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Neutrophil elastase inhibitor (Sivelestat) in the treatment of acute respiratory distress syndrome induced by COVID-19: a multicenter retrospective cohort study

Yuting Li[1], Jianjun Zhao[2], Jiahui Wei[2], Yanhong Zhang[3], Haitao Zhang[4], Ying Li[5], Ting Liao[5], Yang Hu[6], Bo Yuan[7], Xinmei Zhang[8], Wanyan Liu[9], Changgang Liu[10], Qingsong Cui[11], Shunzi Wu[12], Hongmei Jiang[13], Wenge Liu[14], Weiheng Liu[14], Hongguang Xu[14], Gang Li[15], Yuyan Cai[16], Liting Chen[17], Bingwei Chen[18] and Dong Zhang[1*]

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.

Keywords Acute respiratory distress syndrome, COVID-19, Neutrophil elastase, Sivelestat, Survival

*Correspondence:
Dong Zhang
zhangdong@jlu.edu.cn
Full list of author information is available at the end of the article

Introduction

The global health and economic impact of the Coronavirus Disease 2019 (COVID-19) pandemic is profound. At present, COVID-19 has a sporadic epidemic trend. 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]. In COVID-19 related ARDS, inflammatory reaction can lead to a large number of neutrophils activated and release elastase, resulting in lung injury and increased inflammation. Sivelestat may help alleviate lung inflammation and improve lung function by inhibiting the activity of neutrophil elastase, thereby providing some relief to the condition. Sivelestat has not been evaluated for its possible therapeutic effects against SARS-CoV-2 infection. Based on its promising beneficial effects in underlying complications of COVID-19, sivelestat could be considered as a promising modality for better management of COVID-19-induced ARDS [4].

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. The application of sivelestat in COVID-19 is still in the research and exploration stage, and its exact efficacy and application need more clinical studies to further clarify and verify. 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 h 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-h 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 during ICU days, 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).

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. These variables were taken at the same time points. All the variables used in the PSM were taken before sivelestat was administered in the experimental group or the corresponding time in the control group. Creatinine, APACHE II score, Murry score and WBC were taken the day before the sivelestat was administered in the experimental group or the corresponding time in the control group. 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

