Neutrophil Elastase Inhibitor (Sivelestat) in the Treatment of Acute Respiratory Distress Syndrome Induced by COVID- 19: A Multicenter Retrospective Cohort Study

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Abstract

Background

Recent studies suggest that neutrophil elastase inhibitor (Sivelestat) may improve pulmonary function and reduce mortality in patients with acute respiratory distress syndrome. We examined the association between receipt of sivelestat and improvement in oxygenation among patients with acute respiratory distress syndrome (ARDS) induced by COVID-19.

Methods

A large multicentre cohort study of patients with ARDS induced by COVID-19 who had been admitted to intensive care units (ICUs). We used propensity score matching to compare the outcomes of patients treated with sivelestat to those who were not. The differences in continuous outcomes were assessed with the Wilcoxon signed-rank test. Kaplan-Meier method was used to show the 28-day survival curves in the matched cohorts. A log-rank P-test stratified on the matched pairs was used to test the equality of the estimated survival curves. A Cox proportional hazards model that incorporated a robust sandwich-type variance estimator to account for the matched nature of the data was used to estimate hazard ratios (HR). All statistical analyses were performed with SPSS 26.0 and R 4.2.3. A two-sided p-value of < 0.05 was considered statistically significant.

Results

A total of 387 patients met inclusion criteria, including 259 patients (66.9%) who were treated with sivelestat. In 158 patients matched on the propensity for treatment, receipt of sivelestat was associated with improved oxygenation, decreased Murray lung injury score, increased non-mechanical ventilation time within 28 days, increased alive and ICU-free days within 28 days (HR, 1.85; 95% CI, 1.29 to 2.64; log-rank $p < 0.001$), shortened ICU stay and ultimately improved survival (HR, 2.78; 95% CI, 1.32 to 5.88; log-rank $p = 0.0074$).

Conclusions

Among patients with ARDS induce by COVID-19, sivelestat administration is associated with improved clinical outcomes.

Introduction

The global health and economic impact of the Coronavirus Disease 2019 (COVID-19) pandemic is profound. Almost all cases of severe COVID-19 develop acute respiratory distress syndrome (ARDS) and respiratory failure requiring invasive mechanical ventilation, with mortality of approximate 50%[1, 2].

Recent advances in management strategies, for instance, low tidal volume lung-protective ventilation, prone position, have improved the survival of patients with ARDS. However, the treatment for ARDS remains supportive and no effective pharmacological interventions have been proven to reduce mortality of ARDS till now.

In patients with COVID-19, the inflammatory cytokine storm triggered by viral infection destroys the endothelial layer and induces endothelial cell leakage in the lungs[3], and then neutrophils migrate into the alveoli and release large amounts of toxic mediators, including reactive oxygen species and proteases, especially, neutrophil elastase (NE)[4, 5]. The available preclinical and clinical data suggest that NE can cause endothelial injury and increase capillary permeability, which may contribute to the development and progression of ARDS[6, 7]. Additionally, elastase has been shown to activate the spikes proteins of coronaviruses and mediate viral entry[8, 9].

Sivelestat, as a small molecule weight, selective and reversible NE inhibitor, was discovered by a Japanese pharmaceutical company in 1990s[10] and proven to exert substantial protective effects on acute lung injury in animal models[11, 12]. Furthermore, several clinical studies indicated that sivelestat improved pulmonary function, reduced the duration of mechanical ventilation, shorten the length of intensive care unit (ICU) stay and improved 180-day survival rates in ARDS[13, 14]. While an international multicentre double-blind, placebo-controlled Phase II study (STRIVE study) failed to show the effects of sivelestat on 28-day mortality or ventilator-free days in mechanically ventilated patients with ARDS[15].

Overall, these studies do not provide a general consensus on the clinical use of sivelestat and there is still lacking of evidence to support the use of NE inhibitors in ARDS induced by COVID-19. We therefore examined the association between receipt of sivelestat and improvement in oxygenation among a large multicentre cohort of patients with ARDS induced by COVID-19.

Materials and Methods

Setting and subjects

We conducted a retrospective cohort study of patients admitted between December 2022 and May 2023 to general ICUs, respiratory ICUs and emergency ICUs across 14 hospitals in Jilin Province, China. Patients were included in this study if they 1) were equal to or more than 18 years old, 2) had positive COVID-19 reverse transcriptase-polymerase chain reaction test results from upper airway swab, 3) fulfilled the Berlin definition of ARDS[16]. We excluded pregnant or lactating women, those with concomitant severe chronic respiratory diseases or end-stage malignant tumours, patients with duration of hospital stay or sivelestat administration less than 72 hours and patients for whom complete outcome data were not available. Permission to conduct the study was obtained from the Ethics Committee of the First Hospital of Jilin University (No.22K091-001; December 18, 2022; Clinical study of neutrophil elastase in treating ARDS caused by infection), informed consent was waived and data were anonymously collected. We followed the procedures as per the ethical standards of the institute's ethics committee on

human experimentation and according to the Declaration of Helsinki of 1975. Sivelestat sodium was administered through a 24-hour continuous intravenous infusion at a rate of 0.2 mg/kg/h, for a maximum duration of 14 days.

