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Authors: Kacper Dziedzic, Mansur Rahnama-Hezavah, Monika Tomaszewska, Agnieszka Szarpak, Aleksandra Gasecka, Krzysztof Kuleta, Oliwia Fidali, Michal Pruc, Aleksander Ostenda, Magdalena Wierzbnik-Stronska, Aldona Kubica, Francesco Chirico

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BREAKING DOWN THE CLOTTING CONUNDRUM: ANALYZING THE ROLE OF PLASMA TISSUE PLASMINOGEN ACTIVATOR IN COVID-19 PATIENTS THROUGH A SYSTEMATIC REVIEW AND META-ANALYSIS

Kacper Dziedzic[1], Mansur Rahnama-Hezavah[2], Monika Tomaszewska[1], Agnieszka Szarpak[3], Aleksandra Gasecka[4], Krzysztof Kuleta[4], Oliwia Fidali[4], Michal Pruc[5, 6], Aleksander Ostenda[7], Magdalena Wierzbnik-Stronska[7], Aldona Kubica[8], Francesco Chirico[9]

[1]Department of Clinical Research and Development, LUX MED Group, Warsaw, Poland

[2]Chair and Department of Oral Surgery, Medical University of Lublin, Poland

[3]Institute of Outcomes Research, Maria Sklodowska-Curie Medical Academy, Warsaw, Poland

[4]1st Chair and Department of Cardiology, Medical University of Warsaw, Poland

[5]Research Unit, Polish Society of Disaster Medicine, Warsaw, Poland

[6]Department of Public Health, International Academy of Ecology and Medicine, Kyiv, Ukraine

[7]Faculty of Medicine, Academy of Silesia, Katowice, Poland

[8]Department of Cardiac Rehabilitation and Health Promotion, *Collegium Medicum*, Nicolaus Copernicus University, Bydgoszcz, Poland

[9]Post-Graduate School of Occupational Health, Università Cattolica del Sacro Cuore, Rome, Italy

ADDRESS FOR CORRESPONDENCE:

Agnieszka Szarpak

Maria Sklodowska-Curie Medical Academy, Zelaznej Bramy Square 10, 00–136, Warsaw, Poland; e-mail: a.szarpak@covinfo.pl, phone: +48791221241

ABSTRACT

INTRODUCTION: The SARS-CoV-2 virus pandemic has been a global challenge for medical services in terms of patient care and early prognosis of hospitalized patients' situations. Early identification and classification of COVID-19 patients in hospitals is critical for optimal management. The purpose of this study is to compile existing data on tissue plasminogen activator (tPA) concentrations in COVID-19 patients.

MATERIAL AND METHODS: A systematic review and meta-analysis were carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines. Qualified articles were found systematically using relevant databases such as PubMed Central, Scopus, EMBASE, and the Cochrane databases until May 4th, 2023.

RESULTS: Tissue plasminogen activator levels among COVID-19 positive vs negative patients T-PA levels among COVID-19 positive vs negative patients varied and amounted to 26.67 ± 40.65 vs 4.68 ± 3.83, respectively (SMD = 2.49; 95% CI: 1.85 to 3.14; $p < 0.001$). The mean t-PA level among patients requiring ICU admission was 24.06 ± 12.44, compared to 16.55 ± 10.01 for patients not treated in the ICU (SMD = 0.69; 95% CI: −0.68 to 2.05; $p = 0.32$). Moreover, t-PA levels among severe COVID-19 compared to non-severe were 11.89 ± 9.05 and 16.87 ± 20.39, respectively (SMD = 2.74; 95% CI: −0.71 to 6.19; $p = 0.12$). The t-PA values were, respectively: 15.33 ± 8.01 for patients who survived hospital discharge, and 19.04 ± 11.88 for patients who died in hospital due to COVID-19 (SMD = −0.50; 95% CI: −2.45 to 1.44; $p = 0.61$).

CONCLUSIONS: According to this meta-analysis, the key conclusion of this study is that COVID-19 infection is connected to t-PA levels. Nonetheless, extensive prospective studies addressing the possible diagnostic relevance of t-PA as a marker of COVID-19 severity are required to corroborate the presented results.