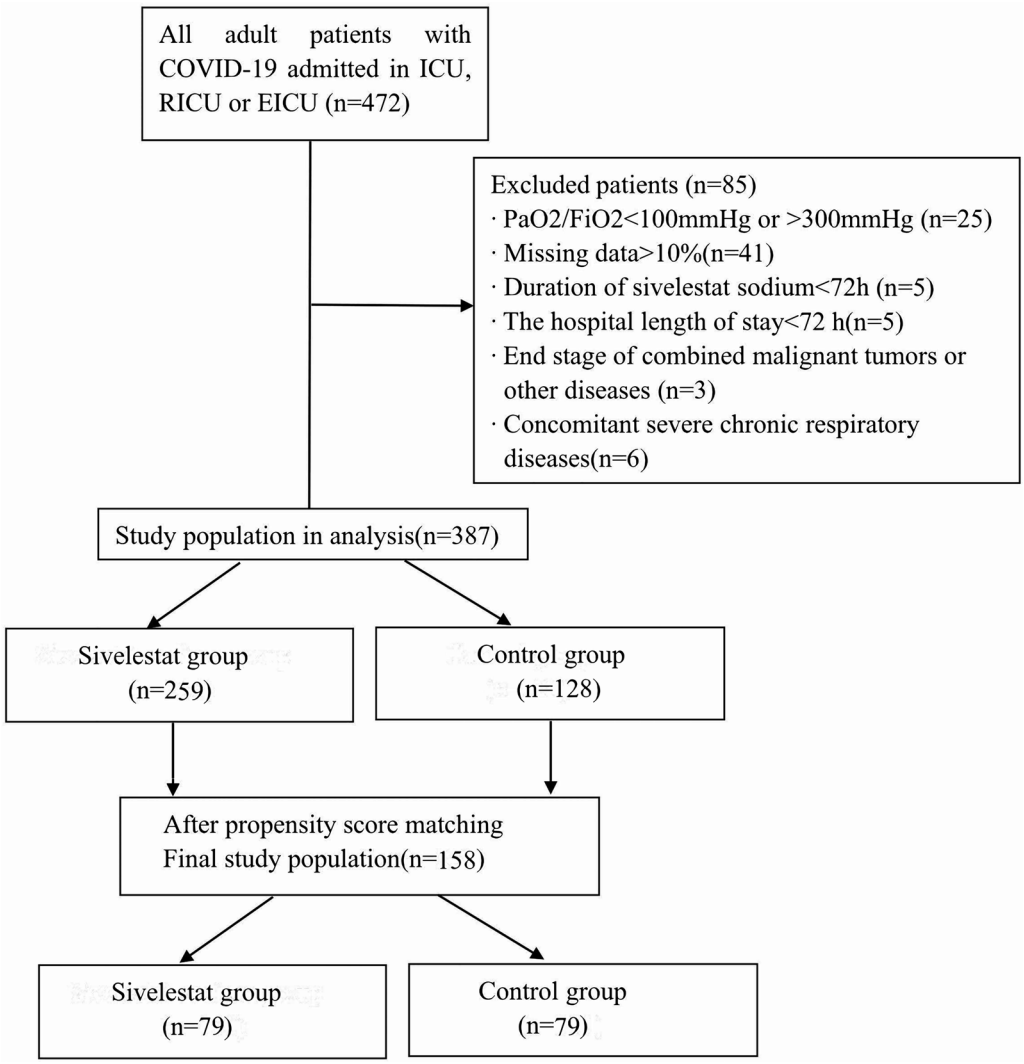

Fig. 1 Flow chart

indicated by the decrease from baseline as shown in Supplementary Table 3.

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 invasive mechanical ventilation(IMV) and 40.5% in the untreated group were intubated. The proportion of patients using non-invasive ventilators in the sivelestat-treated group was 74.7% and that was 59.5% in the untreated group. Non-mechanical ventilation time within 28 days were remarkably longer in the treated group than that in the controls (528 h versus 252.5 h, 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). Figure 4 showed a subgroup analysis of the association between sivelestat and 28-day mortality among patients with or without COVID-19 vaccination history(p for interaction = 0.502).

