

Mortality in COVID-19 patients receiving systemic anticoagulant: A systematic review and meta-analysis

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Abstract

Background: Coronavirus disease 2019 (COVID-19)/Severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) is a pandemic disease that quickly spreads throughout the world. There are no definitive therapeutic recommendations that give benefit results until recently. Recent studies suggest that coagulopathy is one of the complications of COVID-19 that increases the mortality rate regardless of the severity. This systematic review and meta-analysis aims to explore the association between systemic anticoagulant use and mortality in COVID-19 patients with various clinical conditions.

Methods: We performed a comprehensive search from several databases. The anticoagulant used in this study comprises of systemic anticoagulants such as low molecular weight heparin (LMWH) or others. The primary out-

come was all-cause mortality related to anticoagulant use in COVID-19 patients. The meta-analysis was performed to see the significance of anticoagulants in decreasing the mortality rate of COVID-19 patients.

Results: 7064 patients were analyzed from 7 studies. The meta-analysis showed that systemic anticoagulant use was related with lower mortality rate (RR 0.70 [0.51, 0.97], $p < 0.03$; I²: 87%, $p < 0.00001$). The systematic review reported that 4 of 7 studies favor decreasing the mortality rate in COVID-19 patients administered with systemic anticoagulants.

Conclusion: Systemic use of anticoagulants was associated with a lower mortality rate in COVID-19 patients. Further studies are needed for better causation explanation. The implication of this study is to measure the mortality impact of systemic anticoagulant use in COVID-19 patients.

Key words: Systemic anticoagulants, COVID-19, mortality.

Introduction

Coronavirus disease 2019 (COVID-19) is a pandemic disease declared by the World Health Organization on March 11, 2020. This pandemic quickly spreads throughout the world. (1) Albeit

the disease spread globally fast, the therapeutic recommendation is not established because of the lack of definite pathophysiology that leads to the morbidity and mortality of the disease. Recent autopsy studies suggested that coagulopathy was one of the complications that significantly increase the mortality of COVID-19 patients. (2)

The mechanism of thrombus formation in COVID-19 was hypothesized to be related to the endothelium damage. This is in accordance with the evidence of the increasing D-dimer levels in the severe manifestation of the disease. (3) Some studies recommended the anticoagulant use in COVID-19 because of its benefit on reducing mortality. However, those studies were observational; the randomized controlled trial regarding this topic is still in progress (NCT04412304). Low molecular weight heparin (LMWH) is increasingly popular to be administer-

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ed in COVID-19 but mortality study related to the user is still unclear. (4,5)

Therefore, we conducted a systematic review and meta-analysis about the use of systemic anticoagulants as the additional therapy for COVID-19 patients on reducing the mortality rate in terms of safety and efficacy. We hope that this systematic review and meta-analysis could help clinicians consider using systemic anticoagulants for COVID-19 patients.

Methods

Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) were used to accomplish this meta-analysis. We systematically observed PubMed, SCOPUS, EuropePMC, ProQuest, and Cochrane Central Databases with the mesh terms of “COVID-19” or “SARS-CoV-2” and “Systemic Anticoagulant” or “Heparin” that were published within the year of 2020. Duplicate studies were excluded from this meta-analysis. The remaining articles were independently screened for relevance by its abstracts by all of the authors. Full-text of the selected abstracts were read thoroughly, and those that fulfilled our criteria were included in this meta-analysis. The final inclusion of studies was based on the agreements of all investigators. Any disagreement was solved by the consensus of all authors.

Article eligibility and selection

The retrieved articles' titles and abstracts were scanned for potential relevance and review inclusion eligibility. To be included in this meta-analysis, the article had to meet strict criteria, as listed in **Table 1**, with the search and inclusion criteria primarily targeting published studies presenting clinical efficacy and/or safety types of evaluations of low molecular weight heparin or other systemic anticoagulant use in COVID-19 patients. Pre-printed and grey literature journals in the literature search were also included until 20th June 2020.