Data collection

All data were collected via the Electronic Data Capture System (EDC) through its web submission portal (nextedc.cn). Data included age, gender, body mass index (BMI), medical history (including diabetes, hypertension, coronary heart disease and cerebrovascular disease), COVID-19 vaccination history, Acute Physiology and Chronic Health Evaluation (APACHE) II score and Sequential Organ Failure Assessment (SOFA) score at admission, oxygenation index (PaO_2/FiO_2) and Murray lung injury score at various time points, routine biochemistry and hematology variables, and concomitant treatment, including prone position, albumin, glucocorticoids, antiviral agents, antibiotics, anti-inflammatory agents, and immunomodulatory medications.

The Murray lung injury score was proposed by Murray in 1988 as a metric for evaluating acute lung injury[17]. This scoring system evaluates the severity of lung injury based on four components: chest radiographs, hypoxemia levels, positive end-expiratory pressure (PEEP), and respiratory system compliance. More details in **Supplementary Table 1**.

Outcomes

The primary outcome was the PaO_2/FiO_2 ratio on Day 3. Secondary outcomes included 28-day mortality, alive and ICU-free days within 28 days, non-mechanical ventilation time within 28 days, the lengths of stay in the ICU and hospital, proportion of patients requiring extracorporeal membrane oxygenation (ECMO), proportion of patients undergoing endotracheal intubation or tracheotomy, and incidence of adverse events (AEs) or severe adverse events (SAEs).

Statistical Analysis

The Shapiro-Wilk test was used to determine continuous variable normality. Continuous data were reported as mean (standard deviation, SD) or median (interquartile range, IQR) for normally distributed and skewed data, respectively. Categorical data was summarized using counts and percentages. The intergroup difference was compared using the t test or the Wilcoxon rank-sum test for continuous variables, depending on their normality, and the χ^2 test or Fisher exact test for categorical data.

Propensity score matching (PSM) analysis was used to control potential confounders. Patients who received sivelestat treatment were matched 1:1 with patients not using their propensity score. We followed three rules to choose the variables for PSM: (1) potential baseline differences between groups with a p value less than 0.10; (2) potentially relevant variables according to previous studies and clinical considerations; and (3) missing data less than 20%. Collinearity was additionally tested to ensure the independence of each variable. As a result, gender, admission APACHE II score, Murray lung injury score, ICU admission, concomitant albumin use, concomitant antiviral agents use, concomitant anti-

inflammatory medications use, admission serum creatinine, and white blood cell count (WBC) were involved. Multiple Imputation, using Categorical and Regression Trees (CART), was employed to impute missing values for baseline covariates using the R package 'mice'. Patients were matched using the nearest-neighbour algorithm with a calliper width of 0.10 using R package “MatchIT”. Standardized mean difference (SMD) was used to assess the balance of baseline covariates between treatment groups in the matched sample with that in the unmatched sample. A SMD of more than 0.1 and a 2-sided P value of less than 0.05 indicated a significant imbalance in the baseline covariate.

For the matched pairs, the difference in binomial outcomes between groups was assessed with the McNemar test. The differences in continuous outcomes were assessed with the Wilcoxon signed-rank test. Kaplan-Meier method was used to show the 28-day survival curves in the matched cohorts. A log-rank P-test stratified on the matched pairs was used to test the equality of the estimated survival curves. A Cox proportional hazards model that incorporated a robust sandwich-type variance estimator to account for the matched nature of the data was used to estimate hazard ratios (HR).

All statistical analyses were performed with SPSS 26.0 and R 4.2.3. A two-sided p-value of < 0.05 was considered statistically significant.

Results

Cohort Characteristics

A total of 387 patients were enrolled in this study (Fig. 1). Compared with those who did not receive sivelestat therapy, 259 patients (66.9%) treated with sivelestat had a lower severity of disease on admission, manifested as lower APACHEII score (median 17 versus 13, p = 0.023), lower Murray lung injury score (median 2.0 versus 2.0, p = 0.05) and lower C-reactive protein (CRP) levels (median 88.9 versus 62.4 mg/L, p = 0.002). Additionally, sivelestat-treated patients were more likely to receive antiviral agents (3.1% versus 10.8%, p = 0.01)(Table 1).

Table 1
The baseline characteristics and clinical features of included patients.

