–30 indicate arousal by some stimuli and scores of 100–300 indicate coma [13]. Each diagnosis is classified according to the International Classification of Diseases, 10th Revision. Six types of diagnostic information are recorded in the DPC database: "main diagnosis", "admission-precipitating diagnosis", "most resource-consuming diagnosis", "second most resource-consuming diagnosis", "comorbidities present on admission" and "conditions arising after admission" [14]. Physicians are responsible for accurately recording patient data at discharge with reference to medical records, because the diagnosis records are linked to the payment system and reimbursement [15]. Also, we collected hospital-level data from The Annual Report for Functions of Medical Institutions [16].

Patient selection

Data of patients hospitalized between April 2012 and March 2014 were extracted from the DPC database. We identified patients with pneumonia (ICD 10 codes, J10-18) recorded in either "main diagnosis" or "admission-precipitating diagnosis" and included patients requiring mechanical ventilation within 2 days of admission. We excluded patients (1) who started mechanical ventilation 3 days after admission or who did not receive mechanical ventilation, (2) who died within 2 days of admission, (3) whose hospital characteristics and JCS data were missing, (4) who were not prescribed a β-lactam antibiotic during hospitalization, and (5) who were diagnosed as atypical pneumonia (J10-12, 16, 17).

We defined patients who used sivelestat within 2 days of admission as the sivelestat group. Those who did not use sivelestat were defined as the control group.

Outcome

The outcomes of this study were 7- and 30-day mortality.

Statistical analyses

We conducted one-to-one propensity score matching between the sivelestat and control groups. We estimated propensity scores with a logistic regression with use of sivelestat as a dependent variable. Independent variables included age; sex; hospital characteristics (academic or non-academic hospitals and the number of hospital beds); body mass index (BMI); JCS; coexisting respiratory disorders including chronic obstructive pulmonary disease (COPD), asthma, aspiration and pulmonary effusion; existence of heart failure; intermittent hemodialysis: continuous hemodiafiltration (CHDF): extra-corporeal membrane oxygenation (ECMO); use of catecholamine (noradrenaline and dopamine); use of antibiotics; use of drugs for disseminated intravascular coagulation (DIC); use of steroids; use of albumin; use of immunoglobulin; and use of blood transfusion. We ranked β-lactam antibiotics according to their spectrum as in a previous study [17] (Supplementary Table 1). C-statistic was calculated for evaluating the goodness of fit. We set a cut-off at 0.2 of the standard deviation of the estimated propensity scores to achieve a good balance of patient backgrounds between the sivelestat and control groups. We compared 7- and 30-day mortality between the sivelestat and control groups using Chi-square tests and performed a subgroup analysis for patients with and without heart failure. Survival time analysis was conducted using Kaplan–Meier survival plots and log-rank tests in the matched patients. The A-DROP (age, dehydration, respiration, orientation, blood pressure) criteria of the Japanese Respiratory Society [18] was available in the DPC database. However, because value was missing in approximately 30% of the eligible patients, the A-DROP score was not used as a variable. To evaluate the effect of this exclusion, we performed two sensitivity analyses. First, we used direct method, making a new category for patients with missing data. Second, we conducted a complete-case analysis, excluding patients with missing data.

A p value of <0.05 was considered as significant. Statistical analysis was performed with IBM SPSS for Windows, version 22.0 (IBM, Armonk, NY, USA).

Results

During the study period, 41,516 pneumonia patients requiring mechanical ventilation were enrolled in this study (Fig. 1). After excluding 25,045 patients, we identified 16,471 eligible patients, including the sivelestat group ($n = 1707$) and the control group ($n = 14{,}764$). One-to-one propensity score matching created 1516 pairs of patients. The C-statistic was 0.841.

Table 1 shows the baseline characteristics of all eligible patients ($n = 16{,}471$) and propensity-matched patients ($n = 3032$). Before propensity score matching, patients in the sivelestat group were more likely to be older and male; be admitted to academic and high-capacity hospitals; have CHDF and ECMO; receive a greater variety of antibiotics including those of higher rank; receive catecholamines, drugs for DIC, and blood transfusion. They were less likely to have asthma and COPD. After propensity score matching, the baseline characteristics were well balanced between the groups.

