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CORRESPONDENCE

Fibrinolytic therapy for COVID-19: a review of case series

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Thromboembolism is the leading cause of mortality in COVID-19 patients. Thrombi, including pulmonary embolism (PE) and deep vein thrombosis (DVT), range from minor sequelae to fatal complications of SARS-CoV-2 infection [1]. Individuals with pre-existing conditions are more likely to develop thrombi and have poor outcomes [2]. The guidelines from professional societies for the use of fibrinolytic therapy (FT) in COVID-19 are inconsistent [3]. The outcomes of FT for ARDS (acute respiratory distress syndrome) associated with COVID-19 have not been clarified to date. We have summarized 105 COVID-19 patients treated with alteplase (tPA). tPA was applied for thrombolytic (fibrinolytic, generally after the failure of heparin), salvage (rescue for gravely ill patients), or prophylactic therapies for those with a potential of thrombosis [4]. We have compared the morbidity, mortality, complications, laboratory tests of COVID-19 patients with ARDS versus those without ARDS (non-ARDS), and adverse events of fibrinolytic therapy.

METHODS

This pooled study aimed to summarize all reported case series of fibrinolytic therapy for COVID-19. IRB approval and informed consent were not required. Clinical features of all 105 individual cases are presented in Table 1, and additional details are shown in the online supplement. Outcomes were ICU admission, discharge to the general ward, in-hospital death, or discharge home. One-Way ANOVA for continuous variables and χ^2 tests for categorical variables were conducted using R (v4.0.3) and Prism 9 with a two-sided level of significance $P < 0.05$. The results were graphed using the ggplot2 package.

RESULTS

Recipients were from 11 countries and represented multiple ethnicities. The average age was 58.7 ± 14.1 year. There was an insignificant difference in age and gender between ARDS and non-ARDS groups. More respiratory diseases were reported for the ARDS group. In contrast, no other comorbidities were different between the two groups (Table 1). PE associated with ARDS patients was a predominant indication for tPA, while hypoxic stroke and myocardial infarction of non-ARDS was for the non-ARDS group. The total dose of tPA and frequency used for salvage therapy was insignificant between ARDS and non-ARDS groups. Few adverse events were reported.

Plasma D-dimer and fibrinogen levels of patients who died were higher than those who survived. ICU patients had a higher PTT (Table 1). WBC, PTT, fibrinogen, and LDH levels were elevated up to 3-fold in ARDS patients compared with non-ARDS. Further, WBC count was lower among patients who recovered (Fig. 1). Mortality was higher among patients with ARDS, as was the need for ICU care. Fewer patients with ARDS were discharged home. The overall mortality was much high for the patients who developed PE (39.7%), septic shock (63.6%), acute kidney injury (75.0%), MOF (85.7%), and cardiac arrest and heart failure (72.7%). Of ARDS patients, 42% had multiple pulmonary emboli or thrombi. The incidence of acute kidney injury, respiratory failure, and tachycardia/fibrillation was much greater for ARDS patients.

DISCUSSION

tPA was administered generally upon the failure of anti-coagulation therapy, including heparin, aspirin, enoxaparin. Antivirus medicines, antibiotics, and supportive care with various dose, duration, route, and combinations were applied to some patients based on their conditions. The finding of high mortality and the need for ICU care among the COVID-19-associated ARDS may be related to pre-existing respiratory diseases and inflammation [5]. The fatal complications of COVID-19, including PE, shock, cardiac failure, kidney injury, and MOF, further reduce the survival rate. In addition to WBC, increased plasma PTT and fibrinogen levels could signify a poor prognosis. Considering few adverse events associated with fibrinolytic therapy, early and the local application of tPA and others (i.e., uPA, plasminogen, plasmin) combined with precisely anti-inflammation interventions to target case-dependent cytokines and chemokines could improve the survival of COVID-19 patients with critically ARDS. By comparison, fibrinolytic therapy for COVID-19 patients without ARDS or other severe complications significantly improves the outcomes [2]. The main limitation of retrospective study was the scarcity of randomized controlled groups and standardized procedures for laboratory tests, clinical readouts, and fibrinolytic therapy. The randomized controlled trials designed to test the benefits of fibrinolytic therapy are recruiting patients. Nevertheless, this pooled study has implications for the stratification and prognosis of COVID-19-associated ARDS.