KEYWORDS: tissue plasminogen activator; t-PA; COVID-19; SARS-CoV-2; coagulopathy

INTRODUCTION

Since 2019, the global healthcare system has faced a significant challenge in caring for patients and predicting outcomes due to the SARS-CoV-2 pandemic [1, 2]. There are many unknown pathomechanisms behind the complications of the virus, influencing disease severity, and mortality amongst the patients who received modified effective therapy [3]. Research emphasizes the significant role of the disturbed balance between the pro- and anticoagulant systems [4–9]. Even with prophylactic and therapeutic anticoagulation, thromboembolic complications are frequently observed [10, 11] along with markedly increased lysis resistance and prolonged diurnal lysis [12].

Many studies have focused on investigating the concentration of various biomarkers related to endothelial, inflammatory, and coagulation responses during COVID-19 [13–21]. The infection-induced pro-inflammatory environment results in endothelial dysfunction, which may lead to an imbalance between pro-coagulation and anti-coagulation factors. Elevated levels of tissue plasminogen activator (t-PA), and its inhibitor, plasminogen activation inhibitor 1 (PAI-1), fibrinogen, von Willebrand factor, as well as the receptor for interleukin-33, have been revealed in patients plasma. The combination of the biomarkers has also been evaluated as a prognostic factor for thrombosis and mortality [22]. More interestingly, despite the increased level of tPA, hypofibrinolysis as well as hypercoagulability have been observed [8]. The observations prompt further investigation into the impact of specific biomarkers on each other's activities and their influence on COVID-19 clinical outcomes.

Tissue-type plasminogen activator (tPA) and its inhibitor, plasminogen activator inhibitor-1 (PAI-1), are crucial components of the plasminogen activator-plasmin system [23, 24]. The imbalance between tPA and PAI-1 results in dysregulation of fibrinolysis and thrombotic complications [25]. Tissue plasminogen activator is the most extensively studied plasminogen activator and is commonly used clinically as a thrombolytic therapy [26]. The majority of diseases, including viral infections, impact the vascular endothelium and result in impaired function [27]. This endothelial dysfunction causes a decrease in the fibrinolytic activity of the cells, which increases the likelihood of developing blood clots [28].

Thromboembolic complications have the potential to be fatal, particularly in COVID-19 patients with a high risk of such events. It is crucial to evaluate possible risk factors that

are predictors of disease progression and detect changes in the coagulation pathway. The purpose of this investigation is to review existing data on the concentration of tPA levels in COVID-19 patients and perform a meta-analysis to evaluate the correlation between tPA levels and COVID-19 disease, its severity, the likelihood of admission to the intensive care unit, and patients survival.

MATERIAL AND METHODS

This study was intended as a systematic review and meta-analysis and was carried out in compliance with the recommendations of the Cochrane Collaboration Group [29] and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) standards (Table S1). [30]. This study protocol was submitted to PROSPERO (CRD42022380249).

Search strategy and study selection

Two independent reviewers (K.D. and M.P.) carried out the literature search. We searched PubMed Central, Scopus, EMBASE, and the Cochrane Collaboration Library for all relevant studies from January 2020 to May 4th, 2023. We used the phrases “tissue plasminogen activator” OR “t-PA” AND “SARS-CoV-2” OR “new coronavirus” OR “COVID-19” in our search. In addition, the reference lists of the included publications were manually examined for additional studies that were not found in the database search. EndNote X9 was used to import the titles and abstracts found in the database search (Clarivate Analytics, Philadelphia, USA).

Inclusion and exclusion criteria

The adopted inclusion criteria were as follows: (1) original articles; (2) COVID-19 patients in various clinical conditions: mild, moderate, severe, or critical; as well as COVID-19 patients who survive to hospital discharge or decreased; (4) all types of observational studies: cohort, cross-sectional, case-control, longitudinal; and (5) full-text articles available in English. The following were the exclusion criteria: (1) Studies that did not fit the aforementioned criteria; (2) Article types such as letters, conference papers, posters, editorials, review articles, and meta-analyses.

Data extraction

Two reviewers (M.P. and K.D.) independently evaluated the data extraction procedure, and disagreements concerning the selection criteria were argued and resolved by consensus among all authors. A predefined form was used to retrieve data from the included research.