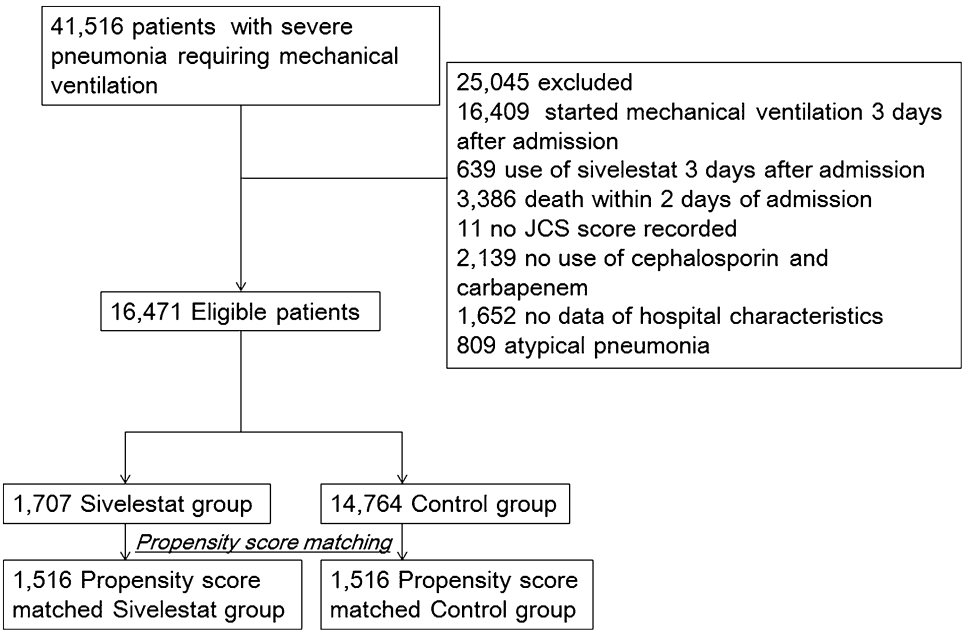

Fig. 1 Patients selection. *JCS* Japan Coma Scale

Table 1 Baseline characteristics of all eligible patients and propensity-matched patients

