The optimal anticoagulation strategy for COVID-19, prophylactic or therapeutic?: a meta-analysis, trial sequential analysis, and meta-regression of more than 27,000 participants

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Abstract
Background: Anticoagulants are promising regimens for treating coronavirus disease 2019 (COVID-19). However, whether prophylactic or intermediate-to-therapeutic dosage is optimal remains under active discussion.

Methods: We comprehensively searched PubMed, Embase, Scopus, Web of Science, Cochrane Library, ClinicalTrials, and MedRxiv databases on April 26, 2022. Two independent researchers conducted literature selection and data extraction separately according to predetermined criteria. Notably, this is the first meta-analysis on COVID-19, taking serious consideration regarding the dosage overlap between the 2 comparison groups of prophylactic anticoagulation (PA) and intermediate-to-therapeutic anticoagulation (I-TA).

Results: We included 11 randomized controlled trials (RCTs) and 36 cohort studies with 27,051 COVID-19 patients. By analyzing all the RCTs, there was no significant difference in mortality between the PA and I-TA groups, which was further confirmed by trial sequential analysis (TSA) (odds ratio [OR]: 0.93; 95% confidence interval [CI]: 0.71–1.22; P = 0.61; TSA adjusted CI: 0.71–1.26). The rate of major bleeding was remarkably higher in the I-TA group than in the PA group, despite adjusting for TSA (OR: 1.73; 95% CI: 1.15–2.60; P = 0.009; TSA adjusted CI: 1.09–2.58). RCTs have supported the beneficial effect of I-TA in reducing thrombotic events. After including all studies, mortality in the I-TA group was significantly higher than in the PA group (OR: 1.38; 95% CI: 1.15–1.66; P = 0.0005). The rate of major bleeding was similar to the analysis from RCTs (OR: 2.24; 95% CI: 1.86–2.69; P < 0.00001). There was no distinct difference in the rate of thrombotic events between the 2 regimen groups. In addition, in both critical and noncritical subgroups, I-TA failed to reduce mortality but increased major bleeding rate compared with PA, as shown in meta-analysis of all studies, as well as RCTs only. Meta-regression of all studies suggested that there was no relationship between the treatment effect and the overall risk of mortality or major bleeding (P = 0.14, P = 0.09, respectively).

Conclusion: I-TA is not superior to PA for treating COVID-19 because it fails to lower the mortality rate but increases the major bleeding rate in both critical and noncritical patients.

Keywords: Anticoagulation, COVID-19, Major bleeding, Mortality, Prophylactic, Therapeutic

Introduction
Coronavirus disease 2019 (COVID-19), an acute respiratory infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused a global pandemic. Although many studies have been conducted, effective treatment of patients with COVID-19 is still needed.[1,2] According to a report by the World Health Organization (WHO), as of May 2, 2022, there were more than 511 million confirmed COVID-19 cases, with approximately 6 million deaths worldwide.[3]

As the understanding of the mechanisms of COVID-19 continues to grow, microthrombi subsequent to the hypercoagulable state...
have been widely recognized as a key factor in organ failure and death.\(^4\)–\(^11\) SARS-CoV-2 enters target cells by binding to the angiotensin-converting enzyme 2 (ACE2) receptor, activating the renin-angiotensin system and the immune system, and triggering the release of angiotensin II and excessive inflammatory factors. This subsequently causes endothelial injury, thus leading to hypercoagulability. As the disease progresses, disseminated viral replication leads to widespread endotheliopathy, aggravating the prothrombotic state.\(^5\)–\(^6\) Several studies have found that patients with COVID-19 have a hypercoagulable state, with altered parameters including D-dimer, prothrombin time, activated partial thromboplastin time, fibrinogen, fibrin degradation product, and platelet count.\(^7\)–\(^12\),\(^13\) The hypercoagulable state provides the necessary conditions for extensive formation of microthrombus.\(^9\)–\(^11\) Parra-Medina et al.\(^10\) identified in 151 autopsies of patients with COVID-19 that 60% had microthrombi in the lungs, heart, kidneys, and liver. In an observational study, diffuse intravascular coagulation was reported in 71.4% of mortalities and 0.6% of surviving patients with COVID-19 during hospitalization.\(^8\) Hypercoagulability and thrombosis in COVID-19 are possible causes of increased mortality.\(^9\) A meta-analysis revealed that the mortality of patients with COVID-19 who took anticoagulants was significantly lower than that of patients who did not use anticoagulants.\(^14\) Therefore, anticoagulants are a promising treatment option for patients with COVID-19, because of their thromboprophylactic effect.

However, the optimal anticoagulant dosage remains controversial. Although the latest versions of the guidelines issued by the WHO and the United States all recommend prophylactic dosage,\(^15\),\(^16\) many studies found that despite using prophylactic anticoagulants, the incidence of thrombotic events is still high rather than intermediate or therapeutic dosage in hospitalized patients with COVID-19 without evidence of thromboembolism.\(^17\)–\(^19\) Therefore, administering a higher anticoagulant dose (intermediate or therapeutic) has been proposed and studied. However, it was also observed that intermediate or therapeutic dosage was not more effective than prophylactic dosage in reducing mortality in patients with COVID-19.\(^17\),\(^20\)

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**Figure 1.** Flowchart of literature selection process. I-TA, intermediate-to-therapeutic anticoagulation; PA, prophylactic anticoagulation.
Consequently, anticoagulant dosage for treating COVID-19 remains debatable.

Therefore, we conducted a meta-analysis, trial sequential analysis (TSA), and meta-regression to determine the optimal anticoagulant dosage, that is, intermediate-to-therapeutic (including intermediate and therapeutic) or prophylactic, for treating COVID-19.

**Materials and methods**

This meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,[21] with the PRISMA checklist provided in Supplementary Table 1, http://links.lww.com/ECCM/A31.

**Literature search**

A strict and comprehensive literature search of eligible studies was performed on April 26, 2022, in PubMed, Embase, Scopus, Web of Science, Cochrane Library, ClinicalTrials, and MedRxiv. The following terms were used in our search strategy: (COVID-19 OR novel coronavirus 2019 OR SARS-CoV-2 OR 2019-nCoV OR SARS-CoV-19 OR coronavirus disease 2019) AND (anticoagulant OR heparin OR Enoxaparin OR Dalteparin OR Fondaparinux OR warfarin OR rivaroxaban OR Dabigatran OR apixaban OR edoxaban OR thrombin inhibitors; Supplementary Table 2, http://links.lww.com/ECCM/A32). This meta-analysis aimed to assess the efficacy and safety of prophylactic anticoagulation (PA) versus intermediate-to-therapeutic (I-TA) therapy in patients with COVID-19. There were no restrictions on the language used, publication status, or publication date.