Quality assessment

Three researchers (K.D., A.O., and M.P.) independently conducted the quality evaluation procedure. Any differences were also settled through discussion among all researchers. The Newcastle-Ottawa scale (NOS) was developed to assess the methodological quality of observational studies with its design. The studies were evaluated as poor, moderate, and high quality according to the NOS criteria, with ratings of 0–3, 4–6, and 7–9, respectively. In addition, if there are more than 10 trials in a single meta-analysis, we do funnel plot tests for asymmetry to evaluate potential publication bias.

Statistical analysis

The STATA software (version 14, StataCorp LLC, College Station, TX, USA) and the RevMan software (version 5.4, The Cochrane Collaboration, Copenhagen, Denmark) were used for all meta-analyses. To generate forest plots of continuous data and examine differences in t-PA concentrations between COVID-19 patients with severe vs non-severe groups or survivor vs non-survivor status during follow-up, standard mean differences (SMD) and 95% confidence intervals (CIs) were determined. A p-value of 0.05 was judged statistically significant. When t-PA levels were provided as medians with an interquartile range, Hozo's method for estimating means and standard deviations was utilized [31]. The p-value of the Q test and the I^2 statistic were used to assess study heterogeneity. A fixed-effects model was adopted since an I^2 of 50% was regarded as exhibiting low or moderate heterogeneity. We also ran a sensitivity analysis to evaluate how each study influenced the pooled estimate.

RESULTS

Study characteristics

Based on the above-mentioned inclusion criteria, we identified 1,548 reports and screened their summaries for eligibility after removing duplicates. 683 articles were screened according to their titles and abstracts. Full-text screening was performed on 27 studies, and data for 13 studies were extracted for this meta-analysis [4–6, 8–10, 12, 22, 25, 32–35]. A flow chart of

the literature search and study selection is presented in Figure 1. Among the included trials, nine studies reported the t-PA values among COVID-19 positive vs. negative patients. Four studies reported the correlation coefficient between t-PA concentration and ICU admission as well as COVID-19 survivability. In turn, three studies referred to the levels of t-PA between severe and non-severe courses of COVID-19.

The systematic review included articles published between 2020 and 2022, comprising a total of 948 COVID-19 participants. Baseline characteristics of selected studies are presented in Table 1. The study quality assessed by using the NOS scores was ≥ 7 for all included trialtrials (Table 1).

Meta-analysis

Nine trials reported t-PA levels among COVID-19 positive vs. negative patients [4–6, 9, 12, 14, 22, 32, 35]. t-PA levels among those groups varied and amounted to 26.67 ± 40.65 vs 4.68 ± 3.83, respectively (SMD = 2.49; 95% CI: 1.85 to 3.14; $p < 0.001$; Figure 2).

The mean t-PA level among patients requiring ICU admission was 24.06 ± 12.44, compared to 16.55 ± 10.01 for patients not treated in ICU (SMD = 0.69; 95% CI: −0.68 to 2.05; $p = 0.32$; Figure S1) [5, 8, 12, 22]. Moreover, t-PA levels among severe COVID-19 compared to non-severe was 11.89 ± 9.05 and 16.87 ± 20.39, respectively (SMD = 2.74; 95% CI: −0.71 to 6.19; $p = 0.12$; Figure S2) [9, 32, 35].

Only four trials reported t-PA levels in surviving and dead COVID-19 patients [25, 33, 34]. The t-PA values were respectively: 15.33 ± 8.01 for patients who survived to hospital discharge, and 19.04 ± 11.88 for patients who died in hospital due to COVID-19 (SMD = −0.50; 95% CI: −2.45 to 1.44; $p = 0.61$; Figure S3).

Discussion

In this systematic review and meta-analysis of 14 studies, including patients from 8 countries, we evaluated the serum t-PA levels of patients infected with COVID-19. Our aim was to assess its correlation with patients' clinical outcomes.

Due to the dramatic situation of patients as well as medical professionals' work overload during the COVID-19 pandemic, we consider it paramount to identify sensitive biomarkers supporting the diagnostics and treatment processes of the most severe patients. Such information might play a key role in the allocation of limited resources and therefore contribute to appropriate patient management.