The results of the three independent observations were matched to find the expected results and exclude the duplicate article. All of the identified articles that met the selection criteria, full versions, or pre-proofed journals were included in the data analysis. A secondary search of the listed citations was also included to ensure that all relevant publications were included. Only English-written articles were included in this systematic review and meta-analysis. The observation of the relevant studies was performed from January 2020 until June 2020.

Data appraisal and extraction

Data extracted from the identified publication were study design and outcome, the number of patients, follow up during intervention, intervention information, efficacy, and safety of the procedures. We used a table in which each information was written descriptively (**Table 2**).

Quality assessment

The quality of the studies were appraised independently by two authors using the Modified Newcastle-Ottawa Scale (NOS). (6) A score of 0-9 was allocated to each study, with studies having a total score of >7 were defined as high quality studies. Any disagreement in the quality assessment was solved by discussion with the third author.

Statistical analysis

To perform a meta-analysis, Review Manager (RevMan) 5.4 (Computer program, The Cochrane Collaboration, London, UK) and Comprehensive Meta-Analysis (CMA) 3.3 (Computer program, New Jersey, USA) were used to perform all statistical analysis. The heterogeneity was considered significant for a p-value of less than 0.05, and its magnitude was determined to be substantial if the I² was greater than 50%. A random-effects model was used to report the results of heterogeneous data. Otherwise, a fixed-effects model was used. Dichotomous variables were analyzed with the Mantel-Haenszel statistical method using risk ratio (RR) as the summary statistic and reported with 95% confidence intervals (CI). Publication bias was screened and described with Funnel Plot.

Results

Characteristics of the included studies

An initial search found 785 potentially relevant papers, of which 253 were immediately excluded due to duplication. After the first screening of titles and abstracts, 504 papers were excluded. An additional of 21 papers were excluded after the full-text review, which resulted in 7 studies that were included in this systematic review and meta-analysis (**Figure 1**).

Among the 7 studies that included 7064 participants, 3 studies were performed in the United States (USA), (7-9) 1 study in China, (4) 2 studies in Spain, (10,11) and 1 study in Italy. (12) All of these studies were retrospective observational and based on hospital care settings.

The baseline characteristics of the included studies were presented in **Table 1**. The mean age of the patients in the included studies was 64 years. Only Paranjpe, et al (8) who did not supply the mean age

information of the patients. Of the 7 included studies, 4 studies focussed on the association between anticoagulant or heparin and the survival of COVID-19 patients, (4,8,10,11) and one among them specifically included the severe COVID-19 patients only, (4) 2 studies reported the possible risk factors of anticoagulant use with clinical outcomes of COVID-19 including mortality, (7,9) and another study reported the thromboembolic complication in COVID-19 patients. (12) At the final screening, 525 titles were excluded due to one or more of the following: 1) no full-text available, 2) not written in English, 3) meet our exclusion criteria, 4) not using LMWH or systemic anticoagulant. A total of 7 publications were included, all of which were retrospective studies (evidence level II). Authors of each study used LMWH such as heparin in different forms and for different purposes.

The highest numbers of patients are 2773 patients in Paranjpe study with the total samples of 7424 participants, while the lowest numbers of patients were 217 patients. There was unfortunately no randomized-controlled trials (RCT) found in our observation.

Quality assessment of NOS consider studies to be highly qualified if the studies received scores of 7 stars or more. In this meta-analysis, 5 studies (4,7-9,11) were considered high quality studies, while the 2 others received fewer than 7 stars (10,12) (**Table 2**).

Anticoagulant use and mortality

To test the impacts of the systemic anticoagulant use on the mortality outcome, we included 6 studies (4-9) with a total of 7064 participants. The data including anticoagulant use in confirmed COVID-19 patients demonstrated 18% (723/4004) mortality rate compared to patients without anticoagulant use 24% (730/3060). The data showed that the systemic anticoagulant use could lower mortality rate in COVID-19 patients (RR 0.70 [0.51, 0.97], $p < 0.03$; I²: 87%, $p < 0.00001$).