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

Table 1 The baseline characteristics and clinical features of included patients

Characteristics	Before matching				After matching			
	Sivevastat (n = 259)	Control (n = 128)	P value	SMD	Sivevastat (n = 79)	Control (n = 79)	P value	SMD
Male, n (%)	158(61.0)	90(70.3)	0.073	0.197	51 (64.6)	52 (65.8)	0.867	0.027
Age, year, median (IQR)	73(64, 81)	72(62, 78)	0.216	0.119	72 (61, 81)	72 (60, 78)	0.789	0.025
BMI, kg/m2, median (IQR)	23.53(21.48, 25.39)	22.95(20.64, 25.39)	0.239	0.154	23.67 (21.91, 26.04)	23.01 (21.08, 25.69)	0.211	0.206
Pre-existing comorbidities, n (%)								
Diabetes	49(18.9)	28(21.9)	0.493	0.073	12 (15.2)	15 (19.0)	0.526	0.101
Hypertension	76(29.3)	41(32.0)	0.588	0.058	24 (30.4)	25 (31.6)	0.863	0.027
CHD	36(13.9)	21(16.4)	0.513	0.070	12 (15.2)	13 (16.5)	0.827	0.035
Admitted to general ICU, n (%)	221 (85.3)	120 (93.8)	0.016	0.278	73 (92.4)	73 (92.4)	1.00	< 0.001
SOFA score, median (IQR)	5(4–8)	6(3–9)	0.978	0.015	5 (3.8, 7.3)	5 (3, 7)	0.566	0.056
APACHE II score, median (IQR)	13(9–21)	17(10–26)	0.023	0.281	13 (8, 21)	13 (8, 20)	0.901	0.007
Lactate, mmol/L, median (IQR)	1.6(1.2–2.2)	1.7(1.2–2.5)	0.193	0.017	1.6 (1.2, 2.1)	1.5 (1.2, 2.4)	0.587	0.150
PaO2/FiO2, mmHg, median (IQR)	162.25(121.60–228.44)	171.21(94.28–235.33)	0.379	0.022	163.4 (127.3, 257.1)	174.0 (103.0, 238.6)	0.400	0.007
Murray lung injury score, median (IQR)	2.0(2.0–2.3)	2.0(2.0–3.0)	0.051	0.248	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	0.636	0.052
Concomitant treatment								
Prone position, n (%)	103(39.8)	47(36.7)	0.562	0.063	28 (35.4)	26 (32.9)	0.737	0.053
Albumin, n (%)	27(10.4)	6(4.7)	0.057	0.218	3 (3.8)	4 (5.1)	1.00	0.062
Glucocorticoids, n (%)	44(17.0)	14(10.9)	0.117	0.175	9 (11.4)	10 (12.7)	0.807	0.039
Antiviral agents, n (%)	28(10.8)	4(3.1)	0.010	0.305	4 (5.1)	3 (3.8)	1.00	0.062
Antibiotics, n (%)	47(18.1)	18(14.1)	0.312	0.111	9 (11.4)	13 (16.5)	0.358	0.147
Anti-inflammatory agents, n (%)	37(14.3)	10(7.8)	0.067	0.208	7 (8.9)	7 (8.9)	1.00	< 0.001
Immunomodulatory agents, n (%)	7(2.7)	2(1.6)	0.724	0.079	2 (2.5)	1 (1.3)	1.00	0.093
COVID-19 vaccination history, n (%)	92(35.5)	40(31.3)	0.404	0.091	30 (38.0)	23 (29.1)	0.238	0.189
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	0.533	67.2 (61.7, 78.4)	76.5 (57.3, 109.8)	0.262	0.008
ALT, U/L, median (IQR)	34.0 (23.0–54.3)	36.9 (23.4–61.5)	0.259	0.033	29.8 (21.8, 49.2)	34.7 (23.8, 60.0)	0.149	0.132
AST, U/L, median (IQR)	30.0 (20.0–44.4)	28.6 (16.9–60.8)	0.803	0.017	28.0 (16.6, 40.7)	28.0 (16.9, 51.0)	0.688	0.124
Total bilirubin, μmol/L, median (IQR)	12.8 (9.2–17.8)	12.8 (8.7–18.2)	0.906	0.118	13.4 (9.4, 17.8)	11.1 (7.9, 17.9)	0.204	0.014
WBC, × 109/L, median (IQR) or mean (SD)	7.86 (5.27–11.59)	9.36 (6.37–14.06)	0.004	0.153	9.20 (4.54)	9.18 (4.04)	0.973	0.011
PLT, $\times 10^9$/L, median (IQR) or mean (SD)	185.5 (137.8–247.0)	183.0 (131.5–238.8)	0.492	0.034	200.9 (86.1)	189.6 (69.4)	0.367	0.145
PCT, ng/ml, median (IQR)	0.56 (0.13–1.46)	0.65 (0.20–2.53)	0.284	0.109	0.53 (0.20, 1.90)	0.42 (0.17, 1.25)	0.251	0.229
CRP, mg/L, median (IQR)	62.4 (7.9–131.1)	88.9 (34.9–179.1)	0.002	0.311	71.8 (8.1, 139.5)	77.8 (36.6, 163.6)	0.142	0.154

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; SMD: standardized mean difference

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

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

SD: standard deviation

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].