As hypercoagulability appears to be an essential hallmark of COVID-19 [36], evaluating markers of coagulation seems reasonable. Normally, there is an equilibrium between coagulation and fibrinolysis. Any imbalance between them might trigger serious conditions. Enhanced coagulation may lead, for instance, to thrombosis, stroke, or myocardial infarction, while hyperfibrinolysis might result in anomalous bleeding [37]. Furthermore, on histopathological examinations of lung specimens from COVID-19 patients with severe disease, fibrin-based occlusions of small vessels have been described as a result of increased blood coagulation [38, 39]. It is also proven that COVID-19 patients present not only hypercoagulability but also impaired fibrinolysis [8]. Coagulopathy in SARS-CoV-2 infection is multifactorial and accompanied by endothelial cell, neutrophil, and platelet activation, in addition to compensatory fibrinolysis. Various mechanisms have been suggested as the reason for coagulation disorders [9].

Changes in the equilibrium between the levels of t-PA and PAI-1 can indicate the procoagulant state brought on by endothelial activation [40]. t-PA is an enzyme responsible for the conversion of plasminogen into plasmin, which constitutes a part of the clot formation process. Despite being a fibrinolytic mediator, t-PA is found to be higher in COVID-19 patients with poor outcomes. This paradox may be explained by the contribution of PAI-1. PAI-1, a major inhibitor of t-PA, can be released from damaged endothelium simultaneously with t-PA [9]. Numerous studies mention an increased plasma level of PAI-1 in COVID-19 patients with poor outcomes [9, 12, 41]. High PAI-1 levels might overcome the fibrinolytic system despite the increased release of t-PA by facilitating the dissociation of t-PA from the surface of vascular endothelial cells (VES). Therefore, cell surface-associated fibrinolytic potential would be decreased [8, 42] and the state mentioned by Hammer as t-PA resistance would occur [12]. These hemostatic abnormalities are exacerbated by the severity of the disease and strongly correlate with proinflammatory status, demonstrating the link between coagulation and inflammation. Both t-PA and PAI-1 release are enhanced by proinflammatory stimuli [5] (Figure 3).

Recent studies have already described hypercoagulability and resistance to fibrinolysis [4]. It is worth mentioning that besides thrombosis, there is research that mentions bleeding events and literature data on hemorrhagic complications in COVID-19 patients during hospitalization [4, 5]. Extremely high levels of tPA enhance fibrinolysis and are associated with mortality in some individuals, which confirms the presence of a subset of patients that may favor fibrinolysis [6]. Since COVID-19 infection is associated with increased thrombotic

risk, prophylactic antithrombotic treatment has been highly recommended. We would like to pay attention to a subset of individuals who favor fibrinolysis and suggest targeted and individualized treatment based on the patient's clinical presentation and diagnostic findings. We believe that the risk of bleeding should always be taken into account. On the other hand, anticoagulant therapy alone might turn out to be less effective in decomposing fibrin clusters because of increased plasma levels of PAI-1 in COVID-19 patients, and more complex treatment may be required [22].

The results of our meta-analysis show the potential clinical role of tPA in patients with COVID-19. Results showed that tPA is significantly higher in COVID-19-positive individuals than in healthy individuals 26.67 ± 40.65 vs 4.68 ± 3.83, respectively ($p < 0.001$). Considering that high levels of t-PA correlate with SARS-CoV-2 infection, this marker may potentially be a tool for the early identification of patients most likely to benefit from early antiviral therapy. Assessment of t-PA plasma levels may also be useful in identifying patients who might be at risk of enhanced fibrinolysis caused by extremely high t-PA levels, as mentioned before.