**Inclusion and exclusion criteria**

Qualification was inspected carefully according to a predefined selection criteria by reviewing the titles, abstracts, full manuscripts, and supplementary materials. We included studies that (1) enrolled adult inpatients with confirmed SARS-CoV-2 infections; (2) compared PA versus I-TA; (3) contained at least one of the following endpoints or outcomes: mortality, major bleeding, thrombotic events, pulmonary embolism, stroke, myocardial infarction, or venous thromboembolism; and (4) were eligible controlled studies. We excluded (1) studies that did not compare PA versus I-TA; (2) studies for which the numerical data of outcomes could not be acquired; (3) studies that applied the dosage of anticoagulants inconsistent with most studies included in our meta-analysis; and (4) studies with unsatisfactory methodological quality. The doses of the 2 anticoagulation regimens used in the included studies are listed in Supplemental Table 3, http://links.lww.com/ECCM/A33. There were few studies in which the specific doses of anticoagulation regimens were not described; we tacitly assumed that the doses used were widely accepted and could be included to avoid selection bias as much as possible.

**Study selection**

Two reviewers independently screened all the titles and abstracts to identify potentially eligible studies. The full text was then used to determine whether they could be included in our meta-analysis. Any discrepancies were resolved by discussion or if consensus could not be reached by a third investigator.

**Quality assessment and data extraction**

The methodological quality of randomized controlled trials (RCTs) and cohort studies was evaluated by 2 independent investigators using the Cochrane risk-of-bias tool Newcastle-Ottawa Scale (NOS), respectively.

Two researchers independently extracted relevant data from each eligible study using a standardized data extraction form. Extracted information included the characteristics of the included studies, baseline characteristics of participants, information on interventions, clinical outcomes, and results of comparison. For the characteristics of the included studies, we extracted the study type and setting, sample size, publication information, etc. For the baseline characteristics of participants, information on age, sex, and comorbidities were extracted. Regarding intervention, drugs and detailed dosages of the 2 regimen groups were extracted. For outcomes, we extracted the information on mortality, major bleeding, thrombotic events, pulmonary embolism, myocardial infarction, stroke, and venous thromboembolism.

**Outcomes and definitions**

The primary efficacy outcome was mortality and the primary safety outcome was the incidence of major bleeding. The secondary outcomes were the rates of thrombotic events, pulmonary embolism, stroke, myocardial infarction, and venous thromboembolism. Definitions of major bleeding, thrombotic events, and critically ill or noncritically ill patients are reported in the respective studies (Supplemental Table 4, http://links.lww.com/ECCM/A34).

**Grading the quality of evidence**

Two investigators assessed the quality of each outcome according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology. [22] The GRADE Profiler

| Table 1 | Baseline Characteristics of Patients With COVID-19 Included in the Meta-analysis |
|---------|----------------------------------|-------------------------------|------------------|
| **Baseline Characteristics** | **I-TA (n = 10,277)** | **PA (n = 16,774)** | **P** |
| Age, mean ± SD | 62.84 ± 15.30 | 62.80 ± 15.99 | 0.88 |
| Male, n (%) | 5583/9009 (61.97%) | 8321/14,430 (57.66%) | <0.0001 |
| Comorbidities, n (%) | | | |
| Diabetes mellitus | 2699/8248 (32.72%) | 3972/13,266 (29.90%) | <0.0001 |
| Cardiovascular disease | 1200/7038 (17.05%) | 1659/10,791 (15.37%) | 0.0029 |
| Hypertension | 3418/6849 (49.91%) | 5322/11,041 (48.20%) | 0.03 |
| Chronic kidney disease | 575/5565 (10.33%) | 1031/9333 (11.05%) | 0.17 |
| Smoker | 862/4508 (19.12%) | 1763/9035 (19.51%) | 0.59 |
| Heart failure | 665/4049 (16.42%) | 643/8270 (7.78%) | <0.0001 |
| Liver disease | 49/3246 (1.51%) | 101/5655 (1.79%) | 0.33 |
| Respiratory disease | 910/7028 (12.95%) | 1011/8109 (12.47%) | 0.38 |
| Cancer | 403/5271 (7.65%) | 764/9696 (7.88%) | 0.61 |