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Table 1. Comparison of ARDS and non-ARDS patients treated with tPA.

	All cases	Non-ARDS	ARDS	*P* value
Age	58.7 ± 14.1	59.9 ± 12.0	56.4 ± 17.1	0.29[b, c]
Gender (total: 33 for non-ARDS vs 58 for ARDS)				
Male	64	23 (69.7%)	41 (70.7%)	0.92[a, c]
Female	27	10 (30.3%)	17 (29.3%)	
Comorbidities (total: 26 for non-ARDS vs 37 for ARDS)				
Hypertension	33	16 (61.5%)	17 (46.0%)	0.50[a]
Diabetes	28	11 (42.3%)	17 (46.0%)	0.86[a]
Dyslipidemia	19	7 (26.9%)	12 (32.4%)	0.73[a]
All cardiovascular illness: Thrombosis	37 28	16 (61.5%) 16 (61.5%)	21 (56.8%) 12 (32.4%)	0.85[a] 0.70
Obesity	14	3 (11.5%)	11 (29.7%)	0.17[a]
All respiratory disease: Respiratory failure	29 10	6 (23.1%) 2 (7.7%)	23 (62.2%) 8 (21.6%)	0.05**[a] 0.002
>3 comorbidities	38	14 (53.8%)	24 (64.9%)	0.66[a]
Fibrinolytic therapy				
TPA (mg/case)	69.1 ± 22.9	67.7 ± 17.2	70.0 ± 26.0	0.67[b]
Rescue therapy	34	5 of 33	29 of 70	0.80[a]
Adverse events (hemorrhage)[ξ]	7	2 of 33	5 of 70	0.85[a]
Indications for tPA (total: 31 for non-ARDS and 45 for ARDS)				
PE	58	7	51	0.001[a]
Stroke and STEMI	25	24	1	<0.00001[a]
Laboratory tests				
WBC (4.5×10^9–11×10^9/L)	22 (18/4)	9.3 ± 2.6	16.6 ± 9.8	0.005***[b]
Lymphocyte (0.9×10^9–2.9×10^9/L)	15 (14/1)	1.7 ± 1.2	0.66	-
Platelet (<150×10^3/mL)	35 (21/14)	241.7 ± 84.4	249.3 ± 120.4	0.82[b]
PTT (60–70 s)	18 (13/5)	16.4 ± 9.0	32.7 ± 3.5	0.004****[b]
APTT (30–40 s)	20 (18/2)	32.7 ± 8.9	36.50 ± 2.12	0.65
Fibrinogen (2–4 g/L)	38 (17/21)	1.0 ± 2.3	2.7 ± 2.9	0.04**[b]
D-dimer (<0.5 μg/mL)	56 (24/32)	10.7 ± 21.9	13.4 ± 22.2	0.62[b]
LDH (140–280 U/L)	7 (4/3)	500.2 ± 235.3	1762.0 ± 723.4	0.01***[b]
Ferritin (24–360 μg/L)	24 (18/6)	1298.5 ± 2361.2	8216.3 ± 17441.4	0.09*[b]
CRP (< 10 mg/L)	25 (14/11)	216.0 ± 477.9	412.0 ± 667.1	0.38[b]
Outcomes (total: 28 for non-ARDS vs 70 for ARDS)				
Death	28	3 (10.7%)	25 (35.7%)	0.05**
ICU	31	3 (10.7%)	28 (40.0%)	0.03**
Out of ICU	14	6 (21.4%)	8 (11.4%)	0.28[a]
Discharged home	25	16 (57.1%)	9 (12.9%)	0.001****[c]
Complications (total: 23 for non-ARDS vs 33 for ARDS)				
Sepsis	3	0 (0%)	3 (9.1%)	0.15[a]
Shock	9	2 (8.7%)	7 (21.2%)	0.27[a]
Multiple organ failure	7	1 (4.3%)	6 (18.2%)	0.164[a]
Multiple PE & thrombus	14	0 (0%)	14/0 (42.4%)	0.0003***[a]
Cardiac arrest/heat failure	5/5	1/2 (4.3%/8.7%)	4/3 (12.1%/9.1%)	0.35[a]/0.32
Respiratory failure	6	0 (0%)	6 (18.2%)	0.03**[a]
Acute kidney injury	5	0 (0%)	5 (15.2%)	0.04*[a]
Tachycardia/fibrillation	8	6 (26.1%)	2 (6.1%)	0.05*[a]