Our study shows the role of tPA in the prediction of ICU admission in patients with COVID-19. The mean t-PA level among patients requiring ICU admission was 24.06 ± 12.44, compared to 16.55 ± 10.01 for patients not treated in ICU ($p = 0.32$). This meta-analysis also shows the potential use of tPA as a prognostic marker of survival in patients with COVID-19. The t-PA values were respectively: 15.33 ± 8.01 for patients who survived hospital discharge and 19.04 ± 11.88 for patients who died in hospital due to COVID-19 ($p = 0.61$). However, we observed lower plasma concentrations of tPA in severe cases compared to non-severe COVID-19 positive cases (11.89 ± 9.05 and 16.87 ± 20.39; $p = 0.12$). Studies that do show significant plasma t-PA level differences between ICU and non-ICU patients [9] or between patients presenting severe and non-severe symptoms [10] have been performed; nevertheless, in our study, these differences didn't reach statistical significance. A biomarker cannot be translated into clinical practice and guidelines for treatment until it is proven to have a significant impact; therefore, the potential use of plasma t-PA levels as a biomarker of disease severity in COVID-19 needs further investigation.

Future studies about tPA concentration are needed to determine the cutoff points for clinical outcomes. This study should be valuable for the ongoing debate on coagulation biomarkers in COVID-19 since it analyzes and summarizes a set of research findings and comes up with conclusions based on the complex assessment of a large cohort.

Limitations

Our meta-analysis should be interpreted with caution due to some limitations. We included mostly prospective studies, which may constitute a risk of introducing bias. Additionally, hospital inpatients and those in critical care may have received higher prophylactic doses of thromboprophylaxis, potentially influencing test results. Other studies were limited by small sample sizes or could not provide longitudinal data. Enrollment of patients in different stages and severity of lung disease leads to heterogeneity, which may influence the interpretation of test results. Therefore, to confirm the findings presented, it is necessary to conduct thorough future studies that investigate whether t-PA can serve as a diagnostic indicator of the severity of COVID-19.

Conclusions

According to this meta-analysis, the key conclusion of this study is that COVID-19 infection is connected to t-PA levels. We indicated its potential usage as a COVID-19 biomarker and demonstrated its possible value in the diagnostic process. Nonetheless, extensive prospective studies addressing the possible diagnostic relevance of t-PA as a marker of COVID-19 severity are required to corroborate the presented results.

Article information and declarations

Data availability statement

The data that support the findings of this study are available on request from the corresponding author (A.S.).

Ethics statement

The data that support the findings of this study are available on request from the corresponding author (A.S.).

Author contributions

Conceptualization — K.D.; methodology — K.D. and M.P.; software — K.D., M.P and A.S.; validation — K.D., M.P., A.O. and A.S.; formal analysis — K.D., M.W.S. and A.S.; investigation — K.D.; resources — K.S. and L.S.; data curation — K.D., M.T., A.S., M.P. and M.W.S.; writing: original draft preparation — K.D., M.P., A.G., K.K., O.F., A.O.; writing: review and editing — K.D., M.R.H., M.T., A.S., A.G., K.K., O.F., M.P., A.K., A.O., M.W.S. and F.C.; visualization — K.D. and A.S.; supervision — K.D. and F.C; project administration — K.D. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare no conflict of interest.

Supplementary material

The Supplementary Material for this article can be found online at: https://journals.viamedica.pl/disaster_and_emergency_medicine/article/view/97097

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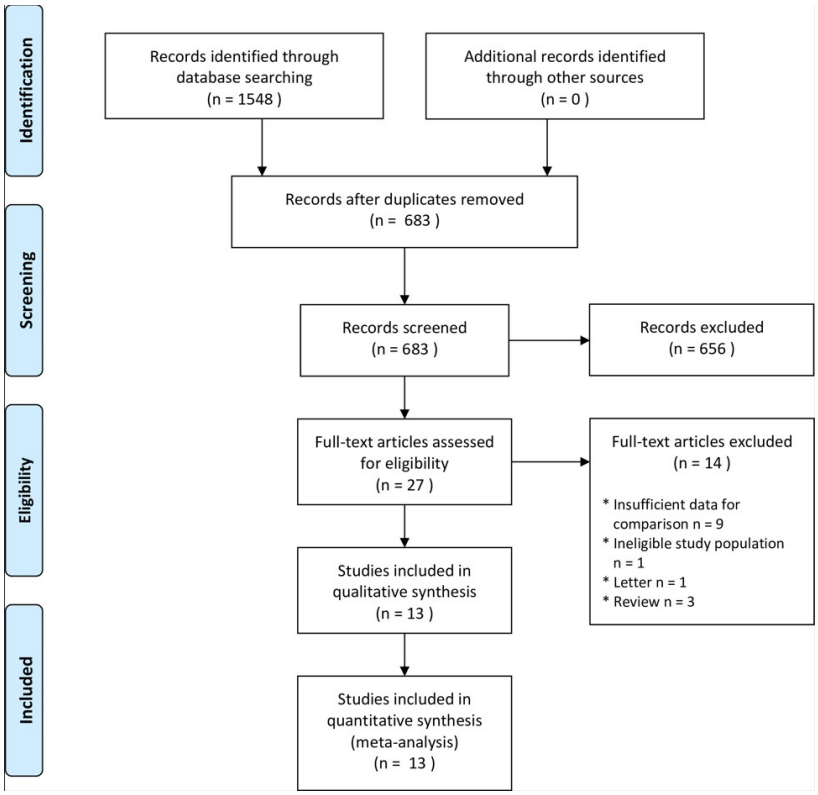

