eJHaem

eJHaem

RESEARCH ARTICLE OPEN ACCESS

Therapeutic Versus Non-Therapeutic Dose Anticoagulation in COVID-19 Infection: A Systematic Review and Meta-analysis of Randomised Controlled Trials

Sushil Selvarajan[1] | Jisha Sara John[2] | Prathap Tharyan[3] | Richard Kirubakaran[3] | Bhagteshwar Singh[2,4,5] | Biju George[1] | Joseph L. Mathew[6] | Priscilla Rupali[2]

[1]Department of Clinical Haematology, Christian Medical College, Vellore, India | [2]Department of Infectious Diseases, Christian Medical College, Vellore, India | [3]Prof. BV Moses Centre for Evidence Informed Healthcare, Christian Medical College, Vellore, India | [4]Department of Clinical Infection Microbiology and Immunology, Institute of Infection Veterinary & Ecological Sciences, University of Liverpool, Liverpool, UK | [5]Centre for Evidence Synthesis in Global Health, Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, UK | [6]Advanced Paediatrics Centre, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Correspondence: Priscilla Rupali (priscillarupali@yahoo.com)

Received: 19 November 2024 | **Revised:** 14 December 2024 | **Accepted:** 19 December 2024

Funding: This work was supported by a research grant from Foreign, Commonwealth & Development Office through the READ-It Consortium (ROC11931038PG RBPS 03469 project/grant/RBPS No. NQ3).

Keywords: COVID-19 | heparin | SARS-CoV-2 | thromboprophylaxis

ABSTRACT

Background: Abnormal coagulation and thrombotic complications prompted many guidelines to recommend thromboprophylaxis for patients hospitalised with COVID-19, but the dose required for prophylaxis remains unclear. This systematic review (SR) analyses the safety and efficacy of therapeutic dose anticoagulation (TDA) versus non-therapeutic dose anticoagulation (NDA) in COVID-19 patients.

Methods: According to the *Cochrane Handbook of Systematic Review of Interventions*, we performed an SR. The protocol is registered in Prospero (CRD42021269197, date 12 August 2021).

Results: In this SR of 18 studies, TDA was shown to reduce all-cause mortality (risk ratio [RR] 0.83; 95% confidence interval [95% CI] 0.70, 0.99) in COVID-19 infection. TDA also reduced thrombosis (RR 0.55; 95% CI 0.48, 0.72) but increased major bleeding (RR 1.87; 95% CI 1.29, 2.69). A stratified analysis according to severity revealed that, in non-critical patients, TDA resulted in mortality benefit (RR 0.79; 95% CI 0.67, 0.94). In critical patients, TDA did not affect all-cause mortality (RR 1.03; 95% CI 0.89, 1.18) but reduced thrombosis (RR 0.65; 95% CI 0.48, 0.86) and increased major bleeding (RR 1.85; 95% CI 1.06, 3.23).

Conclusion: TDA significantly reduced all-cause mortality and thrombosis in non-critical COVID-19 patients at the expense of increased major bleeding. In critical COVID-19, this mortality benefit was not observed.

1 | Introduction

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has adversely impacted humanity in diverse ways. Clinical studies of patients with SARS-CoV-2 initially showed flu-like symptoms, most commonly cough, sore throat, fever, myalgia and fatigue at the onset of COVID-19 illness, proceeding in some to viral pneumonia of varying severity [1–5]. From the early days of the pandemic, abnormal coagulation profiles and thrombotic complications (both venous and arterial) were seen among hospitalised patients [6], with pulmonary embolism (PE) being a common manifestation [7].

Multiple autopsy reports of COVID-19 infection demonstrated unprecedented pulmonary microvascular thrombosis and endothelial damage [8–11], which could be related to the direct viral cytopathic effect on the endothelial cells due to shared receptors with pulmonary alveolar cells [12]. Other etiopathogenetic mechanisms include immune/cytokine-mediated dysregulation of pro-coagulant and anti-fibrinolytic pathways. Heparin, with its pleiotropic activity on inflammatory pathways, in addition to its primary use as a potent anticoagulant, appears to be an ideal intervention in such settings [13].

Although hypercoagulability in COVID-19 has now been well-recognised, uncertainty still exists as to how best to manage clotting risk in these patients. Over the past year, several guidance documents have recommended the use of anticoagulation in hospitalised patients with COVID-19 [14–16]. There is a broad-based consensus that the standard of care is prophylactic dose anticoagulation for all patients admitted with COVID-19 pneumonia.

Guidance presently recommends varying regimens of unfractionated heparin (UFH) or low molecular weight heparin, despite the paucity of evidence regarding the dose of anticoagulation, that is, prophylactic, intermediate or therapeutic (full) dose to be employed in each severity strata of COVID-19. European Society of Cardiology recommendations for antithrombotic therapy in patients hospitalised with moderate to severe COVID-19 suggested prophylactic anticoagulation with heparin only at the time of initiation [17]. It also remains unclear if specific severity subgroups of patients will benefit from TDA without a confirmed thrombotic event. To assess the efficacy and safety of these doses within diverse disease severity strata has been the goal of many completed and ongoing clinical trials.

2 | Methods

Our PICO question was: 'Should therapeutic dose anticoagulation (TDA) or non-therapeutic dose anticoagulation (NDA) be used in the management of COVID-19 patients'?

This systematic review (SR) and meta-analysis of randomised controlled trials (RCTs) comparing TDA versus NDA for thromboprophylaxis in COVID-19 patients was conducted following the Preferred Reporting Items for Systematic Reviews and Meta Analyses Statement [18] and registered on the Open Prospective Register of Systematic Reviews (PROSPERO) Framework (ID: CRD42021269197, date 12 August 2021) [19].

We did a literature search in PubMed (nih.gov), Cochrane Controlled Register of Trials (CENTRAL) | Cochrane Library, i L·OVE evidence (iloveevidence.com) and the COVID-19-specific source COVID-19 living data (covid-nma.com) on 13 January 2024 for peer-reviewed, primary research articles published from database inception up to the date of the literature search. We did not restrict the search by language, country, date or participant demographics. Details of search strategy can be found in Table S1.

We included only RCTs reporting the proportion of mortality, bleeding complications or thrombotic events in those infected with COVID-19 who received either TDA or NDA. We defined the 'TDA', as mentioned in Table 1, and doses less than therapeutic dose was defined as 'NDA' including standard prophylactic dose. We decided to exclude conference abstracts.

Titles and abstracts from the search were imported in Research Information System (.RIS) format and uploaded to the online SR tool Rayyan (Rayyan—Intelligent Systematic Review—Rayyan) for screening and duplicates were removed. Screening of titles and abstracts and full-text portable document formats was done in parallel by two authors (S.S. and J.J.), and a third author (P.R.) was consulted, if conflicts could not be resolved through discussion. Data were then independently extracted (by S.S. and J.J.) with a pre-authorised data extraction sheet. We contacted the investigators of HEP-COVID trial and Remap-CAP for additional information. We contacted the investigators of the ongoing trials to see if data were available for inclusion. Data from the HEP-COVID and COVID-HEP trials were extracted for separate analyses of critical and non-critical patients.

2.1 | Outcomes

The primary outcomes were as follows:

- All-cause mortality at 28 days
- Thrombosis
- Major bleeding

The secondary outcomes were as follows:

- Organ support-free days (i.e., number of days without the need for intensive care unit [ICU]-level organ support, including invasive and non-invasive mechanical ventilation)
- Survival without organ support at 28 days
- Composite outcome of thrombosis or death

The outcome all-cause mortality included all in-hospital deaths as well as up to day 28 if discharged. Thrombosis (defined as number of patients who had at least one thrombotic event, for example, deep vein thrombosis [DVT], PE, etc.), adverse events such as major bleeding (defined as the number of patients in whom at least one major bleeding event was seen as per ISTH criteria for assessing bleeding severity) or thrombocytopenia were also assessed [20].

When multiple articles of the same study population were published, all the articles were assessed and the latest one was considered for the extraction of data and if further data needed clarification, authors were contacted.

There are multiple dosing strategies for anticoagulation based on indication, organ dysfunction, body mass index and adverse drug reactions, based on available literature and package insert recommendations. For the purposes of our analysis, we broadly grouped prophylactic and intermediate doses as NDA (up to and including 1 mg/kg of enoxaparin or equivalent subcutaneously once daily) and TDA as doses higher than 1 mg/kg enoxaparin or equivalent subcutaneously twice daily, defined in Table 1.

TABLE 1 | Dose of anticoagulation.