Publication bias

Publication bias was shown in the funnel plot (**Figure 2**). There was a potential publication bias among the studies included in this meta-analysis, as could be seen that some studies were outside the range of 95% CI in the funnel plot.

Efficacy, mortality, and safety of anticoagulant treatment in COVID-19

Administration of systemic anticoagulant in COVID-19 patients is uprising, but there is still no

evidence of safety and mortality rate correlation. The direct observation related to the correlation of systemic anticoagulants and mortality in COVID-19 patients was conducted by Ayerbe, et al. (10) From 2075 patients that were included in the study, there were 1256 males and 819 females with the average age of 67 and 57 years old, respectively. Among the 1734 patients who received heparin, 242 patients died. There were significant results of the age difference which favor the older age ($p < 0.001$), but there was no association shown for the gender. From the adjustment analysis, heparin was associated with lower mortality in both variables with OR (95% CI): 0.55 (0.37-0.82), $p = 0.003$. This study was in line with a study from Garibaldi, et al (7) who reported a lower mortality event in COVID-19 patients who were given anticoagulants than those that were not given anticoagulants but showed no significant statistic result.

Another study from Lodigiani, et al (12) included 388 patients with COVID-19, of which 16% of the population were admitted to Intensive Care Unit (ICU). Thromboprophylaxis was used in all ICU subjects and 75% in non-ICU-setting. In conjunction, a study depicts the critical role of the coagulopathy pathway in COVID-19, by the increasing occurrence of venous-thrombotic events or venous thromboembolism (VTE). Lodigiani, et al (12) in 2020 conducted a study about COVID-19 and VTE. They included 388 patients (median age 66 years, 68% men, 16% requiring intensive care [ICU]). Thromboprophylaxis was used in all ICU patients and 75% of those in the general ward. Thromboembolic events occurred in 28 patients, with 25 patients given heparin had a mortality rate of 20% (5 patients) and 3 patients without heparin had a mortality rate of 66.7% (2 patients). There was no possible mechanism of the death that was reported from this study. Disseminated intravascular coagulation (DIC) was one of the plausible mechanisms in both subjects. The study reported that 8 patients had DIC of which VTE imaging showed the same correlation as pulmonary embolism, stroke, and acute coronary syndrome. The exact pathomechanism was not fully understood, but coagulation was proven in the COVID-19 patient's autopsy. Therefore, anticoagulants use could be beneficial to prevent thromboembolic events in COVID-19 patients. (13)

Gil, et al (9) in the year 2020, conducted a study about several parameters presented in COVID-19 patients. This study included 270 case series of COVID-19 patients in the new epicenter of

COVID-19, which was New York City. This study concluded that the therapeutic anticoagulant was associated with higher mortality than the prophylactic anticoagulant in COVID-19 patients, although it has not yet proven statistically.

Paranjpe, et al (8) studied the safety and bleeding events of the anticoagulant treatment in COVID-19 patients. From 786 patients who received systemic anticoagulants, the mortality rate was 22.5% compared to 22.8% mortality rate in those who did not receive anticoagulants. From the subanalysis, patients who received anticoagulants were likely to receive invasive mechanical ventilation (29.8% vs 8.1%, $p < 0.001$). In patients who required mechanical ventilation ($n = 395$), in-hospital mortality rate was 29.1%, with the median survival of 21 days for those treated with anticoagulants, compared to 62.7% with a median survival of 9 days in patients who were not treated with anticoagulants. In a multivariate proportional hazards model, the long duration of anticoagulant treatment was associated with a reduced risk of mortality (adjusted HR of 0.86 per day, 95% confidence interval 0.82-0.89, $p < 0.001$).