Characteristics	Before matching			After matching		
	Sivevastat (n = 259)	Control (n = 128)	P value	Sivevastat (n = 79)	Control (n = 79)	P value
Male, n (%)	158(61.0)	90(70.3)	0.073	51 (64.6)	52 (65.8)	0.867
Age, year, median (IQR)	73(64, 81)	72(62, 78)	0.216	72 (61, 81)	72 (60, 78)	0.789
BMI, kg/m^2, median (IQR)	23.53(21.48, 25.39)	22.95(20.64, 25.39)	0.239	23.67 (21.91, 26.04)	23.01 (21.08, 25.69)	0.211
Pre-existing comorbidities, n (%)						
Diabetes	49(18.9)	28(21.9)	0.493	12 (15.2)	15 (19.0)	0.526
Hypertension	76(29.3)	41(32.0)	0.588	24 (30.4)	25 (31.6)	0.863
CHD	36(13.9)	21(16.4)	0.513	12 (15.2)	13 (16.5)	0.827
Admitted to ICU, n (%)	221 (85.3)	120 (93.8)	0.016	73 (92.4)	73 (92.4)	1.00
SOFA score, median (IQR)	5(4–8)	6(3–9)	0.978	5 (3.8, 7.3)	5 (3, 7)	0.566
APACHE II score, median (IQR)	13(9–21)	17(10–26)	**0.023**	13 (8, 21)	13 (8, 20)	0.901
Lactate, mmol/L, median (IQR)	1.6(1.2–2.2)	1.7(1.2–2.5)	0.193	1.6 (1.2, 2.1)	1.5 (1.2, 2.4)	0.587
PaO_2/FiO_2, mmHg, median (IQR)	162.25(121.60-228.44)	171.21(94.28-235.33)	0.379	163.4 (127.3, 257.1)	174.0 (103.0, 238.6)	0.400
Murray lung injury score, median (IQR)	2.0(2.0-2.3)	2.0(2.0–3.0)	**0.051**	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	0.636

Abbreviations: BMI, body mass index; CHD, coronary heart disease; ICU: intensive care unit; SOFA: sequential organ failure assessment; APACHE, acute physiology and chronic health evaluation; ALT: alanine transaminase; AST: Aspartate aminotransferase; WBC: white blood cell; PLT: platelet; PCT: procalcitonin; CRP, C-reactive protein; IQR: interquartile range; SD: standard deviation.

Characteristics	Before matching			After matching		
	Sivevastat (n = 259)	Control (n = 128)	P value	Sivevastat (n = 79)	Control (n = 79)	P value
Concomitant treatment						
Prone position, n (%)	103(39.8)	47(36.7)	0.562	28 (35.4)	26 (32.9)	0.737
Albumin, n (%)	27(10.4)	6(4.7)	0.057	3 (3.8)	4 (5.1)	1.00
Glucocorticoids, n (%)	44(17.0)	14(10.9)	0.117	9 (11.4)	10 (12.7)	0.807
Antiviral agents, n (%)	28(10.8)	4(3.1)	**0.010**	4 (5.1)	3 (3.8)	1.00
Antibiotics, n (%)	47(18.1)	18(14.1)	0.312	9 (11.4)	13 (16.5)	0.358
Anti-inflammatory agents, n (%)	37(14.3)	10(7.8)	0.067	7 (8.9)	7 (8.9)	1.00
Immunomodulatory agents, n (%)	7(2.7)	2(1.6)	0.724	2 (2.5)	1 (1.3)	1.00
COVID-19 vaccination history, n (%)	92(35.5)	40(31.3)	0.404	30 (38.0)	23 (29.1)	0.238
Duration of sivevastat received, days, median (IQR)	6 (4–10)	-	-			
Dose of sivevastat received, g/day, median (IQR)	0.3 (0.3–0.4)	-	-			
Creatinine, μmol/L, median (IQR)	66.7(59.7–83.7)	92.3(58.9-144.2)	< 0.001	67.2 (61.7, 78.4)	76.5 (57.3, 109.8)	0.262
ALT, U/L, median (IQR)	34.0 (23.0-54.3)	36.9 (23.4–61.5)	0.259	29.8 (21.8, 49.2)	34.7 (23.8, 60.0)	0.149
AST, U/L, median (IQR)	30.0 (20.0-44.4)	28.6 (16.9–60.8)	0.803	28.0 (16.6, 40.7)	28.0 (16.9, 51.0)	0.688

Abbreviations: BMI, body mass index; CHD, coronary heart disease; ICU: intensive care unit; SOFA: sequential organ failure assessment; APACHE, acute physiology and chronic health evaluation; ALT: alanine transaminase; AST: Aspartate aminotransferase; WBC: white blood cell; PLT: platelet; PCT: procalcitonin; CRP, C-reactive protein; IQR: interquartile range; SD: standard deviation.