I-TA, intermediate-to-therapeutic anticoagulation; PA, prophylactic anticoagulation; SD, standard deviation.
| Authors          | Study Type | Setting  | Severity | Sample Size | Drugs                | Dosages                                      |
|------------------|------------|----------|----------|-------------|----------------------|----------------------------------------------|
|                  |            |          |          | I-TA        | PA                   | I-TA Dosages                                                                 |
|                  |            |          |          |             |                      |                               |
|                  |            |          |          | 1181        | 1050                 | CrCl ≥ 30 BMI < 40 Enoxaparin, 1 mg/kg sc bid or 1.5 mg/kg sc qd Dalteparin, 200 U/kg sc qd or 100 U/kg sc bid Tinzaparin, 175 U/kg sc qd Heparin, iv bolus with continuous infusion to titrate to anti-Xa 0.3–0.7 IU/mL or corresponding aPTT values |
|                  |            |          |          |             |                      |                               |
|                  |            |          |          |             |                      | CrCl ≥ 30 BMI ≥ 40 Enoxaparin, 1 mg/kg sc bid Dalteparin, 100 U/kg sc bid Tinzaparin, 175 U/kg sc qd Heparin, iv bolus with continuous infusion to titrate to anti-Xa 0.3–0.7 IU/mL or corresponding aPTT values |
|                  |            |          |          |             |                      | CrCl ≥ 30 BMI ≥ 40 Enoxaparin, 40 mg sc qd Dalteparin, 5000 U sc qd Tinzaparin, 4500 U sc qd Fondaparinux, 2.5 mg sc qd Heparin, 5000 U sc q8–12h |
|                  |            |          |          |             |                      | CrCl < 30 Enoxaparin, 1 mg/kg sc bid Dalteparin, 100 U/kg sc bid Tinzaparin, 175 U/kg sc qd Heparin, iv bolus with continuous infusion to titrate to anti-Xa 0.3–0.7 IU/mL or corresponding aPTT values |
|                  |            |          |          |             |                      | CrCl < 30 Enoxaparin, 40 mg sc bid Dalteparin, 5000 U sc qd Tinzaparin, 9000 U sc qd Heparin, 7500 U sc tid |
|                  |            |          |          |             |                      | CrCl > 30 BMI ≥ 40 Enoxaparin, 1 mg/kg sc bid Dalteparin, 100 U/kg sc bid Tinzaparin, 175 U/kg sc qd Heparin, iv bolus with continuous infusion to titrate to anti-Xa 0.3–0.7 IU/mL or corresponding aPTT values |
|                  |            |          |          |             |                      | CrCl > 30 BMI ≥ 40 Enoxaparin, 40 mg sc bid Dalteparin, 5000 U sc qd Tinzaparin, 4500 U sc qd Fondaparinux, 2.5 mg sc qd Heparin, 5000 U sc q8–12h |
|                  |            |          |          |             |                      | CrCl < 30 Enoxaparin, 1 mg/kg sc bid Dalteparin, 100 U/kg sc bid Tinzaparin, 175 U/kg sc qd Heparin, iv bolus with continuous infusion to titrate to anti-Xa 0.3–0.7 IU/mL or corresponding aPTT values |
|                  |            |          |          |             |                      | CrCl < 30 Enoxaparin, 40 mg sc bid Dalteparin, 5000 U sc qd Tinzaparin, 9000 U sc qd Heparin, 7500 U sc tid |
|                  |            |          |          |             |                      | CrCl ≥ 30 BMI ≥ 40 Enoxaparin, 1 mg/kg sc bid Dalteparin, 100 U/kg sc bid Tinzaparin, 175 U/kg sc qd Heparin, iv bolus with continuous infusion to titrate to anti-Xa 0.3–0.7 IU/mL or corresponding aPTT values |
|                  |            |          |          |             |                      | CrCl ≥ 30 BMI ≥ 40 Enoxaparin, 40 mg sc bid Dalteparin, 5000 U sc qd Tinzaparin, 4500 U sc qd Fondaparinux, 2.5 mg sc qd Heparin, 5000 U sc q8–12h |
|                  |            |          |          |             |                      | CrCl < 30 Enoxaparin, 1 mg/kg sc bid Dalteparin, 100 U/kg sc bid Tinzaparin, 175 U/kg sc qd Heparin, iv bolus with continuous infusion to titrate to anti-Xa 0.3–0.7 IU/mL or corresponding aPTT values |
|                  |            |          |          |             |                      | CrCl < 30 Enoxaparin, 40 mg sc bid Dalteparin, 5000 U sc qd Tinzaparin, 9000 U sc qd Heparin, 7500 U sc tid |
| Authors | Study Type | Setting | Severity | Sample Size | Drugs | Dosages |
|---------|------------|---------|----------|-------------|-------|---------|
| Lopes et al. [19] | RCT | Multicenter | Noncritical | 311 | Rivaroxaban | CrCl ≥ 30 BMI < 40 |
| | | | | | Enoxaparin | Rivaroxaban, 15 mg qd |
| | | | | | Fondaparinux | Enoxaparin, 1 mg/kg sc bid or 1.5 mg/kg sc qd |
| | | | | | UFH | UFH, 60 unit/kg iv bolus, then 12 U/kg/h and titrate for anti-Xa 0.3–0.7 IU/mL or corresponding target value of aPTT |
| | | | | | Stable patients: | CrCl ≥ 30 BMI < 40 |
| | | | | | Unstable patients | CrCl ≥ 30 BMI < 40 |
| | | | | | | Enoxaparin, 1 mg/kg sc bid | Enoxaparin, 1 mg/kg sc bid |
| | | | | | | UFH, 60 unit/kg iv bolus | UFH, 60 unit/kg iv bolus, then 12 U/kg/h and titrate for anti-Xa 0.3–0.7 IU/mL or corresponding target value of aPTT |
| | | | | | Intermediate dose | Intermediate dose |
| | | | | | Enoxaparin | Enoxaparin |
| | | | | | Fondaparinux | Fondaparinux |
| | | | | | UFH | UFH |
| | | | | | Stable patients: | CrCl ≥ 30 BMI < 40 |
| | | | | | Unstable patients | CrCl ≥ 30 BMI < 40 |
| | | | | | | Enoxaparin, 1 mg/kg sc bid | Enoxaparin, 1 mg/kg sc bid |
| | | | | | | UFH, 60 unit/kg iv bolus | UFH, 60 unit/kg iv bolus, then 12 U/kg/h and titrate for anti-Xa 0.3–0.7 IU/mL or corresponding target value of aPTT |
| | | | | | Intermediate dose | Intermediate dose |
| | | | | | Enoxaparin | Enoxaparin |
| | | | | | Fondaparinux | Fondaparinux |
| | | | | | UFH | UFH |
| | | | | | Stable patients: | CrCl ≥ 30 BMI < 40 |
| | | | | | Unstable patients | CrCl ≥ 30 BMI < 40 |
| | | | | | | Enoxaparin, 1 mg/kg sc bid | Enoxaparin, 1 mg/kg sc bid |
| | | | | | | UFH, 60 unit/kg iv bolus | UFH, 60 unit/kg iv bolus, then 12 U/kg/h and titrate for anti-Xa 0.3–0.7 IU/mL or corresponding target value of aPTT |

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4. Sadeghi-ipoor et al. [25]

5. Holberg et al. [26]
| Authors               | Study Type | Setting       | Severity | Sample Size | Drugs               | Dosages            |
|----------------------|------------|---------------|----------|-------------|---------------------|--------------------|
| Morici et al.        | RCT        | Multicenter   | All      | 6M          | Enoxaparin          | 40 mg sc bid       |
| Perpue et al.        | RCT        | Multicenter   | Critical | 7           | Enoxaparin          | Intermediate dose  |
| Olymyk et al.        | RCT        | Single center | Critical | 8           | LMWH-Enoxaparin     | 80 or 100 anti-Xa IU/kg sc qd |
| Varona et al.        | RCT        | Multicenter   | Noncritical | 9         | Bemiparin           | 115 IU/kg sc qd    |
| Marcose-Jubilar et al| RCT        | Multicenter   | Noncritical | 10        | Bemiparin           | 115 IU/kg sc qd    |
| Lemos et al.         | RCT        | Single center | All      | 11          | UFH                 | 10,000 IU sc qd    |
| Ionescu et al.       | Cohort study | Multicenter  | All      | 12          | UFH                 | Weight > 120 kg    |
| Nadkarni et al.      | Cohort study | Multicenter  | All      | 13          | UFH                 | UFH, 5000 IU sc qd |