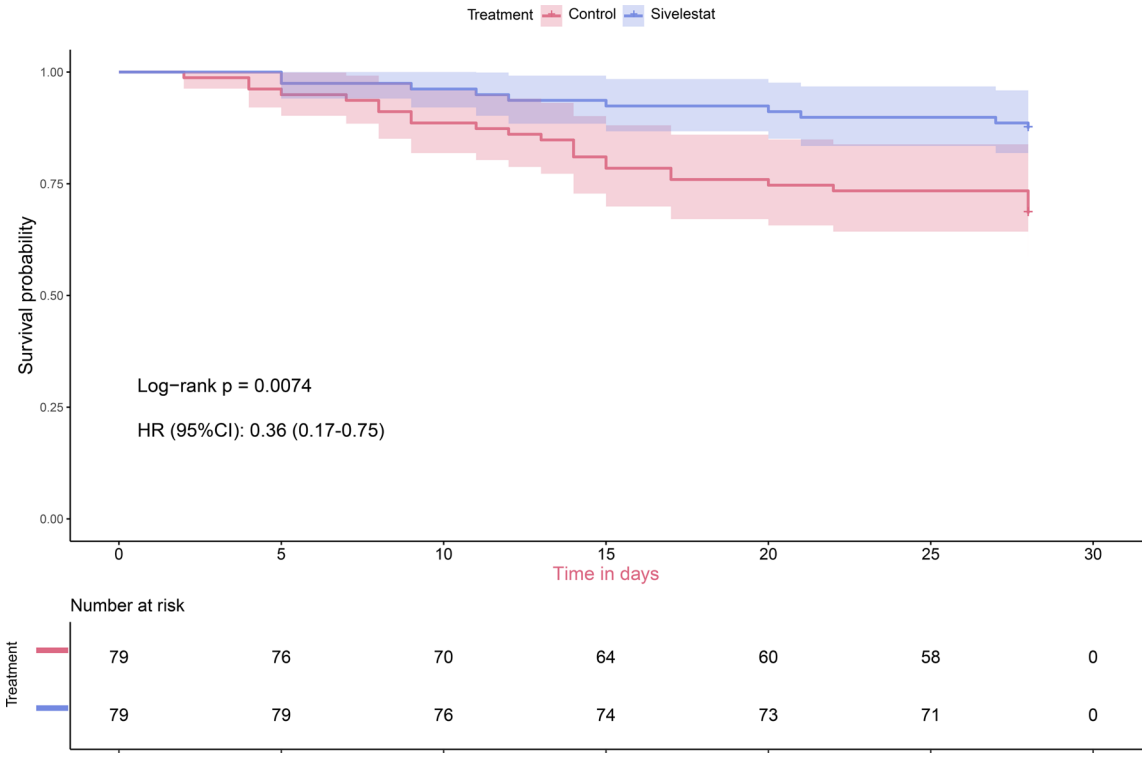

Fig. 2 The Kaplan–Meier curves for the survival. HR denotes hazard ratio. CI denotes confidence interval