Gonzales-Porras study (11) showed that the mortality rate of the total events were noted in 24 patients, of which 14 patients were associated with a high dose of anticoagulant. From the bleeding cause, there was only 1 patient who was related to fatal bleeding occurrence. The study showed the mean age of the patients were 72.48 years. The non-survivor patients presented with the higher levels of international normalized ratio (INR) (1.14 vs 1.09, $p = 0.001$), D-dimer (2.1 mg/l vs 0.9 mg/l, $p < 0.001$) as well as prothrombin time (PT) (13.3 vs 12.7, $p = 0.001$). The treatment with LMWH affected the mortality rate in this study, which 458 (93%) and 143 (72%) patients receiving LMWH were in the survivors and non-survivors groups, respectively ($p < 0.001$). Statistical differences were observed among the three heparin groups in the in-hospital mortality ($p < 0.01$): Among the COVID-19 survivors, 34 (6.9%) patients did not receive LMWH, 318 (64.6%) patients received low-dose LMWH, and 140 (28.5%) received high-dose LMWH, while in the COVID-19 non-survivors, 45 (22.7%) patients did not receive LMWH, 104 (52.5%) patients received low-dose LMWH, and 49 (24.7%) received high-dose LMWH.

Among those who did not receive anticoagulants, 38 (1.9%) individuals had bleeding events, compared to 24 (3%) among those who received anticoagulants ($p = 0.2$). Bleeding events were more common among the intubated patients (30/395; 7.5%) than among those who were not intubated

(32/2378; 1.35%). These findings suggested that systemic anticoagulants may be associated with the improved outcomes among patients who were hospitalized because of COVID-19. However, the potential benefits of systemic anticoagulants, however, need to be weighed against the risk of bleeding and therefore, should be individualized. The correlation of the in-hospital anti-coagulation and the mechanical ventilation use were likely reflected the reservation of the anticoagulants for more severe clinical presentations. Interestingly, there was a correlation of the anticoagulants use and the improved survival after adjusting for the mechanical ventilation variable.

Discussions

This systematic review and meta-analysis were performed to assess the possible association between the systemic anticoagulant treatments with the reduction of mortality rate in COVID-19 patients (**Figure 3**). There was a significant reduction in the mortality rate, (RR 0.70 [0.51, 0.97], $p < 0.03$; I²: 87%, $p < 0.00001$). Because all of the data came from retrospective studies and because the anticoagulants were more likely to be given to the patients with severe conditions, and the dosage use in the included studies in this meta-analysis were vary within and among studies, there was selection bias in this study, although the results were significant. However, the results were still essential for the consideration in the clinical management of COVID-19.

Recently, COVID-19 is unexpectedly taking the world by storm as the first pandemic of the 21st century. Despite its contagious and rather lethally nature, therapeutic recommendations are not clear enough because there is no definite causation that can be taken until recently. Prior studies presented on autopsies by Atallah, et al (2) showed that coagulopathy was one of the suggested causes of mortality in COVID-19 patients. This finding gives insight into the therapy that could alter the coagulopathy, such as systemic anticoagulants, that could be a promising treatment in the future treatment protocol against COVID-19. This study summarized the systemic anticoagulant use or heparin-based related mortality in addition of management of COVID-19 in terms of safety, efficacy, and mortality rate.

In a recent study, coagulopathy allegedly plays a pivotal role in the pathophysiology of COVID-19. This could be proven by the shift of the pro-coagulant pattern to the pathological side. D-dimer levels were significantly elevated in patients who were admitted to the ICU because of the severe

clinical manifestations of COVID-19. (14) The increasing level of D-dimer of more than 1 mg/dl was significantly associated with the mortality in COVID-19 patients. (7) The hospitalized COVID-19 patients were also characterized by substantial in-hospital mortality and a high rate of thromboembolic complications. (12) The alteration of the coagulopathy pathway, such as from anticoagulants, were expected to bring benefits in COVID-19 patients.

The 28-days mortality rate of the heparin user in COVID-19 patients whose D-dimer level were 6-fold greater than normal range was significantly lower than those who were not heparin user, as the activation of the coagulation also contributed to the compartmentalization of the pathogens and reduced their invasion, therefore, anticoagulants treatment in patients without a significant coagulopathy has potential risks. The increasing D-dimer level of more than 1 mg/dl was significantly associated with the mortality in COVID-19 patients. (4) From this study we could learn that it is also essential to know the selection criteria of COVID-19 patients to whom the benefits of anticoagulation weigh the risks.