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| Authors            | Study Type    | Setting     | Severity | Sample Size | Drugs       | Dosages                                      |
|--------------------|---------------|-------------|----------|-------------|-------------|----------------------------------------------|
|                    |               |             |          | I-TA | PA | I-TA | PA | I-TA | PA | I-TA | PA | I-TA | PA |
| I-TA PA I-TA PA I-TA PA | I-TA PA I-TA PA I-TA PA | I-TA PA I-TA PA I-TA PA | I-TA PA I-TA PA I-TA PA | I-TA PA I-TA PA I-TA PA | I-TA PA I-TA PA I-TA PA | I-TA PA I-TA PA I-TA PA | I-TA PA I-TA PA I-TA PA |
| 14 Meizlish et al [33] | Cohort study | Multicenter | All      | 760  | 1395 | Enoxaparin | Enoxaparin | Intermediate dose BMI < 40 | Enoxaparin, 30–40 mg sc qd or | Enoxaparin, 0.4–0.7 mg/kg sc bid or | <0.7 mg/kg sc qd or | <0.4 mg/kg sc bid |
|                    |               |             |          |     |     | UH | UH | BMI < 40 | UFH, 7500 U sc at any frequency | BMi ≥ 40 | UFH, 5000 or 7500 U sc tid | |
|                    |               |             |          |     |     | Bivalirudin | Enoxaparin | Therapeutic dose | Enoxaparin, >0.7 mg/kg sc bid or | ≥1.4 mg/kg qd | UH | Bivalirudin |
|                    |               |             |          |     |     | UH | UH | BMI < 40 | UFH or bivalirudin | Q<30 | |
|                    |               |             |          |     |     | Enoxaparin | UFH | BMI < 40 | UFH | Enoxaparin, >0.7 mg/kg sc qd | 40 or 60 or 80 or 120 mg sc bid | 40 mg sc qd | |
|                    |               |             |          |     |     | UFH | UFH | BMI < 40 | UFH | LMWH, 30–40 mg sc qd or bid | UFH | NM | NM |
| 15 Almohareb et al [34] | Cohort study | Multicenter | All      | 711  | 711  | Enoxaparin | Enoxaparin | Intermediate dose | Enoxaparin, >40 mg qd | Enoxaparin, <40 mg qd | Enoxaparin, 100–200 IU/kg sc qd | NM |
|                    |               |             |          |     |     | UFH | UFH | BMI < 40 | UFH | NM | NM |
| 16 Vaughn et al [35] | Cohort study | Multicenter | All      | 219  | 970  | NM | LMWH | Bemiparin, 115 anti-Xa IU/kg sc qd | Enoxaparin, 1 mg/kg sc qd | LMWH, 40 mg sc bid or 1 mg/kg sc bid | UH | 5000 U sc tid |
|                    |               |             |          |     |     | UFH | UFH | BMI < 40 | UFH | LMWH, 40 mg sc bid or 1 mg/kg sc bid | UH | 5000 U sc tid |
|                    |               |             |          |     |     | UFH | UFH | BMI < 40 | UFH | LMWH, 40 mg sc bid or 1 mg/kg sc bid | UH | 5000 U sc tid |
|                    |               |             |          |     |     | UFH | UFH | BMi ≥ 40 | UFH | LMWH, 40 mg sc bid or 1 mg/kg sc bid | UH | 5000 U sc tid |
| 17 Smadja et al [36] | Cohort study | Multicenter | All      | 261  | 783  | LMWH | LMWH | Bemiparin, 1 mg/kg sc qd | LMWH | LMWH | LMWH |
|                    |               |             |          |     |     | UFH | UFH | BMI < 40 | UFH | LMWH | LMWA |
| 18 Kaur et al [37] | Cohort study | Multicenter | All      | 381  | 652  | LMWH | LMWH | Bemiparin, >40 mg qd | UH | 5000 U sc tid | |
|                    |               |             |          |     |     | UFH | UFH | BMI < 40 | UFH | LMWH | LMWA |
| 19 Albani et al [38] | Cohort study | Single center | All | 312  | 487  | Enoxaparin | Enoxaparin | Intermediate dose | Enoxaparin, >40 mg qd | Enoxaparin, <40 mg qd | Enoxaparin, >40 mg qd | NM |
|                    |               |             |          |     |     | UFH | UFH | BMI < 40 | UFH | LMWH | LMWA |
| 20 Kuno et al [39] | Cohort study | Single center | All | 383  | 383  | Enoxaparin | Enoxaparin | Intermediate dose | Enoxaparin, 100–200 IU/kg sc qd | Enoxaparin, 1 mg/kg sc qd | LMWH, 40 mg sc bid or 1 mg/kg sc bid | UH | 5000 U sc tid |
| 21 Lavino et al [40] | Cohort study | Multicenter | Critical | 274  | 435  | Enoxaparin | Bemiparin | Intermediate dose | Bemiparin, 115 anti-Xa IU/kg sc qd | Bemiparin, 3500 IU sc qd | Enoxaparin, 40 mg sc qd | UH | 5000 U sc tid |
| 22 Kodama et al [41] | Cohort study | Single center | Noncritical | 82  | 498  | Bemiparin | Bemiparin | Intermediate dose | Bemiparin, 1 mg/kg sc qd | 1 mg/kg sc bid or 1.5 mg/kg sc qd | 1 mg/kg sc bid or 1.5 mg/kg sc qd | UH | 5000 U sc tid |
| 23 Gonzalez-Porras et al [42] | Cohort study | Single center | All | 120  | 410  | Enoxaparin | Enoxaparin | Intermediate dose | Enoxaparin, 1 mg/kg sc qd | 0.7–1 IU/mL | 1–3 IU/mL |
|                    |               |             |          |     |     | UFH | UFH | BMI < 40 | UFH | LMWH | LMWA |
| 24 Hsu et al [43] | Cohort study | Single center | All | 64  | 377  | Bemiparin | Bemiparin | Intermediate dose | Bemiparin, 1 mg/kg sc qd | 0.7–1 IU/mL | 1–3 IU/mL |
|                    |               |             |          |     |     | UFH | UFH | BMI < 40 | UFH | LMWH | LMWA |
| 25 Millet et al [44] | Cohort study | Single center | All | 225  | 215  | Apixaban | Apixaban | Intermediate dose | Apixaban, 5 mg sc bid | Apixaban, 2.5 mg sc bid | Apixaban, 2.5 mg sc bid | UH | 5000 U sc tid |
| 26 Mennuni et al [45] | Cohort study | Single center | All | 149  | 287  | NM | NM | Intermediate dose | NM | NM | NM |
| 27 Lynn et al [46] | Cohort study | Single center | All | 152  | 250  | NM | NM | Intermediate dose | NM | NM | NM |
| 28 Motta et al [47] | Cohort study | Single center | All | 75  | 259  | Enoxaparin | Heparin | Intermediate dose | Enoxaparin, 1 mg/kg sc bid or 1.5 mg/kg sc qd | Enoxaparin, 100–200 IU/kg sc qd | Heparin, 5000 U sc tid | |
|                    |               |             |          |     |     | UFH | UFH | BMI < 40 | UFH | LMWH | LMWA |
| 29 Alijuhani et al [48] | Cohort study | Multicenter | Critical | 176  | 176  | UFH | UFH | Intermediate dose | Enoxaparin, 1 mg/kg sc bid or 1.5 mg/kg sc qd | Enoxaparin, 40 mg sc qd | UH | 5000 U sc tid |
| 30 Yu et al [49] | Cohort study | Single center | Moderate, severe, critical | 133  | 215  | Enoxaparin | Apixaban | Intermediate dose | Apixaban, >5 mg bid | Heparin, 5000 U sc tid | |
| 31 Pesavento et al [50] | Cohort study | Single center | Noncritical | 84  | 240  | Fondaparinux | UFH | Intermediate dose | Fondaparinux, 2.5 mg sc qd | Fondaparinux, 2.5 mg sc qd | UH | 15,000 U sc tid |
| Authors            | Study Type | Setting | Severity | Sample Size | Drugs          | Dosages         |
|--------------------|------------|---------|----------|-------------|----------------|-----------------|
| Muoke et al. [51]  | Cohort study | Single center | All      | 102         | LMWH           | 1 mg/kg bid     |
|                    |            |         |          | I-TA        |LMWH           | Heparin, 5000 U sc bid ttd |
|                    |            |         |          | PA          |LMWH           | 40 mg qd        |
| Martinelli et al.  | Cohort study | Single center | All      | 127         | Enoxaparin     | ICU patients    |
|                    |            |         |          | I-TA        |Enoxaparin     | 1 mg/kg bid     |
| Gabara et al. [53] | Cohort study | Single center | Critical | 123         | Enoxaparin     | High intensity of care wards patients |
|                    |            |         |          | I-TA        |Dalteparin     | 0.7 mg/kg bid   |
|                    |            |         |          | PA          |Tinzaparin     | Low intensity of care wards patients |
|                    |            |         |          | I-TA        |Bemiparin      | 1 mg/kg qd      |
|                    |            |         |          | PA          |               | CrCl > 30       |
|                    |            |         |          | I-TA        |Enoxaparin, if > 80 kg: 60 mg sc qd; other condition: 1 mg/kg sc qd |
|                    |            |         |          | PA          |Fondaparinux, 5 mg sc qd | Therapeutic dose |
|                    |            |         |          | I-TA        |Tinzaparin, if > 90 kg: 50 IU/kg sc qd; other condition: 75 IU/kg sc qd |
|                    |            |         |          | PA          |Bemiparin, 5000 IU sc qd | CrCl < 30 |
|                    |            |         |          | I-TA        |Enoxaparin, 1.5 mg/kg sc qd or 1 mg/kg sc bid |
|                    |            |         |          | PA          |Fondaparinux, <50 kg: 5 mg sc qd; 51–100 kg: 7.5 mg sc qd; >100 kg: 10 mg sc qd |
|                    |            |         |          | I-TA        |Tinzaparin, 175 IU/kg sc qd |
|                    |            |         |          | PA          |Bemiparin, 115 IU/kg sc qd | Obese patients |
|                    |            |         |          | I-TA        |Enoxaparin, 40 mg sc qd; other condition: 0.5 mg/kg sc qd |
|                    |            |         |          | PA          |Fondaparinux, 2.5 mg sc qd | LMWH, up to 6000 IU sc bid |
|                    |            |         |          | I-TA        |Tinzaparin, >4500 IU qd Dalteparin, >5000 IU qd |
|                    |            |         |          | PA          |Bemiparin, 2500–4500 IU qd |
| Helms et al. [54]  | Cohort study | Multicenter | Critical | 71          | LMWH           | Obese patients |
|                    |            |         |          | I-TA        |UFH            | LMWH, 100 IU/kg sc qd |
|                    |            |         |          | PA          |UFH            | CRI < 30 mL/min |
|                    |            |         |          | I-TA        |LMWH           | LMWH, without exceeding 10,000 IU bid |
|                    |            |         |          | PA          |UFH            | 500 IU/kg qd    |
| Shah et al. [55]   | Cohort study | Multicenter | Critical | 27          | LMWH           | Obese patients |
|                    |            |         |          | I-TA        |UFH            | LMWH, 100 IU/kg sc qd |
|                    |            |         |          | PA          |UFH            | CRI < 30 mL/min |
|                    |            |         |          | I-TA        |LMWH           | LMWH, without exceeding 10,000 IU bid |
|                    |            |         |          | PA          |UFH            | 500 IU/kg qd    |
| Jonmarker et al.   | Cohort study | Single center | Critical | 85          | Dalteparin     | Obese patients |
|                    |            |         |          | I-TA        |Dalteparin     | Dalteparin, >4500 IU qd Dalteparin, >5000 IU qd |
|                    |            |         |          | PA          |Tinzaparin     | Dalteparin, 2500–4500 IU qd Dalteparin, 2500–5000 IU qd |
| Authors            | Study Type | Setting       | Severity | Sample Size | Drugs          | Dosages                                                                 |
|--------------------|------------|---------------|----------|-------------|----------------|-------------------------------------------------------------------------|
| Daughety et al.    | Cohort study | Single center | All      | 38          | Enoxaparin, Heparin | Enoxaparin, 1 mg/kg bid or 0.5–0.7 IU/mL in patients with renal failure |
| Copur et al.       | Cohort study | Single center | All      | 46          | LMWH            | LMWH 1 mg/kg sc bid or 40 mg sc qd                                      |
| Moll et al.        | Cohort study | Multicenter   | Critical | 47          | Enoxaparin, UFH | Enoxaparin, 40 mg sc qd or 1 mg/kg sc bid                               |
| Voicu et al.       | Cohort study | Single center | Critical | 43          | Enoxaparin, UFH | Enoxaparin, 40 mg sc qd or 1 mg/kg sc bid                               |
| Matli et al.       | Cohort study | Single center | All      | 31          | LMWH, UFH       | LMWH 1 mg/kg sc bid or 40 mg sc qd                                     |
| Poulakou et al.    | Cohort study | Multicenter   | All      | 54          | LMWH            | LMWH 1 mg/kg sc bid or 40 mg sc qd                                     |
| Longhitano et al.  | Cohort study | Single center | All      | 47          | Enoxaparin, UFH | Enoxaparin, 80 U/kg sc qd or 5000 U sc q8 h to 5000 U sc q8 h to 12h   |
| Nadeem et al.      | Cohort study | Single center | Critical | 40          | UFH, Fondaparinux | UFH 15,000 IU sc qd or 1500 IU sc q8 h to 1500 IU sc q8 h to 24h        |
| Elmelhat et al.    | Cohort study | Noncritical   | All      | 39          | Enoxaparin     | Enoxaparin, 1 mg/kg bid or 0.5 mg/kg bid                                |
| Zalivansky et al.  | Cohort study | Single center | All      | 35          | Enoxaparin     | Enoxaparin, 0.5 mg/kg sc bid or 1 mg/kg sc bid or 1.5 mg/kg sc bid or 40 mg sc qd |