Characteristics	Before matching			After matching		
	Sivevastat (n = 259)	Control (n = 128)	P value	Sivevastat (n = 79)	Control (n = 79)	P value
Total bilirubin, μmol/L, median (IQR)	12.8 (9.2–17.8)	12.8 (8.7–18.2)	0.906	13.4 (9.4, 17.8)	11.1 (7.9, 17.9)	0.204
WBC, $\times 10^9$/L, median (IQR) or mean (SD)	7.86 (5.27–11.59)	9.36 (6.37–14.06)	0.004	9.20 (4.54)	9.18 (4.04)	0.973
PLT, $\times 10^9$/L, median (IQR) or mean (SD)	185.5 (137.8–247.0)	183.0 (131.5-238.8)	0.492	200.9 (86.1)	189.6 (69.4)	0.367
PCT, ng/ml, median (IQR)	0.56 (0.13–1.46)	0.65 (0.20–2.53)	0.284	0.53 (0.20, 1.90)	0.42 (0.17, 1.25)	0.251
CRP, mg/L, median (IQR)	62.4 (7.9-131.1)	88.9 (34.9-179.1)	**0.002**	71.8 (8.1, 139.5)	77.8 (36.6, 163.6)	0.142

Abbreviations: BMI, body mass index; CHD, coronary heart disease; ICU: intensive care unit; SOFA: sequential organ failure assessment; APACHE, acute physiology and chronic health evaluation; ALT: alanine transaminase; AST: Aspartate aminotransferase; WBC: white blood cell; PLT: platelet; PCT: procalcitonin; CRP, C-reactive protein; IQR: interquartile range; SD: standard deviation.

Results of propensity-matched analysis

Overall, 79 patients (30.5%) treated with sivelestat were successfully matched to nontreated patients with a similar propensity, achieving full covariate balance (Table 1). The matching process and balances of the covariates after PSM were shown in **Supplementary Fig. 1**. Within this sample, the median PaO_2/FiO_2 on day 3 was 236.7 mmHg among treated patients and 173.3 mmHg in the matched controls ($p < 0.001$) (Table 2). When compared with the baseline, the increase in PaO_2/FiO_2 in the treated patients were remarkably higher on day3 and day5 than those in the untreated patients (all $p < 0.05$) (Table 3). As shown in **Supplementary table 2**, on day 3, there was a significant decrease in the Murry lung injury score in the sivelestat-treated group compared to the controls. While the positive effects of sivelestat on the Murry score were not indicated by the decrease from baseline as shown in **Supplementary table 3**.

Table 2
Clinical outcomes of included patients.

Clinical outcomes	Sivevastat (n = 79)	Control (n = 79)	Difference (95% CI)[a]	P value
PaO_2/FiO_2 on day 3, mmHg, mean (SD)	236.7 (98.4)	173.3 (92.1)	63.5 (31.3, 95.7)	**< 0.001**
Alive and ICU-free days within 28 days, median (IQR)	22 (10–25)	14 (0–22)	5 (1, 8)	**0.001**
28-day mortality, n (%)	10 (12.7)	25 (31.6)	-19.0 (-31.6, -6.4)	**0.012**
Length of ICU stay, days, median (IQR)	5 (2, 11)	8 (4, 14)	-2 (-5, 0)	**0.038**
Length of hospital stay, days, median (IQR)	12 (6, 21)	12 (8, 20)	0 (-3, 2)	0.899
Non-mechanical ventilation time within 28 days, hours, median (IQR)	528 (50, 672)	252.5 (24, 672)	24 (0, 164)	**0.021**
ECMO requirement, n (%)	0	1 (1.3)	-1.3 (-3.7, 1.2)	1.00
Endotracheal intubation, n (%)	20 (25.3)	32 (40.5)	-15.2 (-29.7, 0)	0.067
Tracheotomy, n (%)	3 (3.8)	7 (8.9)	-5.1 (-12.6, 2.5)	0.289

Abbreviations: ICU: intensive care unit; ECMO: extracorporeal membrane oxygenation; 95% CI: 95% confidence interval; IQR: interquartile range; SD: standard deviation.

[a]Difference means the risk difference for binomial outcomes and the median difference for continuous outcomes calculated with mean difference (normal distributed data) or a Hodges-Lehmann estimation of location shift (skewed data) between groups.

Table 3
The increase in PaO_2/FiO_2 compared with baseline.

Variables	Sivevastat (n = 79)	Control (n = 79)	P value
Day 1, mmHg, mean (SD)	21.9 (53.4)	-5.9 (139.8)	0.224
Day 3, mmHg, mean (SD)	53.3 (83.2)	12.9 (97.5)	0.021
Day 5, mmHg, mean (SD)	107.6 (112.1)	27.2 (86.7)	0.014
Day 7, mmHg, mean (SD)	121.5 (100.4)	95.6 (100.2)	0.416

Abbreviations: SD: standard deviation.