A study from Paranjpe, et al (8) showed 177 patients were associated with mortality with 24 bleeding events. The study mentioned that from 24 bleeding events, 9 patients had bleeding before the systemic anticoagulant was started and occurred often in the intubated patients. In this study, the systemic anticoagulation showed a decrease in the mortality (95%CI 0.82-0.89; $p < 0.001$). A study from Gonzaleso-Porras, et al (11) compared the high dose heparin use to the low dose heparin use. The study showed that higher anticoagulant dose was associated with reduced mortality but significant bleeding events. On the subgroup analysis, patients with severe clinical manifestations of COVID-19 were given anticoagulants. It could not be determined whether the anticoagulants effects or the severity of the clinical manifestations of COVID-19 that influence the mortality rate in this study.

Safety of anticoagulants use also must be taking into consideration when treated COVID-19 patients. Major bleeding events are the most com-

monly occurred side effects of the systemic anticoagulants use. A study from Paranjpe, et al (8) showed a slight increase in major bleeding events of COVID-19 patients that were treated with anticoagulants, although it was not statistically significant. In the future, there must be criteria that can stratify the need for anticoagulation in COVID-19 patients so the benefit can exceed the risk of the anticoagulant treatment. Overall, the results showed the benefits of systemic LMWH in reducing the mortality rate in COVID-19 patients either in both severe and non severe COVID-19 manifestations.

There are some limitations in this study, there were only retrospective studies that were analyzed. Three ongoing RCTs were about to be included in this study, but unfortunately these studies were still on sample recruiting process when this meta-analysis was conducted. Age and the other factors related to this study outcomes were not adjusted. The other limiting factors are that there was still no conventional antiviral treatment for COVID-19; thus, the antiviral treatments were varied in types and duration among the studies included in this meta-analysis. So, the conclusion on the anticoagulant effectivity toward the progression of the disease could not be derived. Although this meta-analysis showed significant results, the extrapolation of these data studies should be done with some cautions because no randomized controlled trials analyzed the systemic anticoagulants nor LMWH included in this meta-analysis. Further studies that include RCTs on the effects of the systemic anticoagulation for COVID-19 patients would better explain and confirm the outcomes.

Conclusion

There was an association between the administration of systemic anticoagulants and the mortality rate of COVID-19 patients regardless of the severity. A significant reduction of the mortality rate was found in the COVID-19 patients treated with systemic anticoagulants, which were likely due to the coagulopathy prevention that occurred in the progression of the disease.

Table 1. Article inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Types of studies	Randomized controlled trials evaluating the efficacy of low molecular weight heparin or other anticoagulants in COVID-19 patients regardless of clinical status Non-randomized, controlled trials reporting efficacy were allowed provided that the scope of the research was to evaluate the effect of low molecular weight heparin or other anticoagulants in COVID-19 patients regardless of clinical status	Oral anticoagulants
	All evidence levels, including safety data were acceptable for safety analysis inclusion	<ul style="list-style-type: none"> a. Reviews, editorials, opinions, case reports, case series, comments, and letters without original data b. Non-clinical (i.e., experimental, animal, or in vitro) studies c. Clinical trials with major quality issues and a high risk of bias were excluded from efficacy analysis, but could be included in safety analyses
Types of participants	Patients (irrespective of age, sex, or race) with COVID-19 infection who had received low molecular weight heparin or other systemic anticoagulant or previous anticoagulant use	Patients without COVID-19 infection confirmed or based only on rapid test without RT PCR confirmation
Types of intervention	Low molecular weight heparin or systemic anticoagulant	<ul style="list-style-type: none"> a. Antiplatelet use reported b. Reports non regular use of low molecular weight heparin or anticoagulant
Types of comparators	Non user of low molecular weight heparin or systemic anticoagulant	
Types of efficacy outcome measures	Could include (but not limited to): <ul style="list-style-type: none"> a. Single use of low molecular weight heparin or systemic anticoagulant b. Combination of systemic anticoagulant 	
Safety outcome measures	Could include (but not limited to): <ul style="list-style-type: none"> a. Mortality b. Overall incidence of serious adverse event (quantitative) c. Overall incidence of adverse events related to anticoagulant (quantitative) d. Qualitative assessment of specific adverse events/serious adverse events related to use of anticoagulant regardless of type 	