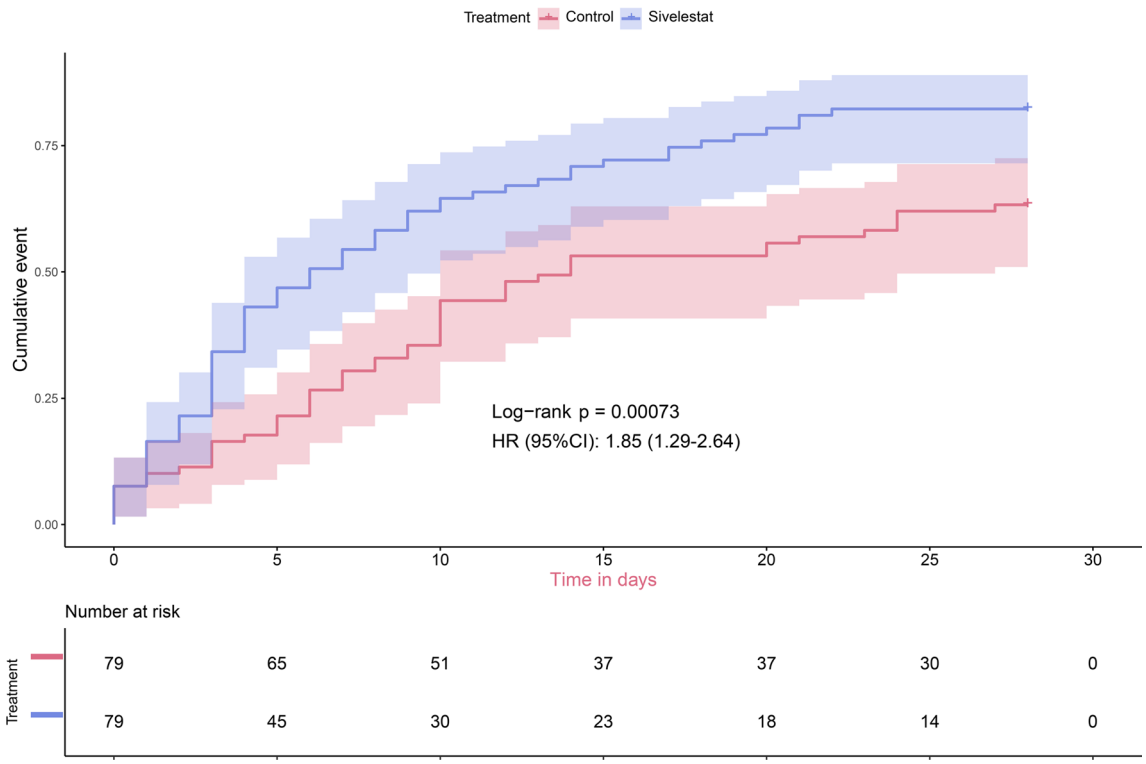

Fig. 3 The Kaplan–Meier curves for the cumulative incidence of alive and out of ICU. HR denotes hazard ratio. CI denotes confidence interval. ICU denotes intensive care unit

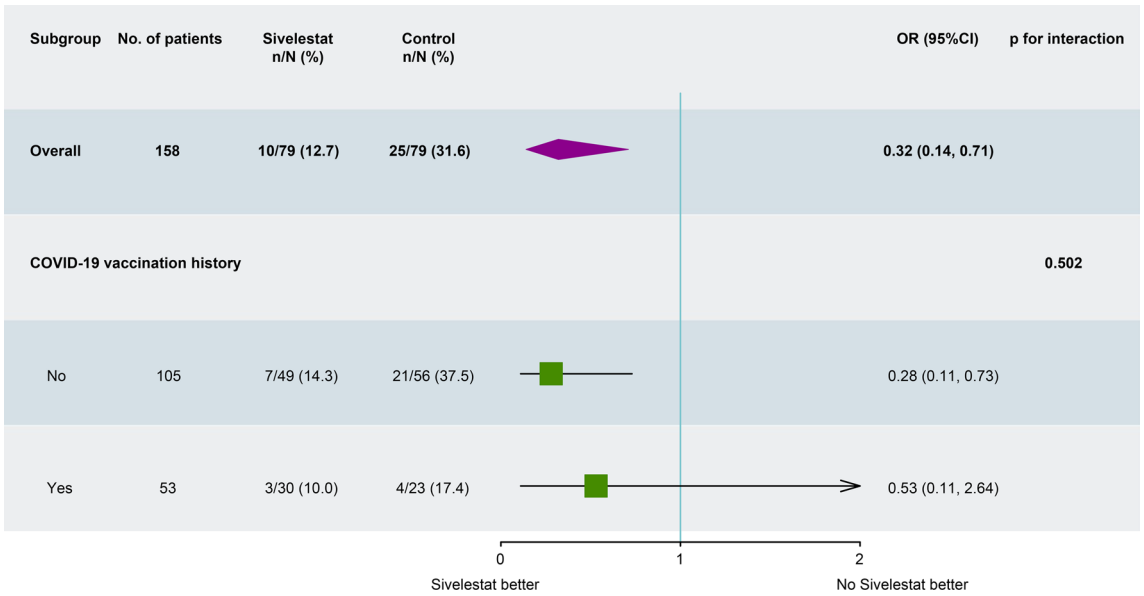

Fig. 4 Subgroup analysis of the association between sivelestat and 28-day mortality among patients with or without COVID-19 vaccination history. OR denotes odds ratio. CI denotes confidence interval

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.