aPTT, activated partial thromboplastin time; BMI, body mass index; CG, creatinine clearance; DOAC, direct oral anticoagulant; DUR, adjusted dose; IU, international unit; IV, intravenous; LMWH, low molecular weight heparin; NM, not mentioned; PA, prophylactic anticoagulation; PA, prophylactic anticoagulation; qd, once a day; qd, once a day; q8h, every 8 hours; q9h, every 9 hours; q12h, every 12 hours; q24h, every 24 hours; tid, three times a day; UFH, unfractionated heparin; Weight, weight-based heparin dose.
Figure 2. Efficacy of intermediate-to-therapeutic versus prophylactic anticoagulation on mortality in patients with COVID-19. (A) Pooled OR and forest plot of mortality. Forty-three studies were included in the statistical analysis, with 9,562 patients in the I-TA and 15,523 in the PA groups. The results showed that the mortality significantly decreased in the PA group compared with I-TA group (OR: 1.38; 95% CI: 1.15–1.66; P = 0.0005). (B) Trial sequential analysis of mortality. The X-axis represents sample size, and the Y-axis represents Z score. The uppermost and lowermost red curves represent trial sequential monitoring boundary lines for positive conclusion. The horizontal blue lines represent the conventional boundaries for statistical significance. The red triangular lines represent the futility boundary. The dark blue line is the Z curve representing the cumulative Z scores of included studies, arranged according to publication date. The RIS of 4,974 was calculated using α = 0.05 (2-sided), β = 0.20 (power 80%), and the relative risk of mortality increase was 34.53%. The results showed that the cumulative Z curve exceeded the RIS line, the final cumulative Z score located in the zone between futility boundaries, and the TSA adjusted the 95% CI to be 0.71 to 1.26. (C) Meta-regression of the association between log OR for mortality and overall risk (%). CI, confidence interval; I-TA, intermediate-to-therapeutic anticoagulation; OR, odds ratio; PA, prophylactic anticoagulation; RIS, required information size; TSA, trial sequential analysis.
(version 3.6) software was used. Quality was downgraded based on the following evaluations: risk of bias, inconsistency, indirectness, imprecision, and other considerations. Quality was upgraded if the magnitude of the treatment effect was very large, if there was evidence of a dose-response relationship, or if all reasonable biases would reduce but not increase the magnitude of the apparent treatment effect. The overall quality of the evidence was rated as “high,” “moderate,” “low,” or “very low.”