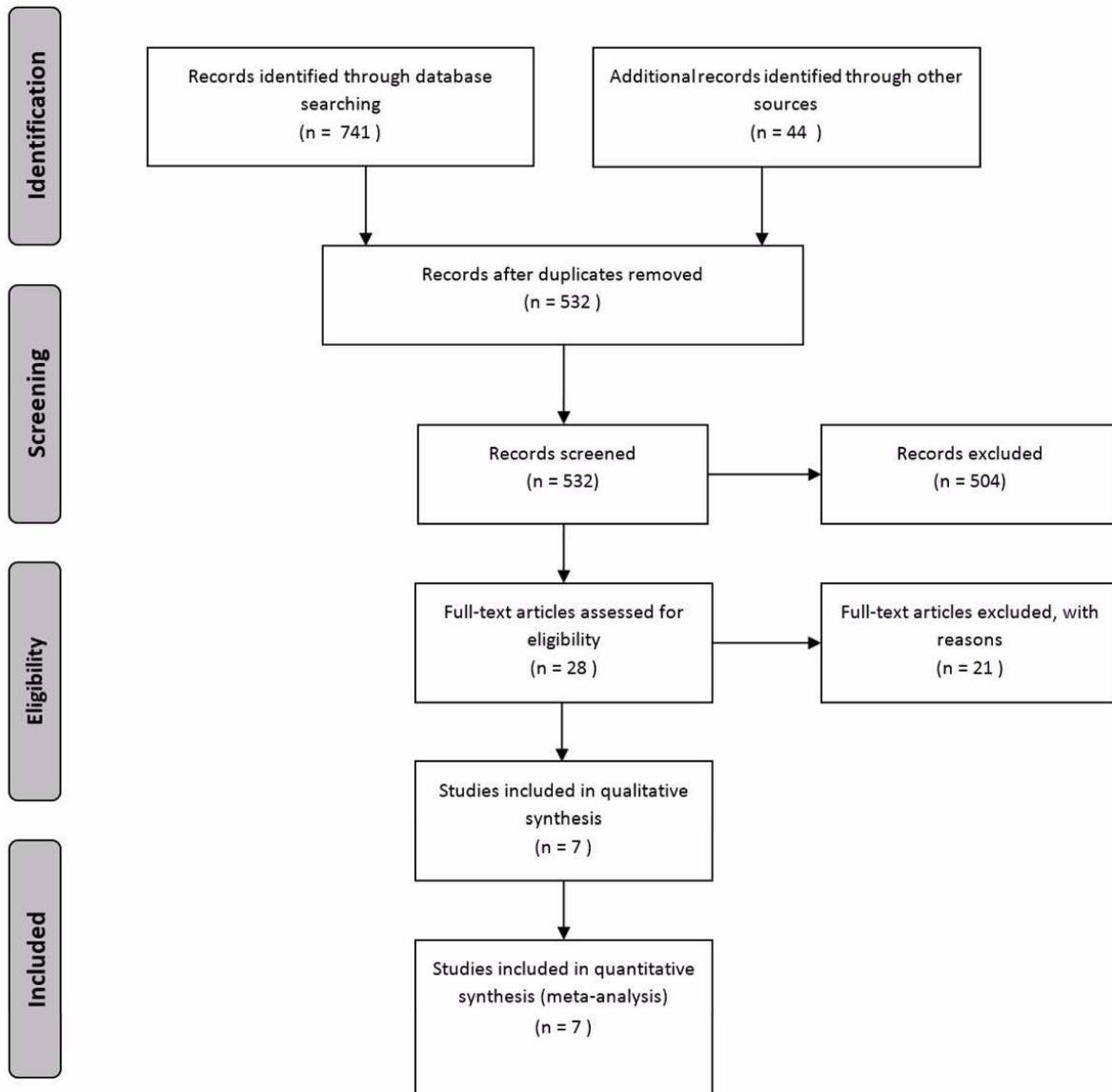
Legend: COVID-19=Coronavirus disease 2019; RT PCR=real time polymerase chain reaction.