Mean ± SD.
TPA tissue-like plasminogen activator, *WBC* white blood cell, *PTT* partial thromboplastin time, *aPTT* activated partial thromboplastin time, *LDH* lactate dehydrogenase, *CRP* C-reactive protein.
[a]χ^2 test.
[b]One-Way ANOVA with a two-sided <0.05.
[c]confirmed with R.
*$P < 0.1$; **$P \le 0.05$; ***$P < 0.01$, ****$P \le 0.001$.
Footnote: Original case reports were with the following PMIDs: 33043052, 32962933, 32735730, 32267998, 33352323, 33133702, 33403100, 32427773, 32497796, 32663257, 32427774, 33634156, 32886934, 32425320, 32508062, 32445784, 32763101, 32780853, 32948531, 32634813, 32513452, 32526545, 33083223, 33066885, 32414622, 32656711, 32907873, 32835021, 32835024, 32706216, 32675154, 32432162, 32864630, 32917441, 32386986, 32952405.
ξ slight hemorrhage was reported in intramuscle, intracranium, upper gastrointestinal tract, mouth, and femur.

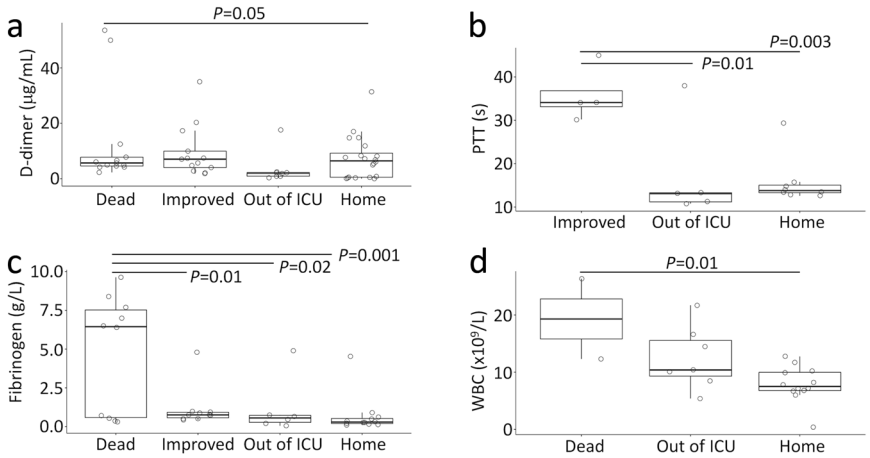

Fig. 1 Trend of outcomes against fibrinolysis and inflammation. D-dimer (**a**), PTT (**b**), fibrinogen (**c**), and WBC (**d**) levels prior to fibrinolytic therapy were compared for four outcomes of all patients. The outcome without sufficient patients ($n < 3$) was removed for PTT (**c**) and WBC (**d**). The full names of abbreviations were described in Table 1.

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AUTHOR CONTRIBUTIONS

HLJ had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: HLJ. Acquisition, analysis, or interpretation of data: RZ, YD, HLJ. Drafting of the manuscript: RZ, HLJ. Critical revision of the manuscript for important intellectual content: RZ, HLJ. Statistical analysis: YD, HLJ. Obtained funding: HLJ and RZ. Administrative, technical, or material support: RZ, YD, HLJ. Supervision: HLJ.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

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