Anti-coagulant	Therapeutic dose (INR 1.5–2.5)	Non-therapeutic dose	
		Intermediate dose	Prophylactic dose
Low molecular weight heparin	Enoxaparin 1 mg/kg q12h and equivalent	Enoxaparin 1 mg/kg q24h and equivalent	Enoxaparin 40 mg q24h (if BMI > 40, then 40 mg q12h) and equivalent
Unfractionated heparin	80 U/kg bolus followed by 18 U/kg/h infusion, targeting an APTT of 55–75 s	7500 U q12h to q8h	5000 U q12h to q8h
Directly oral anticoagulant	Rivaroxaban 20 mg PO OD or apixaban 5 mg BD Dabigatran 150 mg PO BD	Not applicable	Rivaroxaban 10 mg PO OD or apixaban 2.5 mg BD
Fondaparinux	<50 kg: 5 mg once daily SC; 50–100 kg: 7.5 mg once daily SC; >100 kg: 10 mg once daily SC	NA	2.5 mg once daily SC
Edoxaban	60 mg once daily (if body weight > 60 kg) PO or 30 mg once daily (if body weight < 60 kg or CrCl 30–50 mL/min) PO		
Dabigatran	150 mg PO twice daily		
Warfarin	Target INR of 2–3		

Abbreviations: APTT, Activated Partial Thromboplastin Time; BD, Bis in Die (twice daily); BMI, body mass index; CrCl, Creatinine Clearance; DOAC, Direct Oral Anti Coagulants; INR, international normalised ratio; NA, Not Available; OD, Once in a Day; PO, Per Oral; SC, Subcutaneous.

2.2 | Risk of Bias Assessment

We assessed the risk of bias (RoB) of each outcome of interest in each included study using the Cochrane RoB 2 tool [21]. Two review authors (S.S. and J.J.) independently assessed the RoB for each outcome using the RoB 2 tool to record assessments for each outcome. A third review author (P.R.) was consulted when there were discrepancies in judgement and arrived at a decision. We assessed the RoB as outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* [22]. The outcome-specific RoB assessment of each trial is represented in the traffic light format. We assessed the publication bias using funnel plots.

2.3 | Data Analysis

We assessed the efficacy of TDA versus NDA in COVID-19 patients by pooling risk ratios (RRs) using the Mantel–Haenzel random-effects model for RCTs for pooled analysis and fixed-effects model for stratified analysis by severity. An intention-to-treat analyses from the included studies was planned a priori. We used Revman Web (version 8.0.0) to do the meta-analysis and to create forest plots for the visualisation of the analysis and we assessed statistical heterogeneity using the I^2 statistic [23]. The heterogeneity was assessed in outcomes with I^2 value more than 40% with more than 10 studies.

We did stratified analysis of TDA based on the severity of disease, that is, effect of TDA in non-critical and critically ill patients as defined by the WHO COVID-19 clinical management guidelines (Table S2) [24].

2.4 | Assessment of Heterogeneity

We assessed the heterogeneity by visually inspecting the forest plot as well as by looking at the I^2 statistic. We performed sensitivity analysis by sequentially excluding each study and noting the I^2 value and RR for the outcomes that had an I^2 value greater than 40 when more than 10 studies were possible to include in the analysis.

2.5 | Assessing the Certainty of Evidence

We assessed the evidence quality for primary efficacy analyses and safety analyses using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework [25], based on RoB, inconsistency, imprecision, indirectness and reporting bias using the GRADE pro GDT [26].

3 | Results

3.1 | Study and Patient Characteristics

We screened 6690 potentially relevant publications (Figure 1) identified by keyword search (details in Table S2). After excluding all the irrelevant abstracts and duplications, we got 34 full-text articles, of which nine were excluded (12 publications) because of wrong comparators, one wrong study design, two wrong interventions and two were conference abstracts. We included 18 relevant studies with 10,234 patients that compared TDA with NDA. A summary of the characteristics of the included studies is found in Table 2. The outcomes obtained from each study, excluded studies, and ongoing trials are given in Tables S3, S4 and

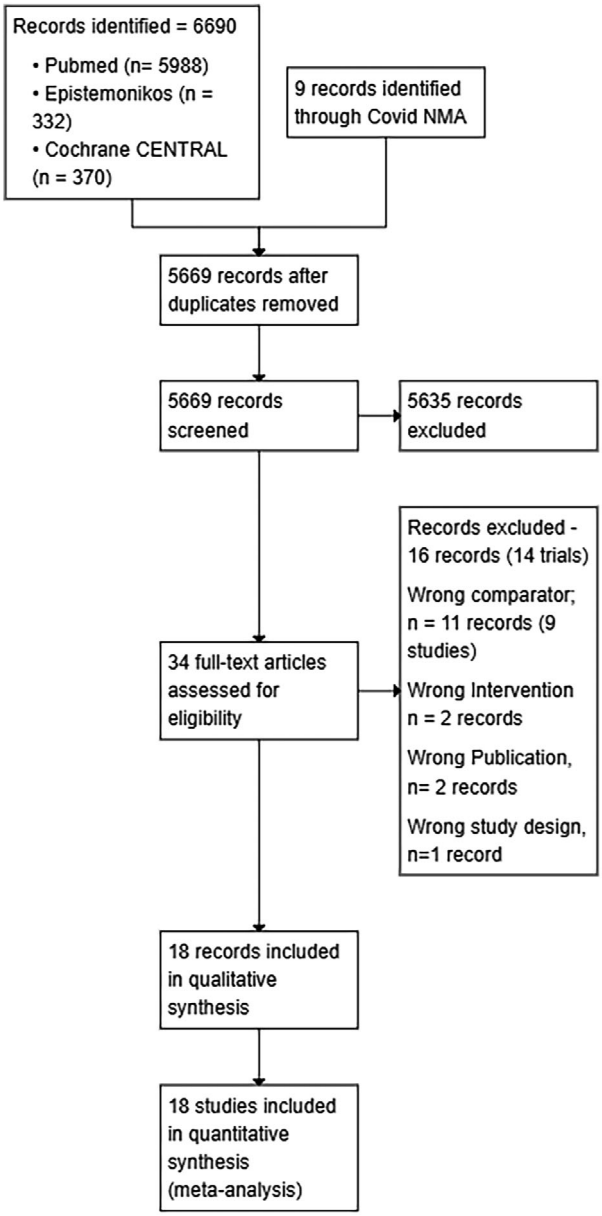

FIGURE 1 | Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) flow diagram.

S5. Studies were also stratified according to severity to assess if the dosages varied across categories of severity.

3.2 | Overall Risk of Bias

We judged six studies to have an overall low RoB [27–32]; 11 studies to have 'some concerns' [33–43] and one study had high RoB [44]. The RoB in each study is represented as a traffic light plot in Figure S1 and the RoB summary is represented in Figure S2.

3.3 | Publication Bias

There was funnel plot (Figure S3) asymmetry caused by two studies [36, 43] favouring NDA. These studies were of some concerns in RoB and were stopped prematurely.

3.4 | Outcome Analysis

Eighteen studies were included in the analysis of outcomes with the summary of findings in Table 3.

3.5 | Primary Outcomes

3.5.1 | All-cause Mortality

Moderate certainty evidence in 18 studies with 10,234 participants revealed that TDA probably reduced all-cause mortality (RR = 0.83; 95% CI = 0.70, 0.99; I^2 = 41%; p = 0.04) overall (Figure 2). The incidence of all-cause mortality was 9.97% (562/5636) in the group of patients on TDA and 12.48% (574/4598) in the NDA group. A sensitivity analysis was performed by sequentially removing each study as there was a moderate heterogeneity in the analysis (Table S7). The sensitivity analysis gave similar effect estimates, excluding any sampling errors.

3.5.2 | Thrombosis

High certainty evidence in 16 studies with 10,081 participants revealed that the TDA reduces thrombosis (RR = 0.59; 95% CI = 0.48, 0.72; I^2 = 0%; p < 0.00001; Figure 3). The incidence of thrombosis was 2.56% (142/5543) in those on TDA versus 5.53% (251/4538) in those on NDA.

3.5.3 | Major Bleeding

High certainty evidence in 17 studies with 10,114 participants revealed that there is an increase in major bleeding in the TDA group compared to the NDA group (RR = 1.87; 95% CI = 1.29, 2.69; I^2 = 0%; p = 0.0001; Figure 4). The incidence of major bleeding was 1.65% (92/5562) and 1.01% (46/4552) in the TDA and NDA groups.