Compared with the number of deaths, the number of patients using anti-inflammatory agents is indeed small. However, there is no statistical difference in the proportion of patients using anti-inflammatory agents between the experimental group and the control group before or after propensity matching. As a result, this will not affect the difference in mortality between two groups. The best evidence available shows no difference between using tocilizumab plus standard care compared to standard care alone for reducing mortality in patients with COVID-19 [27]. Baricitinib reduces the mortality of COVID-19 patients, not including the critically ill [28]. Due to clinical use restrictions, medical resources and capabilities, drug accessibility and cost, baricitinib and tocilizumab were not widely used. Similarly, because of strict indications for the use of ECMO, limited resources, rapid disease progression and individual differences, the number of people using ECMO was significantly lower than the number of deaths.

Since all included patients were under invasive or non-invasive mechanical ventilation, very few patients were administered antiviral drugs such as remdesivir. Recent meta-analysis shows that remdesivir therapy for COVID-19 is not associated with a mortality benefit. However, there is significant reduction in the need for IMV/ECMO [29]. Moreover, the drug supply was insufficient at that time, which led to the inability of most patients to receive remdesivir treatment. As the COVID-19 epidemic continued to evolve, more and more treatments and protocols were being developed. In addition to remdesivir, there were a variety of other antiviral drugs, traditional Chinese medicines and supportive treatment options available in China. Therefore, even if the supply of remdesivir was limited, patients may still receive other effective treatment options.

The risk of severe illness may vary depending on the presence or absence of the COVID-19 vaccine. As a result, we conducted a subgroup analysis of the association between sivelestat and 28-day mortality among patients with or without COVID-19 vaccination history. Sivelestat appeared to reduce 28-day mortality in unvaccinated patients, but had no effect on 28-day mortality in vaccinated patients. However, the p for interaction was not statistically significant. Therefore, whether a patient is vaccinated or not does not affect the therapeutic effect of sivelestat.

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. Fourth, although there was no statistically significant difference in the proportion of patients receiving steroid treatment after matching, a lower proportion of steroid use may affect the prognosis of patients. 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
IMV	Invasive mechanical ventilation

Supplementary Information

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Supplementary material 1.

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Author 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

No datasets were generated or analysed during the current study.

Declarations

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 no competing interests.

Author details

[1]Department of Critical Care Medicine, The First Hospital of Jilin University, Changchun 130021, Jilin, China. [2]Respiratory Intensive Care Unit, Sino-Japanese Friendship Hospital of Jilin Province, Changchun 130033, Jilin, China. [3]Emergency Department, Jilin Province People's Hospital, Changchun 130021, Jilin, China. [4]Department of Critical Care Medicine, Jilin Province People's Hospital, Changchun 130021, Jilin, China. [5]Department of Critical Care Medicine, Tonghua People's Hospital, Tonghua 134001, Jilin, China. [6]Department of Critical Care Medicine, The Third Affiliated Hospital of Changchun University of Chinese Medicine, Changchun 130118, Jilin, China. [7]Respiratory Intensive Care Unit, Siping City Central People's Hospital, Siping 136099, Jilin, China. [8]Department of Critical Care Medicine, Siping City Central People's Hospital, Siping 136099, Jilin, China. [9]Department of Critical Care Medicine, Jilin Hospital of Integrative Chinese and Western Medicine, Jilin 132012, Jilin, China. [10]Department of Critical Care Medicine, Tonghua Central Hospital, Tonghua 134099, Jilin, China. [11]Department of Critical Care Medicine, Yanbian University Affiliated Hospital, Yanji 133099, Jilin, China. [12]Department of Critical Care Medicine, People's Hospital of Hunchun City, Hunchun 133399, Jilin, China. [13]Department of Critical Care Medicine, Baicheng City Hospital, Baicheng 137099, Jilin, China. [14]Department of Critical Care Medicine, Jilin City Central Hospital, Jilin 132011, Jilin, China. [15]Department of Critical Care Medicine, Changchun Central Hospital, Changchun 130041, Jilin, China. [16]Department of Critical Care Medicine, Jilin City People's Hospital, Jilin 132001, Jilin, China. [17]Respiratory Intensive Care Unit, Jilin City People's Hospital,

Jilin 132001, Jilin, China. [18]Department of Epidemiology and Biostatistics, School of Public Health, Southeast University, Nanjing 210009, Jiangsu, China.

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