Figure 3. Effect of intermediate-to-therapeutic versus prophylactic anticoagulation on risk of major bleeding in patients with COVID-19. (A) Pooled OR and forest plot of major bleeding. Twenty-nine studies that reported major bleeding were included, with 6390 patients in the I-TA group and 10,152 in the PA group. The results showed that I-TA significantly increased the incidence of major bleeding compared with PA (OR: 2.24; 95% CI: 1.86–2.69; \( P < 0.00001 \)). (B) Trial sequential analysis of major bleeding. The uppermost and lowermost red curves represent trial sequential monitoring boundary lines for positive conclusion, the red triangle zone represents futility. The vertical red line represents the RIS of 1917, which was calculated using \( \alpha = 0.05 \) (2-sided), \( \beta = 0.20 \) (power 80%), and 105.02% of the relative risk of major bleeding increase. The horizontal blue lines represent the traditional boundaries for statistical significance. The cumulative Z curve represents the data of included studies, which were arranged based on publication date. The cumulative Z curve exceeded the line RIS and the conventional boundary. The TSA adjusted the traditional 95% CI to be 1.09 to 2.58. (C) Meta-regression of the association between log OR for major bleeding and overall risk (%). CI, confidence interval; COVID-19, coronavirus disease 2019; I-TA, intermediate-to-therapeutic anticoagulation; OR, odds ratio; PA, prophylactic anticoagulation; RIS, required information size; TSA, trial sequential analysis.
Data synthesis and analysis

Statistical analysis was performed using Review Manager (version 5.3), STATA (version 12.0), and TSA program version 0.9.5.10 (http://www.ctu.dk/tsa). For dichotomous variables, we calculated the risk ratio (RR), odds ratio (OR), and 95% confidence interval (CI) using the Mantel-Haenszel method. When only RCTs were analyzed, RR was selected as the effect value; otherwise, OR was used. Statistical heterogeneity of the included studies was quantified using $I^2$ values. $I^2$ values more than 50% indicate significant heterogeneity, and a random-effects model was used. Otherwise, a fixed-effects model was used for analysis. Visual inspection and quantitative analysis of publication bias were performed using funnel plots and the Begg's and Egger’s tests, respectively. No statistical difference was considered if $P$ value greater than 0.05. Meta-regression was performed to investigate the association between the treatment effect and overall risk using the event rate of the experimental group. We performed TSA for RCTs to avoid the positive results of meta-analysis being derived from random errors rather than the real effects of interventions. We quantified the required information size (RIS) and trial sequential monitoring boundaries using the O’Brien-Fleming α-spending function. The cumulative Z curve located in regions of, such as the futility area, crossing the trial sequence monitoring boundaries, or neither, may indicate that the result is true negative, true positive, or uncertain, respectively. RIS was calculated using the relative risk increase of 34.53% (mortality) and 105.02% (major bleeding) with a risk of type I error of 5%, at a power of 80%.