The 28-day mortality rate was 12.7% in the treated group and 31.6% in the untreated (p = 0.012). The Kaplan-Meier curves and Cox proportional hazards model showed a significantly improved survival rate

in patients treated with sivelestat than untreated patients (HR, 2.78; 95% CI, 1.32 to 5.88; log-rank p = 0.0074) (Fig. 2).

During hospitalization, 25.3% of patients in the sivelestat-treated group underwent mechanical ventilation and 40.5% in the untreated group were intubated. Non-mechanical ventilation time within 28 days were remarkably longer in the treated group than that in the controls (528 hours versus 252.5 hours, p = 0.021). The treated groups spent less time in the ICU than the controls (5 days versus 8 days, p = 0.038), while both groups spent 12 days in the hospital. The alive and ICU-free days within 28 days were much longer in patients treated with sivelestat than untreated patients (22 days versus 14 days, P = 0.001) (Table 2). Figure 3 showed a beneficial effect of sivelestat on alive and ICU-free days within 28 days (HR, 1.85; 95% CI, 1.29 to 2.64; log-rank p < 0.001).

Adverse events

Adverse event reporting was summarized in **Supplementary table 4**. There was no significant difference between the two groups in number of patients having adverse events or adverse events related to sivelestat. There were two cases of elevated liver enzymes, one of which was considered to be related to sivelestat, and one case of hypoproteinemia in the treated group.

Discussion

In this retrospective observational study, we found that among patients with COVID-19 induced ARDS, sivelestat administration was associated with improved oxygenation, decreased Murray lung injury score, increased non-mechanical ventilation time within 28 days, increased alive and ICU-free days within 28 days, shortened ICU stay and ultimately improved survival. To the best of our knowledge, this is the first clinical study to investigate the effects of a NE inhibitor on ARDS induced by COVID-19. The results of our study are consistent with previous research in ARDS[13, 14, 18–20]. There is increasing evidence that similar respiratory dysfunction and pathobiology occur in patients with COVID-19 and other causes of ARDS[21, 22]. This improved understanding of COVID-19 pathology has significant therapeutic implications as strategies proven effective in conventional ARDS treatment can also be used for COVID-19 induced ARDS.

The existing clinical data on sivelestat use is conflicting, the STRIVE study which enrolled a large, heterogeneous population of mechanically ventilated patients with ARDS, was stopped early on the recommendation of an external Data and Safety Monitoring Board, which noted a negative trend in long-term 180-day mortality rate[15]. One of the putative reasons for the discrepancy between the above-mentioned studies, including our results, and the STRIVE study may be due to the severity of lung injury. Clinical trials reporting positive results with sivelestat therapy had mainly enrolled ARDS patients with a Lung Injury Score < 2.5, whereas the STRIVE study had mainly enrolled patients with a Lung Injury Score > 2.5, which may highlight the critical importance of early intervention with sivelestat[9, 23]. The median lung injury score of ARDS patients in our study was < 2.5, and a positive outcome of sivelestat on

mortality rate was demonstrated. In addition, studies with positive outcomes were mostly conducted among Japanese patients, whereas the STRIVE study was conducted in six countries, United States, Canada, Belgium, Spain, Australia and New Zealand. Therefore, the difference in study populations may have influenced the study results.

Pathogenesis of ARDS is characterized as noncardiogenic pulmonary oedema caused by severe inflammation of endothelial cells of alveolar walls[24]. NE secreted from infiltrated neutrophils further damages alveolar walls, and sivelestat, as a NE inhibitor, was therefore believed to curb this process and alleviate ARDS. With the use of drugs such as sivelestat, the treatment of ARDS to suppress the inflammatory overreaction in the early stages is moving from non-specific to specific inhibition of inflammation, enabling targeted therapy of ARDS[25]. Furthermore, although NE may be an injurious mediator in the early course of ARDS, it may play a crucial immunomodulatory or bactericidal effect later in the course of ARDS[26], stopping NE inhibitor treatment at the appropriate time is therefore a concern. In the available clinical studies, sivelestat has been used for a maximum of 14 days and no significant increase in severe or infection-related adverse events has been reported to date.

The current study had several limitations. First, as a retrospective cohort study that excluded participants with missing data on clinical outcomes, it may suffer from potential selection and ascertainment bias. Second, due to the observational nature and non-randomised treatment allocation, there is a risk that residual selection bias may be responsible for the observed association between sivelestat use and improved clinical outcomes. Although we controlled for available variables associated with sivelestat use or mortality, it is possible that there are unmeasured influential variables that were not controlled for in our propensity score model. Third, although this was a multicentre study, the small sample size and heterogeneous patient population limit the generalisability of our findings. A final limitation is that we did not observe the effects of sivelestat use on long-term outcomes.