Figure 1. Flow diagram of the search strategy and study selection

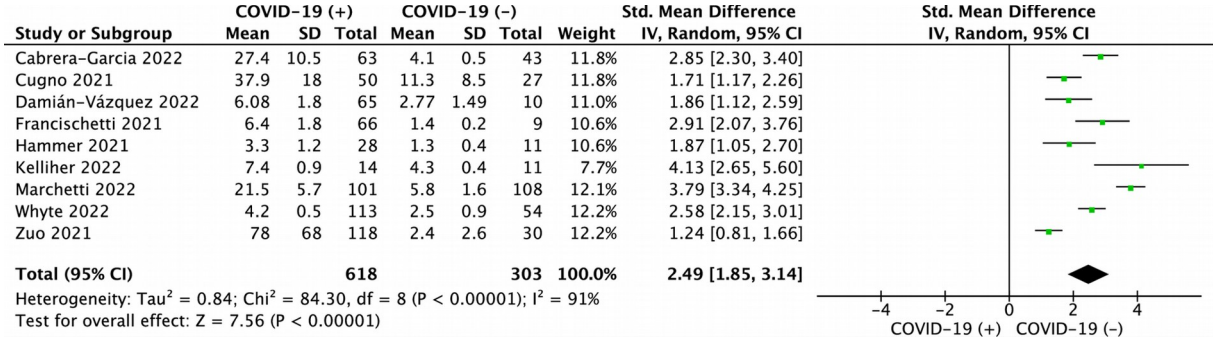

Figure 2. Forest plot of tPA levels among COVID-19 positive vs. negative patients. The center of each square represents the standardized mean differences for individual trials, and the corresponding horizontal line stands for a 95% confidence interval. The diamonds represent pooled results