Variable	All eligible patients			Propensity-matched patients		
	Sivelestat ($n = 1707$)	Control ($n = 14,746$)	Standardized difference	Sivelestat ($n = 1516$)	Control ($n = 1516$)	Standardized difference
Age, mean ± SD	72.35 ± 14.33	65.87 ± 27.00	−28.3	72.62 ± 10.30	73.27 ± 9.84	6.4
Male, *n* (%)	1220 (71.5)	9342 (63.3)	−14.5	1082 (71.4)	1097 (72.4)	1.8
Academic hospital, *n* (%)	319 (18.7)	1946 (13.2)	−12.0	245 (16.2)	245 (16.2)	0.0
Hospital beds, *n* (%)						
≤99	10 (0.6)	177 (1.2)	5.7	9 (0.6)	12 (0.8)	2.0
100–499	829 (48.6)	8178 (55.4)	11.2	757 (49.9)	768 (50.7)	1.2
≥500	868 (50.8)	6409 (43.4)	−12.2	750 (49.5)	736 (48.5)	−1.5
BMI (kg/m^2), *n* (%)						
<25.0	1160 (68.0)	10,895 (73.8)	10.4	1039 (68.5)	1020 (67.3)	−2.2
25.0–34.9	221 (12.9)	1307 (8.9)	−10.5	186 (12.3)	184 (12.1)	−0.3
≥35.0	21 (1.2)	138 (0.9)	−2.3	20 (1.3)	22 (1.5)	0.9
Missing	305 (17.9)	2424 (16.4)	−3.1	271 (17.9)	290 (19.1)	2.6
JCS score, *n* (%)						
0	874 (51.2)	8287 (56.1)	8.0	781 (51.5)	715 (47.2)	−7.1
1–3	385 (22.6)	2780 (18.8)	−7.4	341 (22.5)	374 (24.7)	4.2
10–30	178 (10.4)	1499 (10.2)	−0.7	158 (10.4)	170 (11.2)	2.1
100–300	270 (15.8)	2198 (14.9)	−2.1	236 (15.6)	257 (17.0)	3.1
Respiratory diseases, *n* (%)						
Asthma	45 (2.6)	1190 (8.1)	21.2	43 (2.8)	29 (1.9)	−4.8
COPD	68 (4.0)	1203 (8.1)	15.1	66 (4.4)	54 (3.6)	−3.3
Pleural effusion	74 (4.3)	661 (4.5)	0.6	68 (4.5)	71 (4.7)	0.8
Aspiration	16 (0.9)	172 (1.2)	1.9	16 (1.1)	17 (1.1)	0.5
Heart failure, *n* (%)	506 (29.6)	5016 (34.0)	7.6	459 (30.3)	466 (30.7)	0.8
Interventions, *n* (%)						
Intermittent hemodialysis	39 (2.3)	293 (2.0)	−1.7	32 (2.1)	31 (2.0)	−0.4
CHDF	117 (6.9)	245 (1.7)	−19.3	81 (5.3)	80 (5.3)	−0.2
ECMO	17 (1.0)	26 (0.2)	−7.9	12 (0.8)	10 (0.7)	−1.3
Catecholamines, *n* (%)						
Dopamine	722 (42.3)	2939 (19.9)	−39.3	598 (39.4)	629 (41.5)	3.4
Noradrenaline	505 (29.6)	1859 (12.6)	−33.1	396 (26.1)	404 (26.6)	1.0
Antimicrobial rank						
1	12 (0.7)	546 (3.7)	19.0	12 (0.8)	8 (0.5)	−2.6
2	164 (9.6)	3425 (23.2)	32.4	158 (10.4)	159 (10.5)	0.2
3	152 (8.9)	3083 (20.9)	29.6	150 (9.9)	136 (9.0)	−2.6
4	303 (17.8)	3842 (26.0)	16.8	287 (18.9)	297 (19.6)	1.4
5	1076 (63.0)	3868 (26.2)	−64.2	909 (60.0)	916 (60.4)	0.8
Other antimicrobials, *n* (%)						
Aminoglycoside	8 (0.5)	112 (0.8)	3.2	6 (0.4)	4 (0.3)	−1.8
Fluoroquinolone	351 (20.6)	904 (6.1)	−33.4	279 (18.4)	293 (19.3)	1.9
Tetracycline	148 (8.7)	530 (3.6)	−16.4	121 (7.9)	112 (7.4)	−1.8
Macrolide	142 (8.3)	733 (5.0)	−10.6	119 (7.8)	117 (7.7)	−0.4
Lincomycin	93 (5.4)	389 (2.6)	−11.1	77 (5.1)	76 (5.0)	−0.2
Anti-MRSA drug	108 (6.3)	534 (3.6)	−9.8	85 (5.6)	105 (6.9)	4.5
Antifungal drug	94 (5.5)	194 (1.3)	−17.3	68 (4.5)	68 (4.5)	0.0

Table 1 continued

Variable	All eligible patients			Propensity-matched patients		
	Sivelestat ($n = 1707$)	Control ($n = 14,746$)	Standardized difference	Sivelestat ($n = 1516$)	Control ($n = 1516$)	Standardized difference
DIC drugs, *n* (%)						
Thrombomodulin	147 (8.6)	232 (1.6)	−23.9	97 (6.4)	94 (6.2)	−0.7
Danaparoid sodium	17 (1.0)	54 (0.4)	−5.8	16 (1.1)	16 (1.1)	0.0
Gabexate mesilate	92 (5.4)	117 (0.8)	−19.6	63 (4.2)	51 (3.4)	−3.3
Ulinastatin	55 (3.2)	35 (0.2)	−16.6	29 (1.9)	24 (1.6)	−2.0
Antithrombin	176 (10.3)	254 (1.7)	−27.0	118 (7.8)	119 (7.8)	0.2
Steroid, *n* (%)	826 (48.4)	4012 (27.2)	−35.9	708 (46.7)	705 (46.5)	−0.3
Immunoglobulin, *n* (%)	536 (31.4)	671 (4.5)	−55.1	378 (24.9)	350 (23.1)	−2.6
Albumin, *n* (%)	396 (23.2)	839 (5.7)	−38.7	274 (18.1)	267 (17.6)	−1.0
Blood transfusion, *n* (%)						
Red blood cells	182 (10.7)	590 (4.0)	−19.7	141 (9.3)	138 (9.1)	−0.6
Fresh frozen plasma	68 (4.0)	157 (1.1)	−14.0	45 (3.0)	40 (2.6)	−1.6
Platelets	48 (2.8)	106 (0.7)	−11.9	38 (2.5)	31 (2.0)	−2.5