Conclusion

In this multicentre retrospective observational study using propensity score matching, we found that among patients with COVID-19 induced ARDS, sivelestat administration was associated with improved oxygenation, decreased Murray lung injury score, increased non-mechanical ventilation time within 28 days, increased alive and ICU-free days within 28 days, shortened ICU stay and ultimately improved survival. Given the promising prospects of NE inhibition, further large-scale high-quality randomized controlled trials are warranted to investigate the efficacy and safety of sivelestat in COVID-19 applications.

Abbreviations

ARDS
Acute respiratory distress syndrome
NE

Neutrophil elastase
ICUs
Intensive care units
COVID-19
Coronavirus Disease 2019
HR
Hazard ratios
EDC
Electronic Data Capture System
BMI
Body mass index
APACHE II
Acute Physiology and Chronic Health Evaluation II score
SOFA
Sequential Organ Failure Assessment score
PaO_2/FiO_2
oxygenation index
PEEP
Positive end-expiratory pressure
ECMO
Extracorporeal membrane oxygenation
AEs
Adverse events
SAEs
Severe adverse events
SD
Standard deviation
IQR
Interquartile range
PSM
Propensity score matching
WBC
White blood cell count
CART
Categorical and Regression Trees
SMD
Standardized mean difference
CRP
C-reactive protein.

Declarations

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Authors' contributions

Yuting Li: drafting of the manuscript; material or technique support; critical revision of the manuscript. Jianjun Zhao, Jiahui Wei, Yanhong Zhang, Haitao Zhang, Ying Li, Ting Liao, Yang Hu, Bo Yuan, Xinmei Zhang, Wanyan Liu, Changgang Liu, Qingsong Cui, Shunzi Wu, Hongmei Jiang, Wenge Liu, Weiheng Liu, Hongguang Xu, Gang Li, Yuyan Cai, Liting Chen: acquisition of data. Bingwei Chen: analysis and interpretation of data. Dong Zhang: conceived, designed and supervised the study; analysis and interpretation of data; critical revision of the manuscript; obtained funding. All authors have read the manuscript and approved its submission.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate

Permission to conduct the study was obtained from the Ethics Committee of the First Hospital of Jilin University (No.22K091-001; December 18, 2022; Clinical study of neutrophil elastase in treating ARDS caused by infection), informed consent was waived and data were anonymously collected.

Consent for publication

Not applicable.

Competing interests

The authors declare that there is no conflict of interest regarding the research, authorship, and/or publication of this paper.