3.6 | Secondary Outcomes

3.6.1 | Thrombosis or Death

Low certainty evidence in eight studies with 8540 revealed that TDA may reduce a composite outcome of thrombotic events or deaths (RR = 0.79; 95% CI = 0.65, 0.96; I^2 = 59%; p = 0.02; Figure 5). The incidence of thrombosis or death in the TDA arm was 11.00% (531/4824) and that of NDA was 15.79% (587/3716).

3.6.2 | Survival Without Organ Support at 28 Days

Moderate certainty evidence in six studies with 6800 participants revealed that TDA causes a slight increase in survival without organ support at 28 days compared to NDA (RR = 1.03; 95% CI = 1.01, 1.05; I^2 = 0%; p = 0.002; Figure 6). The survival rate at TDA was 87.13% (3407/3910) and that of NDA was 81.76% (2363/2890).

TABLE 2 | Outcomes extracted from each study.

Study ID	All-cause mortality	Thrombosis	Major bleeding	Thrombosis or death	Survival without organ support	Organ support free days
Connors MJ et al. (2021) ACTIV—IV B (NCT04498273)	×	×	×			
Marcos M et al. (2021) BEMICOP (NCT04604327)	×	×	×			
Verona JF et al. (2022) BEMICOVID 19 (NCT04420299)	×	×	×			
Lopez DR et al. (2021) ACTION-COALITION (NCT04394377)	×	×	×	×		
Sholzberg et al. (2021) RAPID TRIAL (NCT04362085)	×	×	×	×	×	
The REMAP-CAP, ACTIV-4a, and ATTACC Investigators Non-Critical (2021) (NCT04372589, NCT04505774, NCT02735707 and NCT04359277)	×	×	×	×	×	×
Spyropoulos AC et al. (2021) HEP-COVID (NCT04401293)	×	×	×	×		
Labbé V et al. (2023) ANTICOVID TRIAL (NCT04808882)	×	×	×	×	×	×
Olynyk et al. (2021) (CTR [Ukraine]: 0112U001413)	×					
Stone GW et al. (2023) FREEDOM COVID-19 (NCT04512079)	×	×	×	×	×	×
Muñoz-Rivas N et al. (2022) PROTHROMCOVID (NCT04730856)	×	×	×		×	
Lemos ACB et al. (2020) HESACOVID (REBEC RBR-949z6v)	×	×	×			×
The REMAP-CAP, ACTIV-4a and ATTACC Investigators—Critical (2021) (NCT04372589, NCT04505774, NCT02735707 and NCT04359277)	×	×	×	×		×
Bohula EA et al. (2022) COVIDPACT (NCT04409834)	×	×	×			
Rashidi F et al. (2022) (IRCT20200515047456N1)	×		×			
Blondon M (2022) SWISS COVID-HEP (NCT04345848)	×	×	×	×		
Rauch Krohnert U (2023) COVID-PREVENT (NCT044160048)	×	×	×			

3.6.3 | Organ Support-free Days

Organ support-free days were measured differently among the various studies with three studies reporting in median days and interquartile range (IQR) [34, 35, 38], one study reporting adjusted odds ratio, and one study reporting in mean days ± standard deviation (SD) [39]. One study reported both median and IQR, and mean and SD [28]. Since, they could not be pooled into a meta-analysis, the extracted data are represented in Table S6.

3.7 | Subgroup Analysis (Disease Severity)

Subgroup analyses were done to identify the impact of TDA versus NDA in various severity of COVID-19 illness. We analysed

TABLE 3 | Summary of findings.

***Question*: Is TDA compared to NDA useful in COVID-19 patients?**

***Patient or population*: COVID-19 patients**
***Setting*: Hospitalised or ambulatory patients with mild to critical disease**
***Intervention*: Therapeutic Dose of Anticoagulation (TDA)**
***Comparison*: Non-Therapeutic Dose of Anticoagulation (NDA)**

	Anticipated absolute effects[a] (95% CI)					
Outcomes	**Risk with NDA**	**Risk with TDA**	**Relative effect (95% CI)**	**No. of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
All-cause mortality	125 per 1000	105 per 1000 (87–125)	RR 0.83 (0.70–0.99)	10234 (18 RCTs)	⨁⨁⨁◯ Moderate[b,c,d]	TDA probably reduces all-cause mortality slightly compared to NDA
Thrombosis	55 per 1000	33 per 1000 (26–40)	RR 0.59 (0.48–0.72)	10081 (16 RCTs)	⨁⨁⨁⨁ High	TDA reduces thrombosis, when compared with NDA
Major bleeding	10 per 1000	20 per 1000 (14–29)	RR 1.87 (1.29–2.69	10114 (17 RCTs)	⨁⨁⨁⨁ High	TDA increases major bleeding, compared with NDA
Thrombosis or death	158 per 1000	125 per 1000 (103–152)	RR 0.79 (0.65–0.96)	8540 (8 RCTs)	⨁⨁◯◯ Low[c,e]	TDA may reduce the thrombotic events or death compared to NDA
Survival without organ support 28 days (excluding patients on organ support at baseline)	817 per 1000	841 per 1000 (825–858)	RR 1.03 (1.01–1.05)	6800 (6 RCTs)	⨁⨁⨁◯ Moderate[c]	TDA probably results in an increase in survival without organ support at 28 days (excluding patients on organ support at baseline), compared with NDA

Note: Grading of Recommendations, Assessment, Development and Evaluations (GRADE) Working Group grades of evidence—*high certainty*: we are very confident that the true effect lies close to that of the effect estimate. *Moderate certainty*: we are moderately confident in the effect estimate—the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. *Low certainty*: our confidence in the effect estimate is limited—the true effect may be substantially different from the estimate of the effect. *Very low certainty*: we have very little confidence in the effect estimate—the true effect is likely to be substantially different from the estimate of effect.

Abbreviations: CI, confidence interval; NDA, non-therapeutic dose of anticoagulation; RR, risk ratio; TDA, therapeutic dose of anticoagulation.

[a]The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b]Not downgrading for moderate heterogeneity ($I^2 = 41\%$), as the sensitivity analysis by sequentially removing each trial also shows similar effect sizes with lower heterogeneity values (check the table: sensitivity analysis).

[c]Downgrading by one level for serious indirectness: the differences in mechanisms of action and drug delivery caused concerns in comparability between the two interventions (DOACs and heparins) for these outcomes. Aspects such as the anti-inflammatory effects of heparins and dosages used in the Rivaroxaban regimen were also discussed in this regard. These putative differences in pharmacological characteristics between Rivaroxaban and heparin, beyond their direct antithrombotic effects, informed the decision to downgrade for indirectness in the outcomes not related to thrombosis or bleeding.

[d]Not downgrading for imprecision.

[e]Downgraded by one level for moderate heterogeneity ($I^2 = 59\%$).