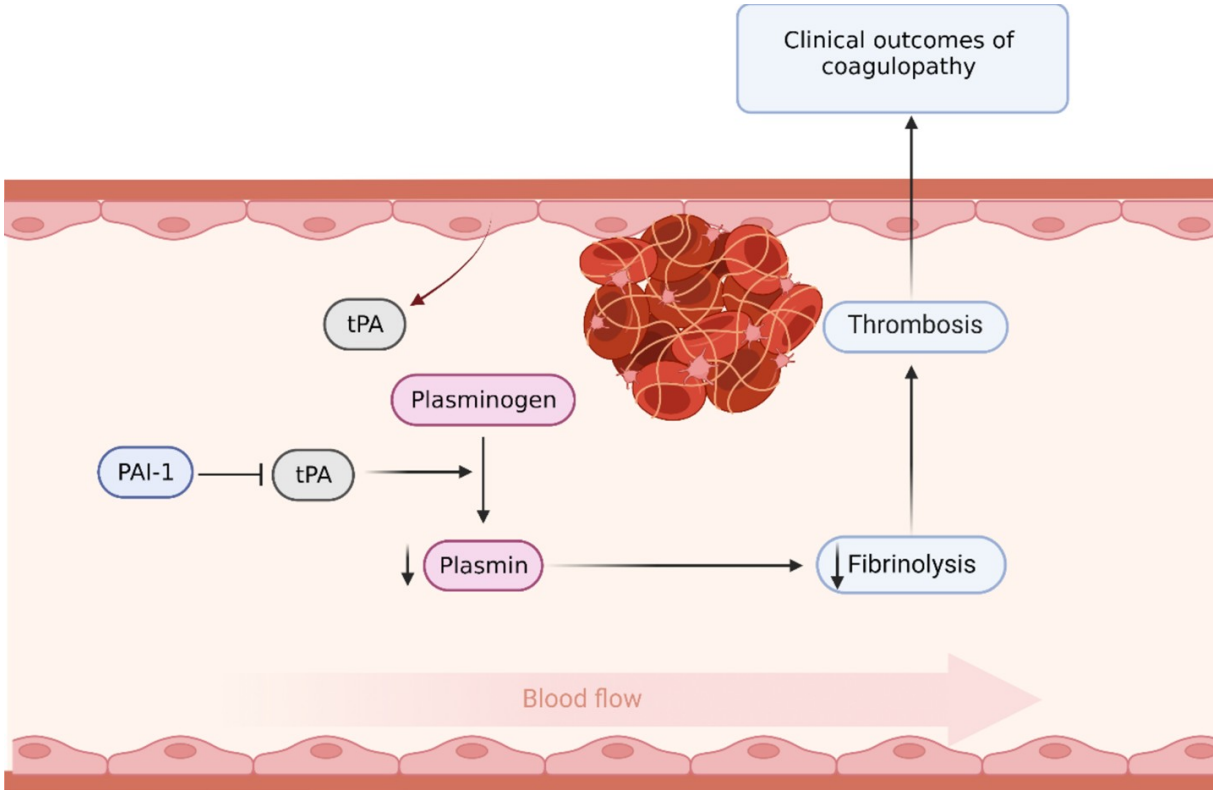

Figure 3. A visualization illustrating the effects of tPA

Table 1. Baseline characteristics of included trials

Study	Country	Study design	Study groups	No. of patients	Age	Sex, male	NOS
Cabrera-Garcia et al., 2022	USA	Prospective cohort study	ICU	47	61	28	8
			Non-ICU	16	59	8	
			COVID-19 (+)	63	60 (55–69)	36	
			COVID-19 (−)	43	45 (30–61)	20	
Cugno et al., 2021	Italy	Single center cohort study	Severe	46	NS	NS	8
			Non-severe	102	NS	NS	
			COVID-19 (+)	148	63 (26–92)	87	
			COVID-19 (−)	27	55 (34–78)	19	
Damián-Vázquez et al., 2022	Mexico	Single center cohort study	Severe	28	53.5 (17.4)	23 (82.1)	8
			Non-severe	37	44.7 (12.4)	19 (51.4)	
			COVID-19 (+)	65		42	
			COVID-19 (−)	10	46.2 (13.5)	7 (70.0)	
Francischetti et al., 2021	USA	Single center cross-sectional study	Severe	26	66 (34–78)	14 (53.8)	8
			Non-severe	40	47 (22–65.2)	19 (47.5)	
			COVID-19 (+)	66		33	
			COVID-19 (−)	9	47 (23–51)	5 (55.0)	
Gualtierotti et al., 2022	Italy	Single center cohort study	Survivors	57	68.2 (15.5)	34 (59.6)	7
			Non-survivors	8	79.8 (5.6)	3 (37.5)	
Hammer et al., 2021	Germany	Retrospective observational descriptive study	ICU	20	60 (55–75)	18	8
			Non-ICU	9	44 (14–76)	4	
			COVID-19 (+)	29		22	
			COVID-19 (−)	11	38 (25–47)	6	
Kelliher et al., 2022	Ireland	Single center cohort study	COVID-19 (+)	14	69.7 (16.9)	7	8
			COVID-19 (−)	11	61.6 (15.6)	3	
Marchetti et al., 2022	Italy	Two-center prospective study	ICU	46	62 (9)	35	8
			Non-ICU	55	71 (12)	38	
			COVID-19 (+)	101	NS	NS	
			COVID-19 (−)	108	NS	NS	
Nougier et al., 2020	France	Retrospective cohort study	ICU	48	62.8 (13.1)	NS	7
			Non-ICU	30	60.2 (14.6)	NS	
Ranucci et al., 2020	Italy	Prospective study	Survivors	8	59.6 (53.8–63.4)	7 (87.5)	8
			Non-survivors	12	69.4 (63.6–72.3)	9 (75.0)	