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Figures

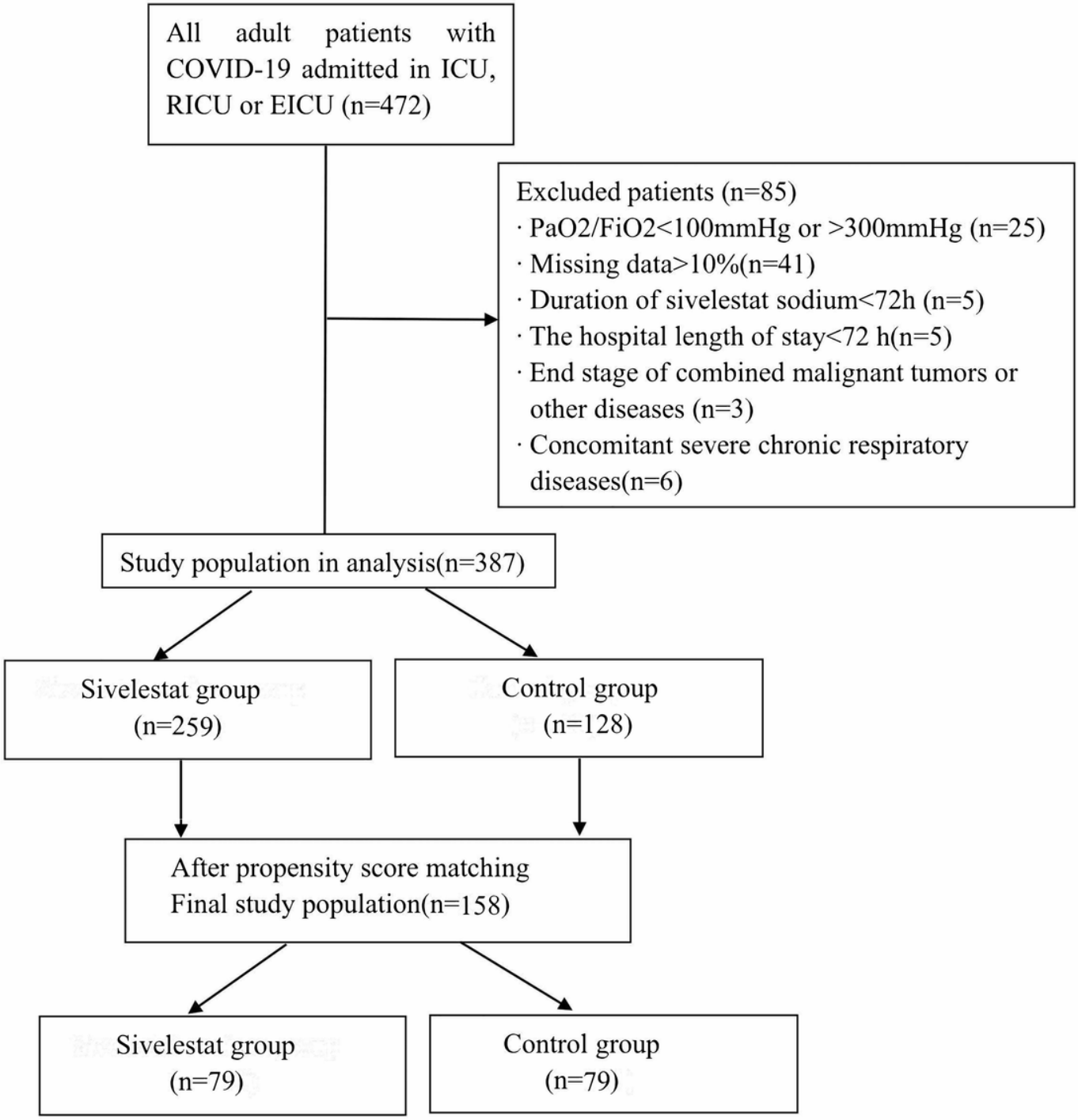

Figure 1

Flow chart.

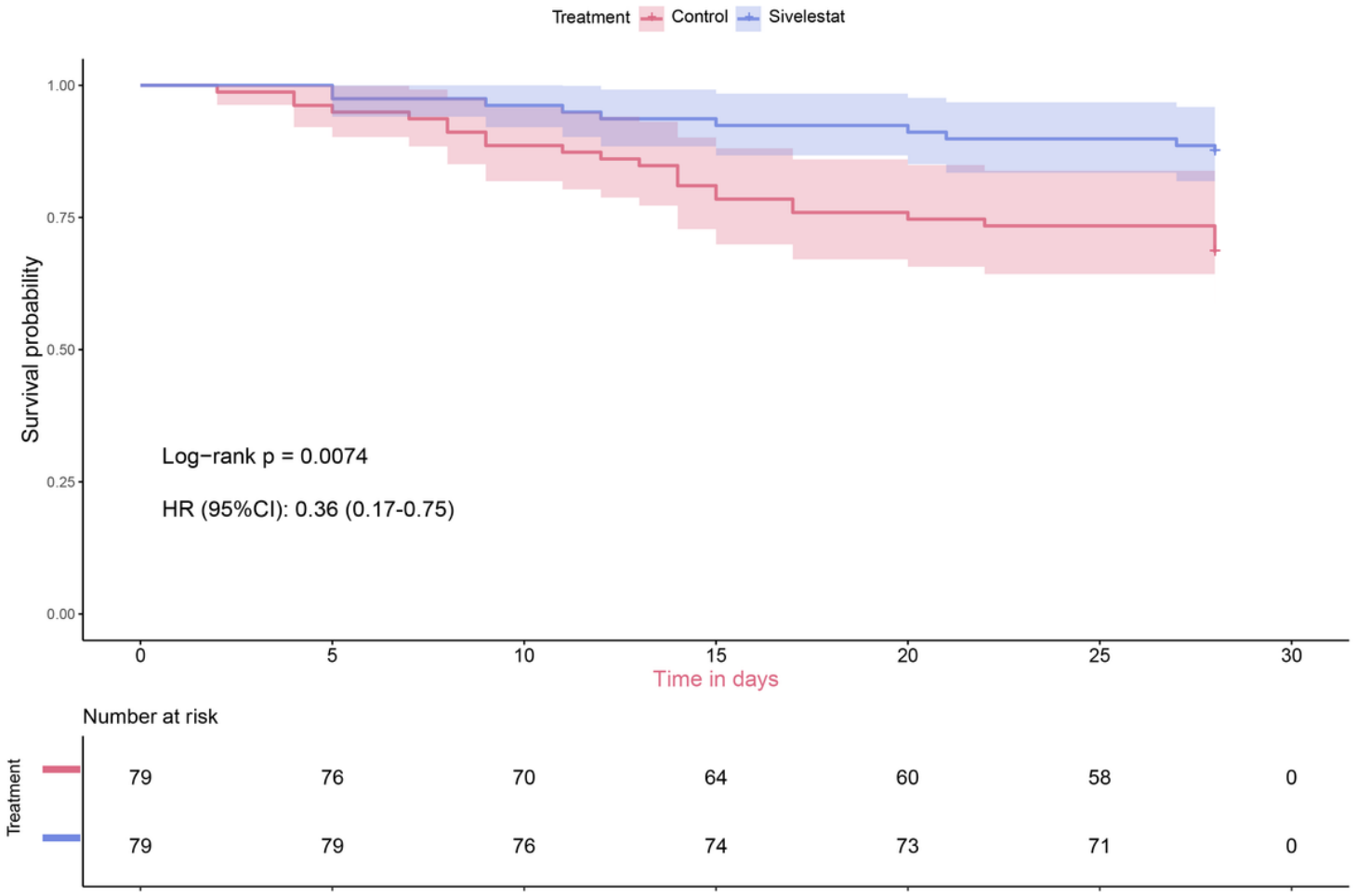

Figure 2

The Kaplan-Meier curves for the survival. HR denotes hazard ratio. CI denotes Confidence interval.