Results

Results of literature selection

Through a database search, we identified 47 studies, including 11 RCTs and 36 cohort studies. A detailed literature selection flowchart is shown in Figure 1. In total, 27,051 inpatients with COVID-19 were enrolled, of whom 16,774 underwent PA and 10,277 underwent I-TA. The baseline characteristics of the included patients are shown in Table 1. Among the studies, 23 were single center and 24 were multi-center. Thirteen studies enrolled critically ill patients only, 8 studies enrolled noncritically ill patients only, and 26 studies were unspecified. The characteristics of the included studies are shown in Table 2.

Mortality

Mortality was reported in 43 studies with 15,523 patients and 9562 patients treated with PA and I-TA, respectively. Meta-analysis of all 43 studies showed that patients with COVID-19 who received I-TA exhibited significantly higher mortality than patients who received PA (24.82% vs 18.45%; OR: 1.38; 95% CI: 1.15–1.66, $P = 0.0005$; Fig. 2A).

To investigate RCTs and real-world studies separately, we performed a subgroup analysis. When only RCTs were included, the results showed that mortality was comparable between the I-TA and PA groups (16.77% vs 17.52%; OR: 0.93; 95% CI: 0.71–1.22; $P = 0.61$; Fig. 4). TSA was performed for 11 RCTs to adjust the results. During TSA, 1 study was excluded because of the small sample size. The cumulative Z curve exceeded the RIS line and was situated within the region of futility boundaries, confirming the negative result from the meta-analysis (TSA adjusted CI, 0.71–1.26), as shown in Figure 2B. However, in real-world studies, pooled mortality was significantly lower in patients receiving I-TA than in those treated with PA (Fig. 4). We assume that in real-world practice, physicians might be prone to prescribe I-TA to patients with more serious conditions.

Regarding disease severity, we conducted a subgroup analysis of critically ill and noncritically ill patients. The mortality was similar between I-TA and PA groups in both critically ill and noncritically ill patients (Fig. 5A). When only RCTs were selected, there was no significant difference in mortality between the 2 treatment regimens in both critically ill and noncritically ill patients (Fig. 5B). This finding was supported by meta-regression of all studies, which suggested that there was no relationship between the treatment effect and overall risk of mortality ($P = 0.14$; Fig. 2C).

Major bleeding

Pooled results from 29 studies documenting major bleeding illustrated that I-TA significantly increased the rate of major bleeding compared with PA in patients with COVID-19 (4.49% vs 2.19%; OR: 2.24; 95% CI: 1.86–2.69; $P < 0.00001$). Further meta-analysis...
of RCTs confirmed this conclusion, after adjusting for TSA (2.29% vs 1.37%; OR: 1.73; 95% CI: 1.15–2.60; P = 0.009; TSA adjusted CI, 1.09–2.58). TSA showed that the cumulative Z curve exceeded the RIS line and the trial sequential monitoring boundary, confirming that I-TA has a disadvantage due to the increased major bleeding rate (Figs. 3A, B).

In subgroup analysis based on the type of study or the severity of patients, major bleeding rate showed the same trend, which was also supported by meta-regression (P = 0.09; Fig. 3C). In a small subgroup of critically ill patients in all studies or RCTs only, I-TA tended to increase the rate of major bleeding, but it did not reach statistical significance, compared with PA.

Thrombotic events
Sixteen studies that reported thrombotic events were included, with 3546 patients in the I-TA and 4623 in the PA groups, respectively. The results showed that there were no significant differences in the rates of thrombotic events, pulmonary embolism, myocardial infarction, stroke, or venous thromboembolism between the I-TA and PA groups (Fig. 6). The results from the RCT subgroup supported the idea that I-TA could reduce the incidence of thrombotic events (Fig. 4). Regarding disease severity, noncritically ill patients might benefit from I-TA with a reduced rate of thrombotic events compared with PA (Fig. 5A). RCTs supported the beneficial effect of I-TA in decreasing thrombotic events in both the critically ill and noncritically ill groups (Fig. 5B).

Quality assessment
We used the Cochrane risk-of-bias tool and NOS to assess the quality of RCTs and cohort studies, respectively (Fig. 7). The quality of the controlled studies included in the meta-analysis was satisfactory.

Publication bias
Funnel plots were used to analyze the publication bias. Intuitively, the studies were distributed almost symmetrically on both sides (Fig. 8). Furthermore, the absence of publication bias was demonstrated by Begg’s and Egger’s tests (Begg’s test, P = 0.87; Egger’s test, P = 0.29).

Grade recommendation
The overall evidence for each outcome of the RCTs and cohort studies was qualified using the GRADE framework. It showed that the certainties of evidence for the outcomes of mortality, major bleeding, and thrombotic events of the RCTs were “moderate.” In detail, we adjudicated the risk of bias as “serious” mainly because all RCTs were open labeled. We found no significant downgrade points for inconsistency, indirectness, imprecision, or publication bias. For cohort studies, the certainties of evidence for the outcomes of mortality, major bleeding, and thrombotic events were “low,” “moderate,” and “very low,” respectively. Specifically, the quality of evidence for major bleeding escalated because of the large effect value. Thrombotic events were downgraded because of “serious” imprecision with a large 95% CI. The GRADE tables are described in detail in Supplementary Table 5, http://links.lww.com/ECCM/A35.