Sehgal et al., 2021	India	Prospective study	Survivors	59	NS	36	8
			Non-survivors	9	NS	7	
Whyte et al. 2022	UK	Prospective study	COVID-19 (+)	113	60.8 (12.6)	66 (58.4)	8
			COVID-19 (−)	24	64.4 (18.3)	10 (41.7)	
Zuo et al., 2021	USA	Prospective study	COVID-19 (+)	118	61 (17)	64	7
			COVID-19 (−)	30	NS	NS	

NOS — Newcastle Ottawa Scale; NS — not specified

Supplementary Material

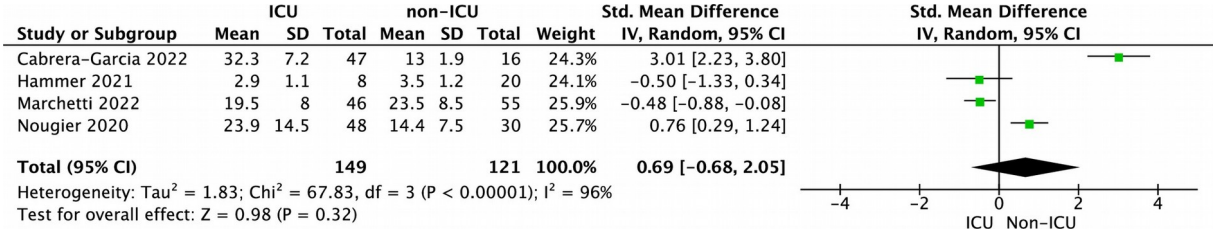

Figure S1. Forest plot of tPA levels among COVID-19 ICU vs non-ICU patients. The center of each square represents the standardized mean differences for individual trials, and the corresponding horizontal line stands for a 95% confidence interval. The diamonds represent pooled results

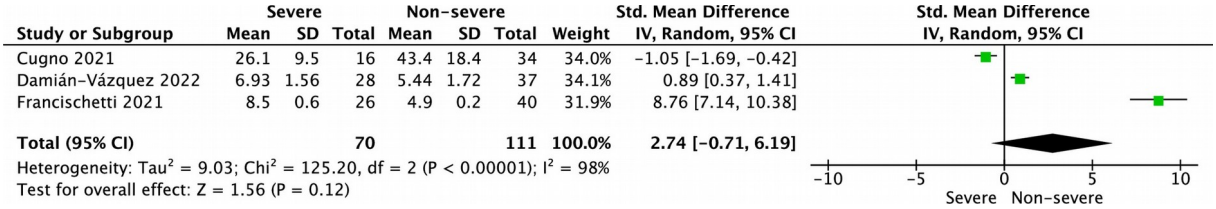

Figure S2. Forest plot of tPA levels among COVID-19 severe vs non-severe patients. The center of each square represents the standardized mean differences for individual trials, and the corresponding horizontal line stands for a 95% confidence interval. The diamonds represent pooled results

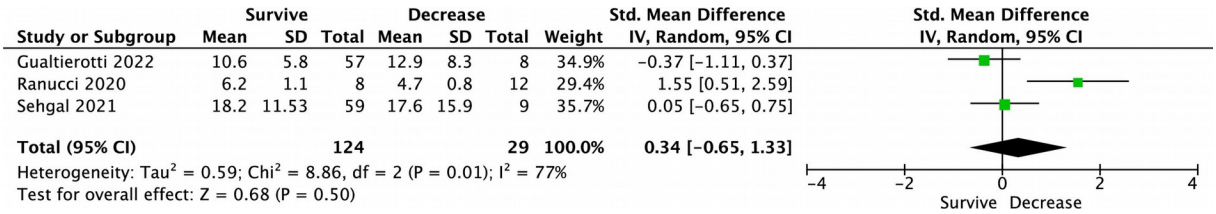

Figure S3. Forest plot of tPA levels among COVID-19 surviving vs desceased patients. The center of each square represents the standardized mean differences for individual trials, and the corresponding horizontal line stands for a 95% confidence interval. The diamonds represent pooled results