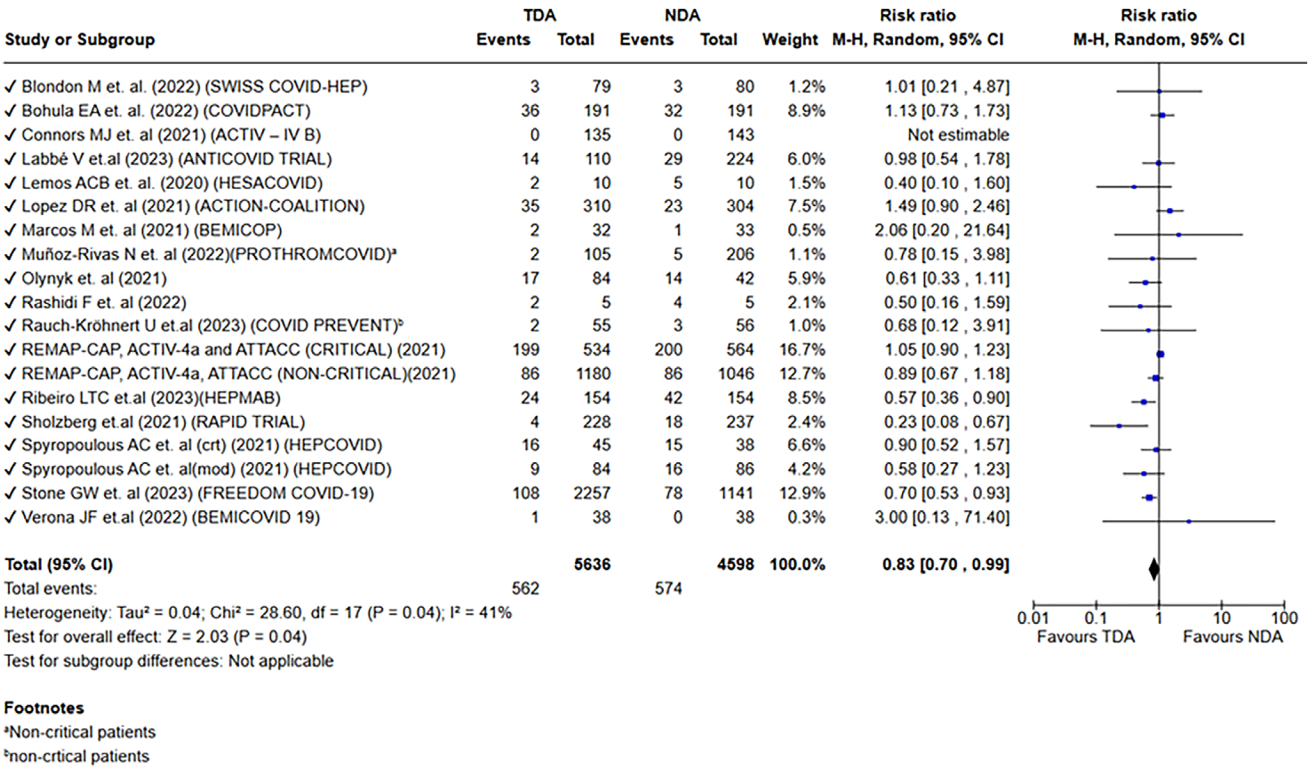

FIGURE 2 | Pooled analysis: all-cause mortality.

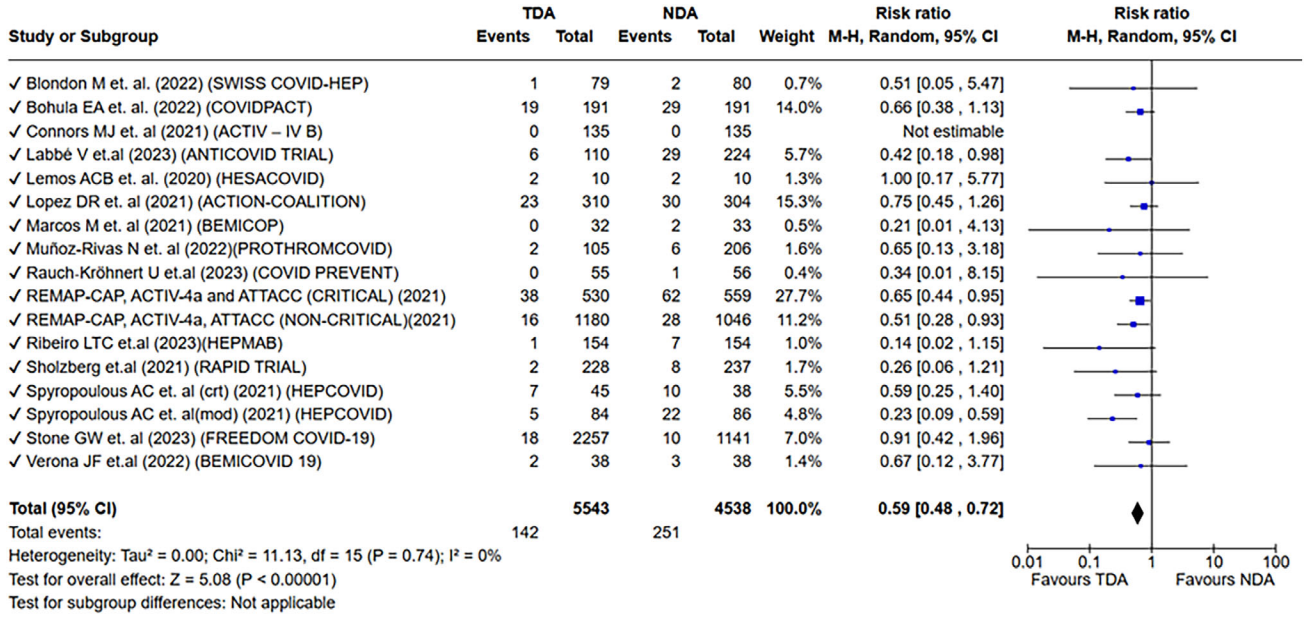

FIGURE 3 | Pooled analysis: thrombosis.

the outcomes of patients with critical and non-critical COVID-19 illness separately. The studies that included ambulatory patients and patients with overlapping disease severity were excluded [29, 34, 42].

3.8 | WHO Non-critical Group

Outcomes from 10 studies [28, 30–32, 34, 36, 39–41, 43] were analysed together.

- All-cause mortality: 10 studies with 7562 patients revealed mild reduction in all-cause mortality in patients using TDA versus NDA (RR = 0.79; 95% CI = 0.67, 0.94; $I^2 = 41\%$; $p = 0.08$). The incidence of all-cause mortality was 6.08% (266/4373) in the TDA group and 7.65% (244/3189) in the NDA group (Figure 7).
- Thrombosis: nine studies with 7436 participants showed that TDA reduces thrombosis (RR = 0.55; 95% CI = 0.41, 0.74; $I^2 = 0\%$; $p = 0.0004$). The incidence of thrombosis was 1.58%

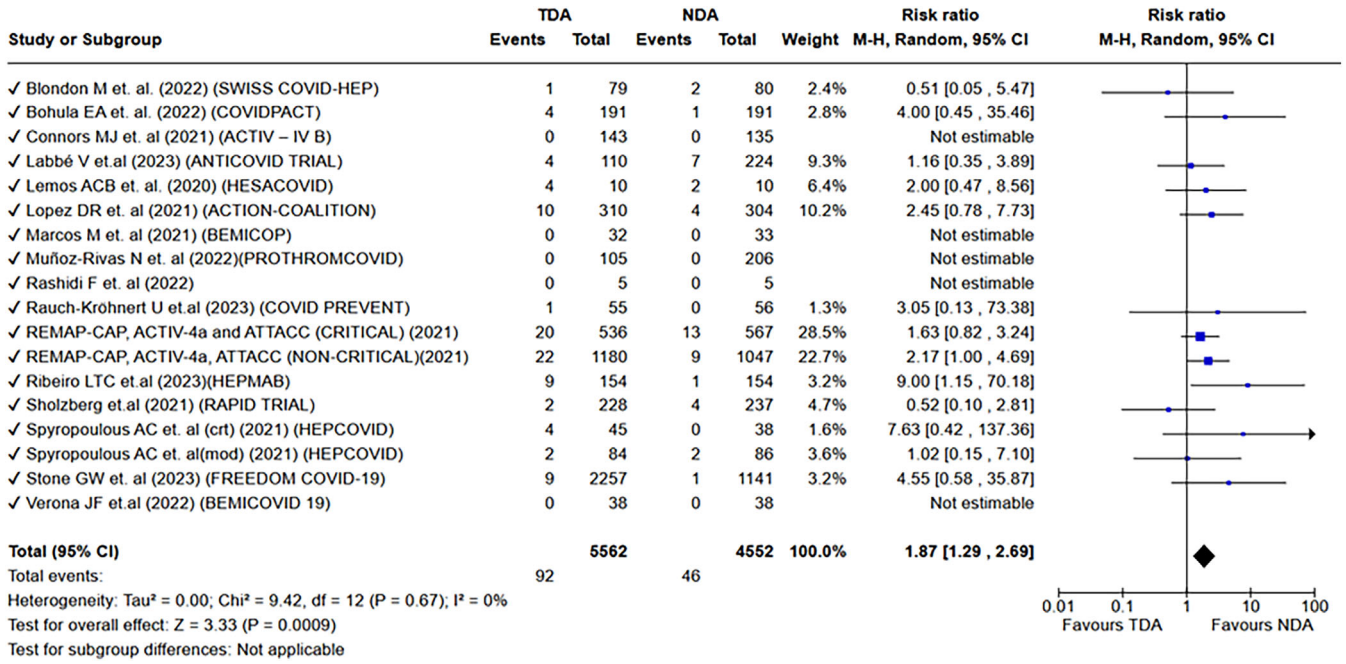

FIGURE 4 | Pooled analysis: major bleeding.