SD standard deviation, *BMI* body mass index, *JCS* Japan Coma Scale, *COPD* chronic obstructive pulmonary disease, *CHDF* continuous hemodiafiltration, *ECMO* extracorporeal membrane oxygenation system, *MRSA* methicillin-resistant *Staphylococcus aureus*

Table 2 Comparison of 7- and 30-day mortality between sivelestat and control groups

	Sivelestat, % (no.)	Control, % (no.)	*p* value
7-day mortality			
All eligible patients	11.0 (187/1707)	7.6 (1127/14764)	<0.001
Propensity-matched patients	10.2 (154/1516)	10.9 (166/1516)	0.516
30-day mortality			
All eligible patients	29.9 (511/1707)	19.7 (2902/14764)	<0.001
Propensity-matched patients	29.0 (439/1516)	29.0 (440/1516)	1.000

Table 3 Relative risk and risk difference of 7- and 30-day mortality in propensity-matched patients

Outcome	Relative risk	95% CI	Risk difference	95% CI
7-day mortality	0.928	0.754–1.141	0.008	−0.014 to 0.030
30-day mortality	0.998	0.892–1.115	0.001	−0.032 to 0.033

CI confidence interval

Table 2 shows comparison of the 7- and 30-day mortality between the groups. Before matching, there were significant differences between the sivelestat and control groups in both 7-day mortality (sivelestat vs. control 11.0 vs. 7.6%, $p < 0.001$) and 30-day mortality (sivelestat vs. control 29.9 vs. 19.7%, $p < 0.001$). After propensity score matching, there were no significant differences in 7-day mortality (sivelestat vs. control 10.2 vs. 10.9%, $p = 0.516$) and 30-day mortality (sivelestat vs. control 29.0 vs. 29.0%, $p = 1.000$). Relative risks and risk differences in 7- and 30-day mortality are shown in Table 3.

Of the 16,471 eligible patients, there were 4951 without an A-DROP score. Results of the two sensitivity analyses were similar to the main analysis. After propensity score matching, there were no significant differences in 7-day mortality and 30-day mortality between the sivelestat and control groups.

The results of the subgroup analyses are shown in Table 4. There were no significant differences in mortality between the sivelestat and control groups in patients with and without heart failure. The Kaplan–Meier survival curves for the propensity score-matched sivelestat and control groups are shown in Fig. 2. There was no significant difference between the sivelestat and control groups (log-rank Chi-square 0.852, $p = 0.356$).

Table 4 Subgroup analysis of 7- and 30-day mortalities in propensity-matched groups

	Sivelestat, % (no.)	Control, % (no.)	*p* values	Odds ratio (95% CI)
7-day mortality				
With heart failure	7.0 (30/426)	10.6 (45/426)	0.090	0.6 (0.4–1.0)
Without heart failure	11.7 (123/1049)	12.5 (131/1049)	0.639	0.9 (0.7–1.2)
30-day mortality				
With heart failure	26.1 (111/426)	28.6 (122/426)	0.442	0.9 (0.6–1.2)
Without heart failure	30.2 (317/1049)	30.3 (318/1049)	1.000	1.0 (0.8–1.2)

CI confidence interval

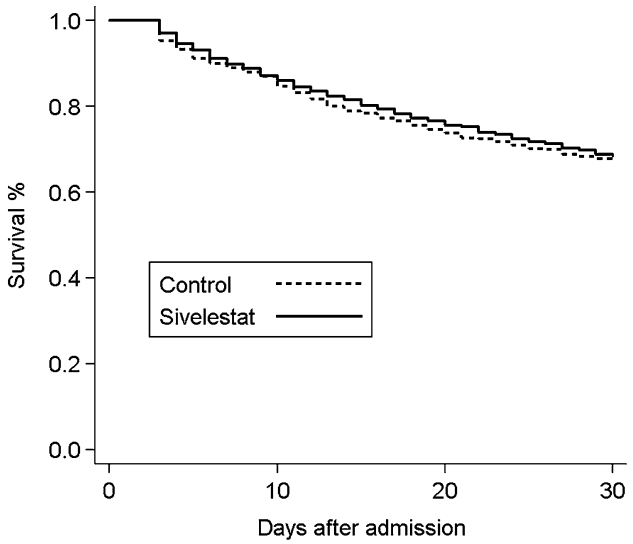

Fig. 2 Kaplan–Meier survival plots for patients treated with or without sivelestat in propensity-matched groups