Table 2. Characteristics of the included studies

Author and year	Study design	Country	Quality score	Characteristic of participant	Age (mean)	n (A vs B)	Mortality (A vs B)	Follow up	Intervention	Efficacy
Ayerbe, et al, 2020	Retro-spective cohort	Spain	6	Hospitalized COVID-19 patients	67.57	1734 vs 341	242 vs 59	During hospitalization, 201 still admitted at the time collecting data	Heparin, detail not mentioned	Heparin associated with lower mortality when the model was adjusted for age and gender
Garibaldi, et al, 2020	Retro-spective cohort	USA	7	Hospitalized COVID-19 patients	63	571 vs 261	59 vs 54	During hospitalization	Prophylactic and therapeutic doses heparin or enoxaparin	Characteristic of data and patient risk factor for severe outcome
Gil, et al, 2020	Retro-spective cohort	USA	7	Hospitalized COVID-19 patients	61.3	178 vs 39	57 vs 13	During hospitalization	Prophylactic or therapeutic doses of anticoagulation (LMWH, apixaban, UFH, warfarin, bivalirudin)	Cause of mortality and anticoagulant was not explained
Gonzales-Porras, et al, 2020	Retro-spective cohort	Spain	7	Hospitalized COVID-19 patients	72.48	611 vs 79	153 vs 45	During hospitalization	Non heparin vs low dose heparin vs high dose heparin	Reduce mortality in unselected adult patients
Lodigiani, et al, 2020	Retro-spective cohort	Italy	6	Hospitalized COVID-19 patients with thromboembolic complication	68.4	25 vs 3	5 vs 2	During hospitalization	LMWH (enoxaparin 120-160 mg/day or 8000 IU qd, nadroparin 5700-9600 IU bid, fondaparinux 10-30 mg), UFH therapeutic dose	High thromboembolic events No data specifically for thrombo propylaxis user
Paranjpe, et al, 2020	Retro-spective cohort	USA	7	Hospitalized COVID-19 patients	N/A	786 vs 1987	177 vs 453	During hospitalization	Systemic anticoagulation	Reduced risk of overall mortality
Tang, et al, 2020	Retro-spective cohort	China	7	Hospitalized severe COVID-19 patients	65.1	99 vs 350	30 vs 104	28 days	UFH (10000-15000 IU/day) or LMWH (40-60 mg enoxaparin/day) for 7 days or longer	Reduce mortality in unselected adult patients

Legend: COVID-19=Coronavirus disease 2019; N/A=not available; A=anticoagulant group; B=control group; LMWH=low molecular weight heparin; UFH=unfractionated heparin; IU=international unit.

Figure 1. PRISMA flow diagram for the included studies



Legend: PRISMA=Preferred Reporting Items for Systematic reviews and Meta-Analysis.

Figure 2. The meta-analysis of effect of anticoagulant on the mortality. Comparison mortality between anticoagulant use and control