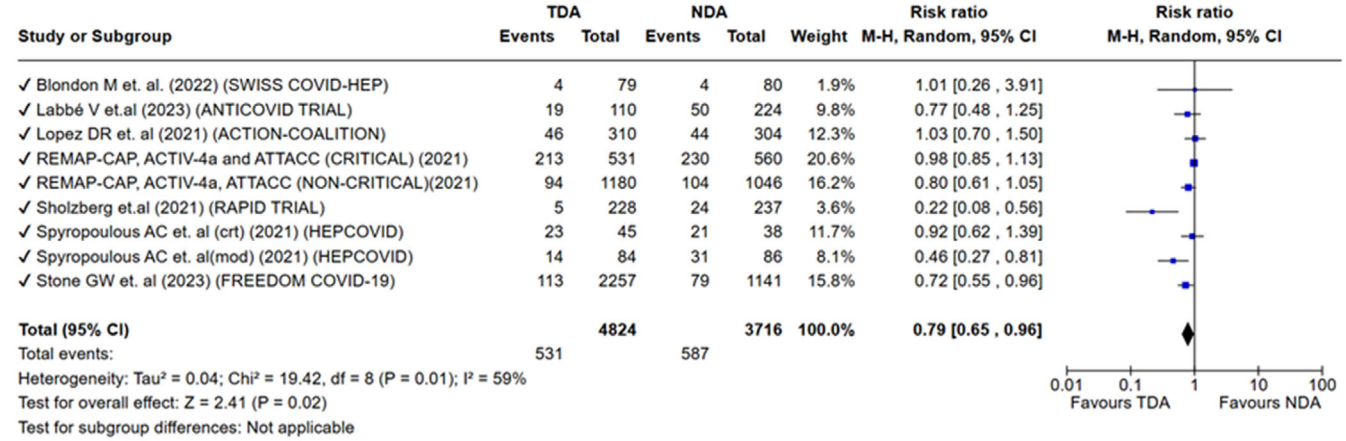

FIGURE 5 | Pooled analysis (thrombosis or death).

(68/4289) in the TDA group and 3.49% (110/3147) in the NDA group (Figure S4).

- Major bleeding: nine studies with 7437 participants showed that TDA increases the incidence of major bleeding (RR = 1.98; 95% CI = 1.17, 3.36; $I^2 = 0\%$; $p = 0.02$). The incidence of major bleeding was 1.07% (46/4289) in the TDA group and 0.63% (20/3148) in the NDA group (Figure S5).
- Thrombosis or death: six studies with 6873 participants showed that TDA reduces thrombosis or death (RR = 0.78; 95% CI = 0.62, 0.86; $I^2 = 68\%$; $p = 0.02$). The incidence of thrombosis or death was 6.70% (272/4059) in the TDA group and 10.02% (282/2814) in the NDA group (Figure S6).
- Survival without organ support at 28 days: six studies with 6800 participants revealed that TDA causes a slight increase in survival without organ support at 28 days compared to NDA (RR = 1.04; 95% CI = 1.01, 1.06; $I^2 = 0\%$; $p = 0.002$). The survival rate was 87.13% (3407/3910) in the therapeutic group and 81.76% (2363/2890) in the non-therapeutic group (Figure S6).

3.9 | WHO Critical Group

Outcomes from six studies [27, 32, 33, 35, 38, 44] were analysed together in the critical category of patients.

- All-cause mortality: six studies with 1681 participants showed that there is no effect of TDA on all-cause mortality as compared to NDA (RR = 1.03; 95% CI = 0.89, 1.18; $I^2 = 0\%$; $p = 0.72$). The incidence of all-cause mortality was 31.12% (258/829) in the TDA group and 30.39% (259/852) in the NDA group (Figure 7).

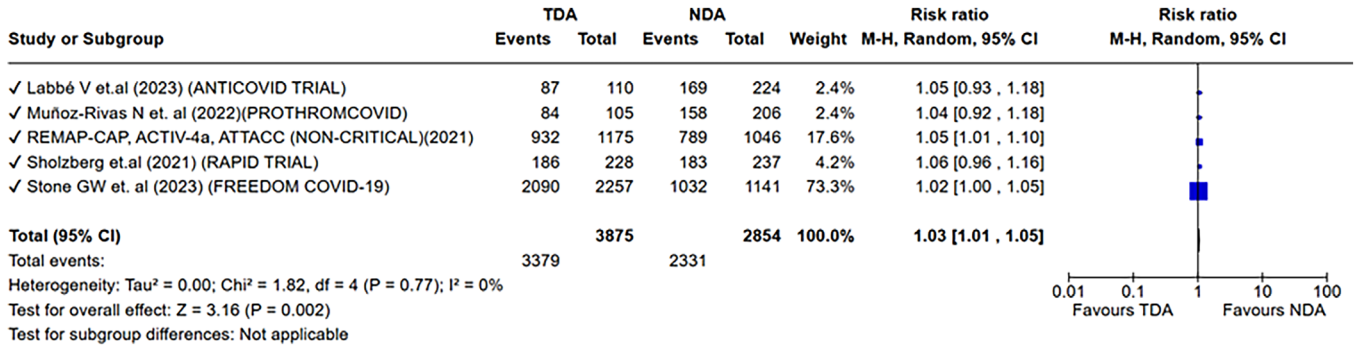

FIGURE 6 | Pooled analysis: survival without organ support at 28 days.

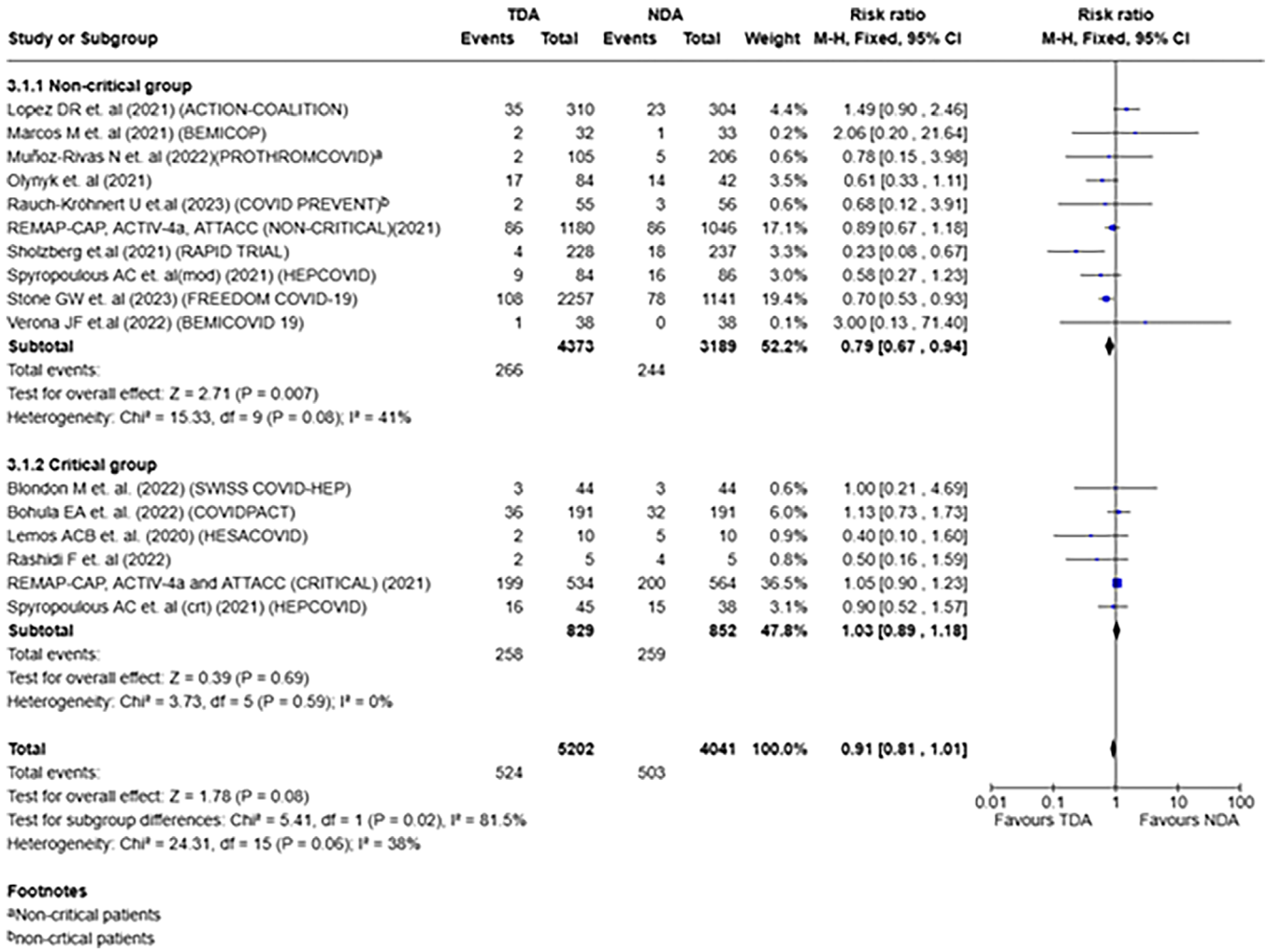

FIGURE 7 | Stratified analysis according to disease severity: all-cause mortality.