Discussion
This meta-analysis included 47 clinical studies involving 27,051 patients with COVID-19. The results revealed that compared with patients with COVID-19 who received PA, the mortality of patients receiving I-TA was slightly higher. The major bleeding rate was remarkably higher in patients receiving I-TA than in those receiving PA. No statistical difference was found in the rates of thrombotic events, pulmonary embolism, myocardial infarction, stroke, or venous
significantly between the 2 treatment groups. These results indicate that PA is a better choice for patients with COVID-19. Subgroup analysis of RCTs showed that there was no significant difference in mortality between the 2 treatment groups, as proven by TSA, and the major bleeding rate was remarkably higher, which was also confirmed by TSA. Meanwhile, the incidence of thrombotic events was markedly lower in the I-TA group than in the PA group. In both critically ill and noncritically ill patients, I-TA failed to reduce mortality but increased the major bleeding rate compared with PA, which was also supported by meta-regression.

Similar to SARS(67) and H1N1(68), thrombosis is a pathological feature of SARS-CoV-2 infection.(69) Several studies have demonstrated increased levels of coagulation biomarkers in patients with COVID-19,(70,71) the degree of which was positively correlated with disease severity and poor prognosis.(72-74) Anticoagulant administration in patients with COVID-19 has been confirmed to decrease mortality.(75) In clinical practice, commonly used anticoagulants include heparinoids (eg, unfractionated heparin and low molecular weight heparin [LMWH]), factor Xa inhibitors (eg, fondaparinux, rivaroxaban, and apixaban), direct thrombin inhibitors (eg, dabigatran and bivalirudin), and vitamin K antagonists (eg, warfarin). Heparin binds to antithrombin, causing a conformational change that accelerates the inactivation of IIa, IXa, Xa, and XIIa factors, thereby blocking the coagulation cascade and exerting an anticoagulant effect.(74) Compared with heparin, LMWH has more precise target inhibition, but less ability to inhibit other coagulation factors and lower anticoagulation speed.(75) Strikingly, LMWH not only exhibits an anticoagulant effect but also interferes with the binding of SARS-CoV-2 to the ACE2 receptor, thereby limiting viral infectivity and reducing mortality.(76) Oral anticoagulants had no antiviral effect, but patients with COVID-19 using oral anticoagulants also had a reduced risk of mortality compared with those without.(77) Anticoagulation might be an effective way to reduce thrombosis and subsequent organ damage in patients with COVID-19; however, the optimal dosage of anticoagulants remains debatable.(17,19,23,78)
Disease contributes to the efficacy of I-TA and PA regimens, subgroup analysis and meta-regression were performed. This showed that in both critically ill and noncritically ill patients with COVID-19, the 2 anticoagulant regimens did not affect mortality. Subgroup analysis of RCTs showed a consistent result. Hence, increasing the dose of anticoagulants did not reduce mortality.

The major bleeding rate, as the safety outcome, agreed with common sense. Compared with PA, I-TA significantly increased the rate of major bleeding, which was also confirmed by TSA. Moreover, in the subgroup analysis of RCTs and cohort studies or of critically ill and noncritically ill patients, the same result was observed. However, among the critically ill patients in the subgroup of all studies or RCTs only, the major bleeding rate between groups was similar but was not statistically significant, which may be due to the small sample size.

For thrombotic events, the overall analysis did not find a distinct difference between the 2 regimens; however, subgroup analysis of the RCTs and noncritically ill patients supported the beneficial effect of I-TA in lowering the risk of thrombotic events. The delicate balance between anticoagulation strategies, bleeding, and thrombotic complications should be carefully considered. Critically ill patients with COVID-19, who are characterized by long-term immobilization, systemic inflammation, platelet activation, and endothelial dysfunction, are more likely to develop thromboembolism. A retrospective analysis of 400 patients with COVID-19 showed that the incidence of thrombotic events was 4.7% (95% CI, 2.4–8.0) and 18.1% (95% CI, 12.1–25.3) in noncritically ill and critically ill patients, respectively. However, our overall findings did not show that I-TA reduced thrombotic events compared with PA in critically ill patients.
ill patients. In addition to considering possible confounding factors in cohort studies, the overwhelming inflammatory response and concomitant thrombosis were too pronounced in critically ill patients to recover. Meanwhile, in noncritically ill patients, I-TA might sustain an appropriate balance, which may explain the above result.\[^{[82]}\] In brief, this study suggests that I-TA is superior to PA in terms of reducing the rate of thrombotic events.

Our study had several limitations. One limitation is that cohort studies have a lower level of evidence than RCTs do. Although cohort studies inevitably have bias, they provide wider insights into real-world practice, especially during the COVID-19 pandemic. The other limitation is that we tried to perform more subgroup analyses, such as types of anticoagulants, but the related data were difficult to extract from studies.

This study has several strengths compared with similar studies. First, all eligible studies until April 26, 2022, were enrolled to yield the latest evidence on this topic. Second, this is the first meta-analysis to focus on the heterogeneity of the definitions of PA and I-TA among studies. To solve this problem, we checked the doses of anticoagulants in each study and excluded 9 studies to avoid dosage overlap between the 2 comparison groups. Third, to achieve a robust conclusion, we performed TSA and meta-regression, which are important for fully understanding the results. This is also the first study to use the TSA approach for this topic. Finally, we used the GRADE framework in addition to other assessment tools to evaluate the quality of the evidence. We believe that this meta-analysis, TSA, and meta-regression will provide valuable information for clinical practice and further research.

**Conclusion**

I-TA was not superior to PA in terms of reducing mortality but increased the risk of major bleeding. For patients with a high risk of thrombosis and low risk of bleeding, I-TA is appropriate. Further larger-scale RCTs are still needed.

**Conflict of interest statement**

Yuguo Chen is the Editor-in-Chief of *Emergency and Critical Care Medicine*, and Feng Xu is an Editorial Board member of *Emergency and Critical Care Medicine*. The article was subject to the journal’s standard procedures, with peer review handled independently of the Editor-in-Chief, this Editorial Board member, and their research groups. The authors declare no conflict of interest.

**Author contributions**

Guo M and Xing J contributed to the literature research and data extraction. Guo M and Han Q contributed to quality evaluation. Cao S and Xue L helped with the literature search. De Y and Wang X helped with the data extraction. Hao P, Li C, Wang J, and Xu F provided valuable advice on these methods. Yuan Q, Pan C, Wang H, and Bian Y provided valuable advice for the manuscript writing. Guo M, Han Q, and Shan Z wrote the first version of the manuscript. Pang J and Chen Y contributed to study design and manuscript revision.

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Ethical approval of studies and informed consent
Not applicable.

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