Discussion

Using a national inpatient database in Japan, our propensity-score matched analysis showed no significant association between sivelestat use and mortality in pneumonia patients requiring mechanical ventilation.

Previous studies on the efficacy of sivelestat were limited due to small sample sizes [4, 6, 10]. A strength of this study was the use of a large dataset collected from approximately 1000 hospitals across Japan. Also, previous studies used several surrogate outcomes, including length of stay in the intensive care unit, ventilator free days (VFD) or respiratory function. However, these studies failed to evaluate mortality because of their small sample sizes. Another strength of the present study was the assessment of mortality.

It is notable that there were significant differences in mortality between the sivelestat and control groups before propensity score matching. The sivelestat group was more likely to receive treatments and interventions, suggesting that the sivelestat group had multiple complications in addition to pneumonia.

Propensity score matching is a powerful tool by which we can simulate a randomized experiment-like situation by comparing groups with similar observed characteristics without specifying the relationships between confounders and outcomes [19, 20]. After propensity score matching, we found no significant differences in either 7- or 30-day mortality between the sivelestat and control groups.

Mortality of ARDS patients was reported to be 35–65% in previous studies from 1985 and 2004 [21–24]. In a systematic review of 72 studies between 1994 and 2006, the overall pooled mortality rate for all studies was 43% and there was a decrease in overall mortality rates of approximately 1.1% per year over the period [25]. In the present study, 30-day mortality of the pneumonia patients requiring mechanical ventilation was 29.0% (439/1516) in the sivelestat group after propensity score matching. This was comparable with mortality of ARDS patients in previous studies, considering the decrease in mortality of ARDS patients over time. This implies that candidates for sivelestat use were successfully selected into our cohort.

A previous multinational RCT showed that sivelestat use had no significant effect on either 28-day mortality or VFD in the patients with ALI [10]. In an RCT for ALI patients with SIRS, sivelestat was effective in shortening VFD, but there was no significant decrease in mortality [6]. These studies failed to show the effect of sivelestat on decreasing mortality of ARDS patients. The present study also did not show a significant association between sivelestat use and decreasing mortality.

Pathogenesis of ARDS is a noncardiogenic pulmonary edema caused by severe inflammation of endothelial or epithelial cells of alveolar walls [26]. Neutrophil elastase secreted from activated neutrophils damages alveolar walls, and sivelestat, a neutrophil elastase inhibitor, was therefore believed to be effective for ARDS. However, ARDS is a complex inflammatory condition in which other inflammatory cells are also activated. Thus, suppression of neutrophil activation may not be sufficient for treating ARDS.

Several limitations of this study should be acknowledged. The present study was a retrospective observational

study using an administrative database. The database lacked information of microorganisms in the lower respiratory tract, and other respiratory diseases cannot be completely excluded. Also, some patients could have been intubated for reasons other than respiratory failure due to pneumonia. Data on several possible confounders were not available: for example, P/F ratio, radiological findings, and severity index such as Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score, lung injury score, and DIC score [14]. Although the A-DROP score was available in the DPC database, approximately 30% of the patients lacked the information, and the score was not used in our analysis. Nevertheless, the results of the two sensitivity analyses support the robustness of our findings. In addition, dosages of used drugs and data on ventilator settings were not available. Lastly, we included pneumonia patients under mechanical ventilation since pneumonia is reported to be the most frequent and important cause of ARDS [2, 3], and atypical pneumonia patients were not enrolled. The results may not be generalizable to other ARDS patients.

In conclusion, in this large retrospective nationwide database study using propensity score matching, there was no apparent relationship between use of sivelestat and mortality in pneumonia patients requiring mechanical ventilation.

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