- Thrombosis: five studies with 1662 participants showed that TDA reduces thrombosis as compared to NDA (RR = 0.65; 95% CI = 0.48, 0.86; I^2 = 0%; p = 0.004). The incidence of thrombosis was 8.17% (67/820) in the TDA group and 12.47% (105/842) in the NDA group (Figure S4).
- Major bleeding: six studies with 1757 participants showed TDA increases major bleeding as compared to NDA (RR = 1.85; 95% CI = 1.06, 3.23; I^2 = 0%; p = 0.05). The incidence of major bleeding was 3.97% (33/831) in the TDA group and 2.10% (18/855) in the NDA group (Figure S5).
- Thrombosis or death: three studies with 1262 participants showed that TDA had no effect on reducing the composite outcome of 'thrombosis or death' as compared to NDA (RR = 0.97; 95% CI = 0.85, 1.11; I^2 = 0%; p = 0.67). The incidence of thrombosis was 38.70% (240/620) in the TDA group and 39.71% (255/642) in the NDA group.

3.10 | Number Needed to Treat-NNH Graph

The Number Needed to Treat (NNT) graph was generated for the outcomes all-cause mortality, thrombosis and major bleeding (Figure S8).

3.11 | Sensitivity Analysis

A sensitivity analysis was performed, and the results are shown in Tables S7 and S8.

4 | Discussion

COVID-19, caused by SARS-CoV-2, is a complex disease characterised by a wide range of symptoms. SARS-CoV-2 targets endothelial cells resulting in its dysfunction, which may lead to systemic damage, abnormal coagulation and the development of life-threatening complications such as PE and sepsis. Inflammation activates blood cells to encourage thrombin-mediated clot formation; besides, it releases cytokines such as tumour necrosis factor-alpha and interleukin-1 and -6, all participating in COVID-19 coagulopathy [45]. Tissue factor expression, on mononuclear cells, thus induced by the 'cytokine storm' in COVID-19, activates the coagulation cascade. Complement activation, enhanced von Willebrand factor release and antiphospholipid antibodies are some of the other mechanisms leading to critical vascular complications [45–47].

Studies show that about 17% of hospitalised COVID-19 patients experience venous thromboembolism (VTE), including 12.1% with DVT and 7.1% with PE. Additionally, 7.8% face bleeding complications, with 3.9% experiencing major bleeding, especially in critically ill patients [48].

A study that examined the incidence of VTE and arterial thromboembolism (ATE) following a COVID-19 diagnosis in five countries: the Netherlands, Italy, Spain, the UK and Germany, found significant variation in the risk of VTE across these countries [49].

The 90-day cumulative incidence of venous thrombosis ranged from two per 1000 in the Netherlands to eight per 1000 in Spain, while ATE incidence varied from one per 1000 in the UK up to eight per 1000 in Spain. Older age was associated with a higher risk of VTE after COVID-19, with a significantly increased risk of death following thrombotic events. In England, the cumulative excess risk of arterial thromboses within 49 weeks was 25 per 1000 and for venous thromboses was six per 1000, while in Sweden, the reported risk for venous events within 30 days was about two per 1000 [50].

This review indicates that, compared with NDA, patients receiving TDA had a lower composite endpoint of death or thrombosis, driven by a significantly lower rate of thrombotic events. This benefit is accompanied by increased major bleeding. In a stratified meta-analysis, TDA conferred no benefit in the critical group with regard to death or thrombosis but a minor benefit in the non-critical group. Application of TDA in COVID-19 patients for decreasing thrombosis risks, therefore, needs to be weighed against increased risks of major bleeding, which can be life threatening. Even though bleeding events were also higher in the TDA group, only seven of them were reported to be fatal [30, 34, 39] and one fatal bleeding event occurred in the NDA group. Even early in the pandemic, it was clear that anticoagulation increased the survival of patients, but the dosing of anticoagulation remained controversial.

An existing SR comparing escalated-dose (intermediate-dose or therapeutic-dose) versus standard-dose prophylactic anticoagulation regimen in critically and non-critically ill COVID-19 patients requiring hospitalisation revealed no reduction in all-cause mortality but was associated with an increase in major bleeding [51]. Escalated doses were associated with lower rates of VTE but had no significant effect on systemic arterial embolism or myocardial infarction/stroke [36, 38, 39]. A living SR by Reis et al. [52, 53] similar to our meta-analysis revealed that TDA was beneficial for non-critical patients in terms of both mortality and thrombotic events. A similar review suggested a pragmatic approach using prophylactic dose anticoagulation in critically ill patients and TDA in non-critically ill patients [54]. Our analysis approach was unique from the above reviews in that we used a clinically relevant categorisation of the anticoagulation dose (see section on 'Strengths').

Several studies have investigated the efficacy of TDA in reducing the need of mechanical ventilation and progression of the disease. Despite its small size, HESACOVID trial found that a therapeutic dose of anticoagulant (enoxaparin or UFH) significantly reduced the need for mechanical ventilation and improved blood gas parameters in a small group of patients with severe disease [35]. The RAPID trial, involving 465 patients with elevated D-dimer values, compared standard prophylactic and therapeutic doses of heparin. While the TDA did not significantly reduce the primary outcome (a composite of death, invasive mechanical ventilation, non-invasive mechanical ventilation, or admission to ICU), it was associated with a significantly lower mortality rate [31]. The BEMICOP Study compared therapeutic and prophylactic doses of bemiparin in COVID-19 patients with non-severe pneumonia but elevated D-dimer. The primary efficacy outcome (a composite of death, ICU admission, mechanical ventilation, moderate/severe acute respiratory distress, and VTE or ATE) did not differ significantly between the two groups [36].

Two trials used novel oral anticoagulants, that is, rivaroxaban and apixaban, which act by directly inhibiting the factor Xa, rather than heparin. Heparin has been reported to also have an anti-inflammatory action, which may have also contributed to improved outcomes in COVID-19 [29, 30]. However, it also carries bleeding risks, which need careful monitoring in COVID-19 patients [55]. However, the absolute contribution of this mechanism if any would need to be explored further in clinical trials.

Long COVID-19, a multi-systemic condition affecting characterised by persistent symptoms beyond 4 weeks involves ongoing vascular endothelial damage that promotes platelet adhesion and coagulation, leading to impaired organ function [56, 57]. Early intervention including anticoagulation may protect the vascular endothelium, reduce thrombotic risks and improve the quality of life for affected patients [58].

4.1 | Strengths and Limitations

Our SR included only RCTs and classified the COVID-19 severity as per the WHO classification [Table S1] [21] and attempted to derive the dose of anticoagulation required according to severity strata [Table 1]. We defined anticoagulation doses as TDA and NDA, with intermediate doses falling under NDA. Unlike other reviews that compared prophylactic versus escalated doses, many platform trials (e.g., REMAP-CAP, ACTIV-4a and ATTACC) applied escalated anticoagulation doses as prophylaxis across severity levels. Only the HEP-COVID trial disaggregated data by disease severity [22, 26].

One of the limitations in our analysis is that we have not distinguished between anticoagulation types. As aforementioned we considered therapeutic anticoagulation as per standard definitions specific for the various agents and have pooled data from the trials that used rivaroxaban, apixaban and heparins—including UFH, enoxaparin, tinzaparin and bemiparin.

5 | Conclusion

To conclude, TDA is beneficial in moderate to severe COVID-19 patients as it reduces the thrombosis and mortality, but with an increase in major bleeding. At present TDA is not beneficial in critical ill COVID-19 patients.

Author Contributions

Sushil Selvarajan and Jisha Sara John selected studies, assessed the risk of bias, extracted data, synthesised data, and prepared initial drafts of backgrounds, methods, results, discussion and summary of findings table. Richard Kirubakaran and Bhagteshwar Singh helped to complete the methods. Biju George and Priscilla Rupali did the conceptualisation of the PICO and reviewed the manuscript. Prathap Tharyan and Joseph L. Mathew reviewed the methods and summary of findings. All authors read and approved the final review version prior to publication.