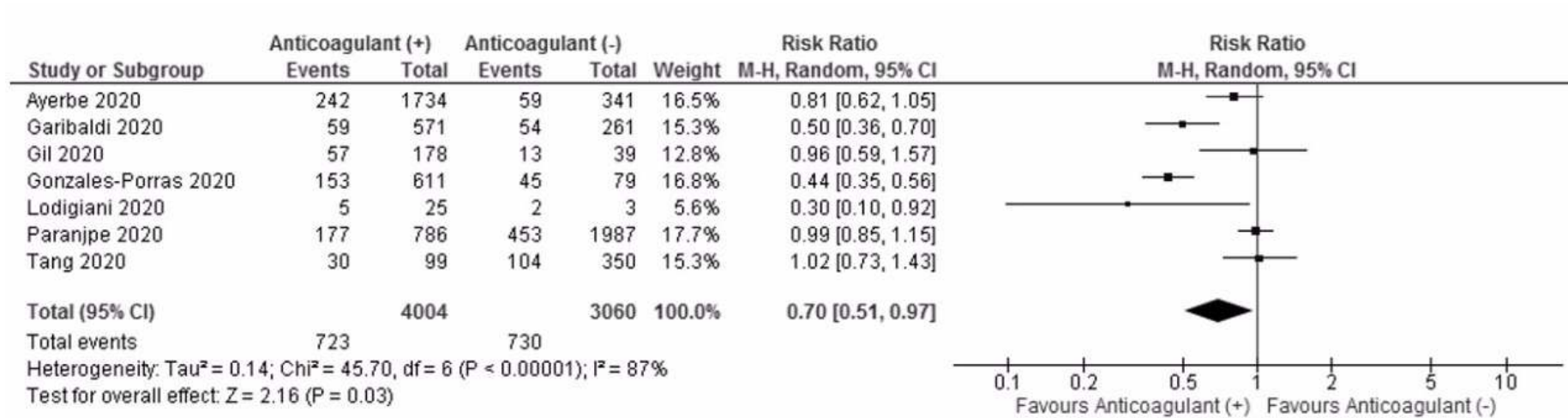
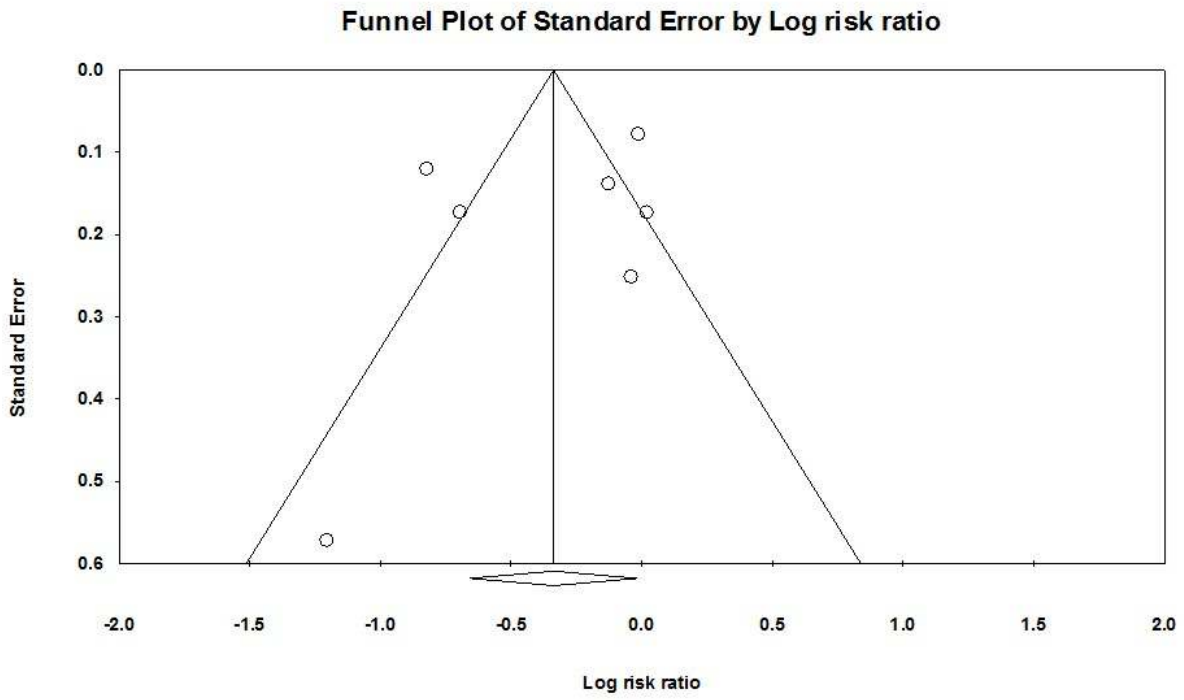


Figure 3. Funnel plot analysis



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