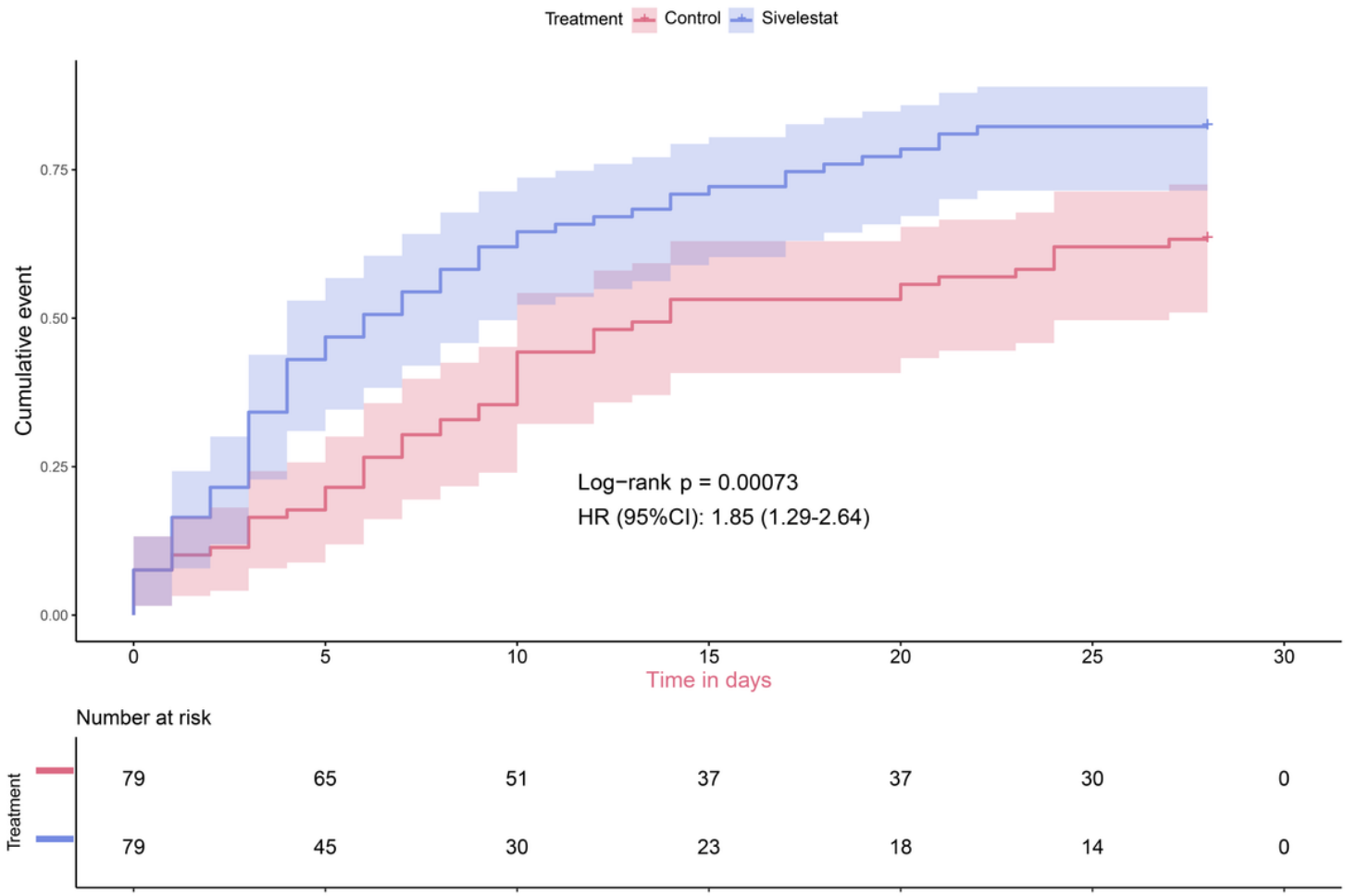

Figure 3

The Kaplan-Meier curves for the cumulative incidence of alive and out of ICU. HR denotes hazard ratio. CI denotes Confidence interval. ICU denotes intensive care unit.

Supplementary Files

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- SupplementalTableandFigures.docx