Acknowledgements

We acknowledge the assistance of Ewan Golliger of REMAP-CAP, ACTIV-4a and ATTACC Investigators and Alex Spyropoulous of HEP-COVID trial for their valuable assistance in providing additional data as well as the clarification of the trial data. We acknowledge the kind assistance of Hanna Alexander, Jane Miracline and Naveena Princy of IDTRC, at CMC Vellore for editing the manuscript. This work was supported by a research grant from Foreign, Commonwealth & Development Office through the READ-It Consortium (ROC11931038PG RBPS 03469 project/grant/RBPS No. NQ3). This systematic review is registered with the International Prospective Register of Systematic Reviews (PROSPERO) under the ID: CRD42021269197 (dated 12 August 2021).

Ethics Statement

This is a systematic review of primary trials and only a secondary analysis of data already published has been done. No patients were directly involved in this analysis. Hence, an ethics approval is not required.

Conflicts of Interest

The authors declare they have no conflicts of interest.

Data Availability Statement

This is a secondary analysis of data collected from primary clinical trials all of which have been referenced. All data used in this systematic review have been included in the manuscript, supplementary material and cited references. In case of further queries please contact corresponding author.

Clinical Trial Registration

The authors have confirmed clinical trial registration is not needed for this submission.

References

1. J. F. W. Chan, S. Yuan, K. H. Kok, et al., "A Familial Cluster of Pneumonia Associated With the 2019 Novel Coronavirus Indicating Person-to-Person Transmission: A Study of a Family Cluster," *The Lancet* 395, no. 10223 (2020): 514–523.

2. N. Chen, M. Zhou, X. Dong, et al., "Epidemiological and Clinical Characteristics of 99 Cases of 2019 Novel Coronavirus Pneumonia in Wuhan, China: A Descriptive Study," *The Lancet* 395, no. 10223 (2020): 507–513.

3. W. J. Guan, Z. Y. Ni, Y. Hu, et al., "Clinical Characteristics of Coronavirus Disease 2019 in China," *New England Journal of Medicine* 382, no. 18 (2020): 1708–1720.

4. C. Huang, Y. Wang, X. Li, et al., "Clinical Features of Patients Infected With 2019 Novel Coronavirus in Wuhan, China," *The Lancet* 395, no. 10223 (2020): 497–506.

5. D. Wang, B. Hu, C. Hu, et al., "Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China," *JAMA* 323, no. 11 (2020): 1061–1069.

6. N. Tang, D. Li, X. Wang, and Z. Sun, "Abnormal Coagulation Parameters are Associated With Poor Prognosis in Patients With Novel Coronavirus Pneumonia," *Journal of Thrombosis and Haemostasis* 18, no. 4 (2020): 844–847.

7. F. A. Klok, M. Kruip, N. J. M. van der Meer, et al., "Incidence of Thrombotic Complications in Critically Ill ICU Patients With COVID-19," *Thrombosis Research* 191 (2020): 145–147.

8. M. Ackermann, S. E. Verleden, M. Kuehnel, et al., "Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in COVID-19," *New England Journal of Medicine* 383, no. 2 (20209): 120–128.

9. B. T. Bradley, H. Maioli, R. Johnston, et al., "Histopathology and Ultrastructural Findings of Fatal COVID-19 Infections in Washington State: A Case Series," *The Lancet* 396, no. 10247 (2020): 320–332.

10. S. B. Polak, I. C. Van Gool, D. Cohen, J. H. von der Thüsen, and J. van Paassen, "A Systematic Review of Pathological Findings in COVID-19: A Pathophysiological Timeline and Possible Mechanisms of Disease Progression," *Modern Pathology* 33, no. 11 (2020): 2128–2138.

11. D. Wichmann, J. P. Sperhake, M. Lütgehetmann, et al., "Autopsy Findings and Venous Thromboembolism in Patients with COVID-19," *Annals of Internal Medicine* 173, no. 4 (2020): 268–277.

12. M. Hoffmann, H. Kleine-Weber, S. Schroeder, et al., "SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and is Blocked by a Clinically Proven Protease Inhibitor," *Cell* 181, no. 2 (2020): 271–280. e8.

13. L. Gozzo, P. Viale, L. Longo, D. C. Vitale, and F. Drago, "The Potential Role of Heparin in Patients with COVID-19: Beyond the Anticoagulant Effect. A Review," *Frontiers in Pharmacology* 11 (2020): 1307, 1-8, https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2020.01307/full.

14. A. Cuker, E. K. Tseng, R. Nieuwlaat, et al., "American Society of Hematology 2021 Guidelines on the Use of Anticoagulation for Thromboprophylaxis in Patients With COVID-19," *Blood Advances* 5, no. 3 (2021): 872–888.

15. L. K. Moores, T. Tritschler, S. Brosnahan, et al., "Prevention, Diagnosis, and Treatment of VTE in Patients with Coronavirus Disease 2019: CHEST Guideline and Expert Panel Report," *Chest* 158, no. 3 (2020): 1143–1163.

16. M. Bartoletti, O. Azap, A. Barac, et al., "ESCMID COVID-19 Living Guidelines: Drug Treatment and Clinical Management," *Clinical Microbiology and Infection* 28, no. 2 (2022): 222–238.

17. Task Force for the management of COVID-19 of the European Society of Cardiology. "ESC Guidance for the Diagnosis and Management of Cardiovascular Disease During the COVID-19 Pandemic: Part 2-care Pathways, Treatment, and Follow-up," *European Heart Journal* 43, no. 11 (2022): 1059–1103.

18. M. J. Page, J. E. McKenzie, P. M. Bossuyt, et al., "The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews," *BMJ* 372 (2021): n71.

19. OSF, "Anticoagulation Doses Used in Management of COVID-19 Patients, Stratified by Severity: A Systematic Review and Meta-Analysis of RCTs [Internet]," 2024 [cited 2024 Jun 21], https://osf.io/bqw7x/#!.

20. F. Rodeghiero, A. Tosetto, T. Abshire, et al., "ISTH/SSC Bleeding Assessment Tool: A Standardized Questionnaire and a Proposal for a New Bleeding Score for Inherited Bleeding Disorders," *Journal of Thrombosis and Haemostasis* 8, no. 9 (2010): 2063–2065.

21. J. A. C. Sterne, J. Savović, M. J. Page, et al., "RoB 2: A Revised Tool for Assessing Risk of Bias in Randomised Trials," *BMJ* 366 (2019): l4898.

22. J. P. T. Higgins, J. Thomas, J. Chandler, eds., *Cochrane Handbook for Systematic Reviews of Interventions Version 6.4 (updated August 2023)* (Cochrane, 2023), www.training.cochrane.org/handbook.

23. "Review Manager (RevMan) [Computer program]. Version: 8.0.0," *The Cochrane Collaboration*, June 20, 2024 at 12:10 GMT, www.revman.cochrane.org.

24. World Health Organization, "Therapeutics and COVID-19: Living Guideline, 31 March 2021," *World Health Organization*, (2021), https://iris.who.int/handle/10665/340374.

25. H. J. Schünemann, J. Brożek, G. H. Guyatt, and A. Oxman eds., *Handbook for Grading the Quality of Evidence and the Strength of Recommendations Using the GRADE Approach (Updated October 2013)* (GRADE Working Group, 2013), https://gdt.gradepro.org/app/handbook/handbook.html.

26. *GRADEpro GDT [Computer program] [Internet]* (Hamilton (ON): McMaster University (developed by Evidence Prime), 2024), https://www.gradepro.org/.

27. M. Blondon, S. Cereghetti, J. Pugin, et al., "Therapeutic Anticoagulation to Prevent Thrombosis, Coagulopathy, and Mortality in Severe COVID-19: The Swiss COVID-HEP Randomized Clinical Trial," *Research and Practice in Thrombosis and Haemostasis* 6, no. 4 (2022): e12712.

28. G. W. Stone, M. E. Farkouh, A. Lala, et al., "Randomized Trial of Anticoagulation Strategies for Noncritically Ill Patients Hospitalized with COVID-19," *Journal of the American College of Cardiology* 81, no. 18 (2023): 1747–1762.

29. J. M. Connors, M. M. Brooks, F. C. Sciurba, et al., "Effect of Antithrombotic Therapy on Clinical Outcomes in Outpatients with Clinically Stable Symptomatic COVID-19: The ACTIV-4B Randomized Clinical Trial," *JAMA* 326, no. 17 (2021): 1703–1712.

30. R. D. Lopes, P. G. M. De Barros e Silva, R. H. M. Furtado, et al., "Therapeutic versus Prophylactic Anticoagulation for Patients Admitted to Hospital With COVID-19 and Elevated D-dimer Concentration (ACTION): An Open-Label, Multicentre, Randomised, Controlled Trial," *The Lancet* 397, no. 10291 (2021): 2253–2263.

31. M. Sholzberg, G. H. Tang, H. Rahhal, et al., "Effectiveness of Therapeutic Heparin versus Prophylactic Heparin on Death, Mechanical Ventilation, or Intensive Care Unit Admission in Moderately Ill Patients With COVID-19 Admitted to Hospital: RAPID Randomised Clinical Trial," *BMJ* 375 (2021): n2400.

32. A. C. Spyropoulos, M. Goldin, D. Giannis, et al., "Efficacy and Safety of Therapeutic-Dose Heparin vs Standard Prophylactic or Intermediate-Dose Heparins for Thromboprophylaxis in High-Risk Hospitalized Patients with COVID-19: The HEP-COVID Randomized Clinical Trial," *JAMA Internal Medicine* 181, no. 12 (2021): 1612–1620.

33. E. A. Bohula, D. D. Berg, M. S. Lopes, et al., "Anticoagulation and Antiplatelet Therapy for Prevention of Venous and Arterial Thrombotic Events in Critically Ill Patients with COVID-19: COVID-PACT," *Circulation* 146, no. 18 (2022): 1344–1356.

34. V. Labbé, D. Contou, N. Heming, et al., "Effects of Standard-Dose Prophylactic, High-Dose Prophylactic, and Therapeutic Anticoagulation in Patients with Hypoxemic COVID-19 Pneumonia: The ANTICOVID Randomized Clinical Trial," *JAMA Internal Medicine* 183, no. 6 (2023): 520–531.

35. A. C. B. Lemos, D. A. do Espírito Santo, M. C. Salvetti, et al., "Therapeutic versus Prophylactic Anticoagulation for Severe COVID-19: A Randomized Phase II Clinical Trial (HESACOVID)," *Thrombosis Research* 196 (2020): 359–366.

36. M. Marcos-Jubilar, F. Carmona-Torre, R. Vidal, et al., "Therapeutic Versus Prophylactic Bemiparin in Hospitalized Patients With Nonsevere COVID-19 Pneumonia (BEMICOP Study): An Open-Label, Multicenter, Randomized, Controlled Trial," *Thrombosis Haemostasis* 122, no. 2 (2022): 295–299.

37. O. Oliynyk, W. Barg, A. Slifirczyk, et al., "Comparison of the Effect of Unfractionated Heparin and Enoxaparin Sodium at Different Doses on the Course of COVID-19-Associated Coagulopathy," *Life* 11, no. 10 (2021): 1032.

38. The ATTACC, ACTIV-4a, and REMAP-CAP Investigators, "Therapeutic Anticoagulation With Heparin in Critically Ill Patients With COVID-19," *New England Journal of Medicine* 385, no. 9 (2021): 777–789.

39. The ATTACC, ACTIV-4a, and REMAP-CAP Investigators, "Therapeutic Anticoagulation With Heparin in Noncritically Ill Patients With Covid-19," *New England Journal of Medicine* 385, no. 9 (2021): 790–802.

40. U. Rauch-Kröhnert, M. Puccini, M. Placzek, et al., "Initial Therapeutic Anticoagulation With Rivaroxaban Compared to Prophylactic Therapy With Heparins in Moderate to Severe COVID-19: Results of the COVID-PREVENT Randomized Controlled Trial," *Clinical Research in Cardiology* 112, no. 11 (2023): 1620–1638.

41. N. Muñoz-Rivas, J. Aibar, C. Gabara-Xancó, et al., "Efficacy and Safety of Tinzaparin in Prophylactic, Intermediate and Therapeutic Doses in Non-Critically Ill Patients Hospitalized With COVID-19: The PROTHROMCOVID Randomized Controlled Trial," *Journal of Clinical Medicine* 11, no. 19 (2022): 5632.

42. L. T. C. Ribeiro, G. Landoni, V. C. Quintão, et al., "Effect of Heparin and Tocilizumab in Patients with Severe COVID-19: The HEPMAB Randomized Clinical Trial," *medRxiv* 2023: 2023.12.22.23300466.

43. J. F. Varona, E. Núñez, B. M. Fernández Félix, J. M. Castellano Vázquez, and A. Cubillo, "Efficacy and Safety of Therapeutic vs. prophylactic Bemiparin in Noncritically Ill Patients With COVID-19 Pneumonia," *European Journal of Internal Medicine* 99 (2022): 106–108.

44. F. Rashidi, S. Barco, P. Rezaeifar, et al., "Tissue Plasminogen Activator for the Treatment of Adults With Critical COVID-19: A Pilot Randomized Clinical Trial," *Thrombosis Research* 216 (2022): 125–128.

45. M. E. Farkouh, G. W. Stone, A. Lala, et al., "Anticoagulation in Patients with COVID-19," *Journal of the American College of Cardiology* 79, no. 9 (2022): 917–928.

46. M. Kohansal Vajari, M. Shirin, A. Pourbagheri-Sigaroodi, M. E. Akbari, H. Abolghasemi, and D. Bashash, "COVID-19-Related Coagulopathy: A Review of Pathophysiology and Pharmaceutical Management," *Cell Biology International* 45, no. 9 (2021): 1832–1850.

47. H. Jing, X. Wu, M. Xiang, L. Liu, V. A. Novakovic, and J. Shi, "Pathophysiological Mechanisms of Thrombosis in Acute and Long COVID-19," *Frontiers in Immunology* 13 (2022): 992384.

48. D. Jiménez, A. García-Sanchez, P. Rali, et al., "Incidence of VTE and Bleeding among Hospitalized Patients with Coronavirus Disease 2019," *Chest* 159, no. 3 (2021): 1182–1196.

49. E. Burn, T. Duarte-Salles, S. Fernandez-Bertolin, et al., "Venous or Arterial Thrombosis and Deaths Among COVID-19 Cases: A European Network Cohort Study," *The Lancet Infectious Diseases* 22, no. 8 (2022): 1142–1152.

50. W. Whiteley and A Wood, "Risk of Arterial and Venous Thromboses After COVID-19," *The Lancet Infectious Diseases* 22, no. 8 (2022): 1093–1094.

51. L. Ortega-Paz, M. Galli, D. Capodanno, et al., "Safety and Efficacy of Different Prophylactic Anticoagulation Dosing Regimens in Critically and Non-critically Ill Patients With COVID-19: A Systematic Review and Meta-Analysis of Randomized Controlled Trials," *European Heart Journal—Cardiovascular Pharmacotherapy* 8, no. 7 (2022): 677–686.

52. S. Reis, A. Faske, I. Monsef, et al., "Anticoagulation in COVID-19 Patients—An Updated Systematic Review and Meta-Analysis," *Thrombosis Research* 238 (2024): 141–150.

53. S. Reis, M. Popp, S. Schießer, et al., "Anticoagulation in COVID-19 Patients—An Updated Systematic Review and Meta-Analysis," *Thrombosis Research* 219 (2022): 40–48.

54. R. Ferrandis, P. Sierra, and A. Gomez-Luque, "COVID-19 Thromboprophylaxis. New Evidence," *Revista Española de Anestesiología y Reanimació (English Edition)* 71, no. 1 (2024): 34–47.

55. E. Gómez-Moyano, J. Pavón-Morón, J. Rodríguez-Capitán, et al., "The Role of Heparin in Postural Orthostatic Tachycardia Syndrome and Other Post-Acute Sequelae of COVID-19," *Journal of Clinical Medicine* 13, no. 8 (2024): 2405.

56. O. L. Aiyegbusi, S. E. Hughes, G. Turner, et al., "Symptoms, Complications and Management of Long COVID: A Review," *Journal of the Royal Society of Medicine* 114, no. 9 (2021): 428–442.

57. C. Wang, C. Yu, H. Jing, et al., "Long COVID: The Nature of Thrombotic Sequelae Determines the Necessity of Early Anticoagulation," *Frontiers in Cellular and Infection Microbiology* 12 2022: 1-14, https://doi.org/10.3389/fcimb.2022.861703.

58. A. Carfì, R. Bernabei, and F. Landi, Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent Symptoms in Patients after Acute COVID-19. *JAMA* 324, no. 6 (2020): 603–605.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.