Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2022 Mar 02; 10(F):241-245.
https://doi.org/10.3889/oamjms.2022.8701
eISSN: 1857-9655
Category: *F - Review Articles*
Section: *Meta-synthesis Review Article*

Low Molecular Weight Heparin Doses and Ventilator Airway Necessity in the COVID-19 Patients: Systematic Review and Meta-analysis

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Edited by: Eli Djulejic
Citation: Yueniwati Y, Syaban MFR, Purnomo AF, Kinesya E, Mannagalli Y, Pasaribu EA, Lutfiana NC, Purnomo AS. Low Molecular Weight Heparin Doses and Ventilator Airway Necessity in the COVID-19 Patients: Systematic Review and Meta-analysis. Open Access Maced J Med Sci. 2022 Mar 02; 10(F):241-245. https://doi.org/10.3889/oamjms.2022.8701
Keywords: Anticoagulants; COVID-19; Mechanical ventilation; Mortality; Bleeding
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Received: 25-Jan-2022
Revision: 12-Feb-2022
Accepted: 20-Feb-2022

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Anticoagulant therapy is recommendation for COVID-19 infection. However, the mechanical ventilation needed for COVID-19 is still high.

AIM: The aim of the study was to determine comparison therapeutic and prophylactic dose LMWH for mechanical necessity in COVID-19 infection.

METHODS: A systematic literature search articles online from studies published between 2020 and 2021 that met our inclusion criteria and were retrieved from scientific databases such as Cochrane, ProQuest, and PubMed. The primary measure was a composite bad outcome, which included mechanical ventilation, mortality. and bleeding risk.

RESULTS: There were 3432 patients from seven study included in this meta-analysis for necessity of mechanical ventilation in COVID-19 patients that used prophylactic and therapeutic anticoagulants. Prophylactic dose of anticoagulant showed no difference for the need for mechanical ventilation necessity for COVID-19 patients (RR = 0.54; 95% CI = 0.20–1.48; p = 0.23). However, prophylactic anticoagulant showed more safe for bleeding incidence (RR = 0.27; 95% CI = 0.18–0.39; p = <0.00001) and reduce mortality (RR = 0.52; 95% CI = 0.46-0.58; p = <0.00001).

CONCLUSION: LMWH anticoagulant dose not associated with reduce mechanical ventilation necessity but prophylactic dose prefers rather than therapeutic dose for reduce mortality and risk of bleeding.

Introduction

Coronavirus is included on the family of Coronaviridae known able to produce mild respiratory infection in humans. On December 2019, there was major outbreak of coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). The virus spread fast from mainland China to Thailand and every other country resulting in a pandemic [1]. Patients with severe illness mostly accompanied with dyspnea and hypoxemia typically require supplemental oxygen and monitoring for worsening respiratory symptom resulting in Acute Respiratory Distress Syndrome (ARDS) that requires ventilation. The optimal oxygen saturation for adults with COVID-19 is 92–96% [2], [3], [4], [5]. In Wuhan, 14% patients were severe and 5% were critical [6]. The rates of mechanical ventilation on ICU admitted COVID-19 patients range from 29.1 to 89.9% and non-ICU admission ranges from 2.3% up to 33.1% [7]. Severe COVID-19 is associated with increased risk of venous thromboembolism events (VTE). The prevalence of pulmonary embolism (PE) is estimated 32% and deep vein thrombosis (DVT) estimated 27% on COVID-19 patients. The risk is higher on ICU admitted patients, severe COVID-19, high D-dimer values, and lower use of prophylactic anticoagulants [8].

Anticoagulation strategy prevents excessive blood clotting and reduces microthrombus development. It will be reduce significantly organ dysfunction. The World Health Organization (WHO) suggested thromboprophylaxis with either unfractionated or low molecular weight heparin, despite the fact that the risk-benefit ratio had not been established (LMWH) [9], [10].

However, clinical benefit of LMWH is unknown especially in mechanical ventilation necessity, and it is unknown whether patients should be maintained on prophylactic or therapeutic dosages of LMWH. As a result, we did a systematic review and meta-analysis to determine the efficiency of heparin in mechanical

ventilation necessity. In addition, we also analyzed severe bleeding and mortality to know the efficacy and side effect.

Methods

Search strategy

We conducted systematic search data from journals published across the world comparing LMWH anticoagulant doses in September 2021. We collected articles online from studies published between 2020 and 2021 that met our inclusion criteria and were retrieved from scientific databases such as Cochrane, ProQuest, and PubMed. The keywords that were used to search articles are "COVID-19 OR Coronavirus OR SARS-CoV-2 OR 2019-nCoV" AND "anticoagulant OR thrombolytic OR Low Molecular Weight Heparin OR LMWH OR heparin OR Enoxaparin" AND "Definitive Airway" AND "Bleeding" AND "Mortality" AND "RCT" OR "Randomized controlled trial OR Cohort". In addition, we collected all relevant publications data through the list of references in all available articles and removed duplicate articles result. Our major objective was to establish a definitive airway necessary.

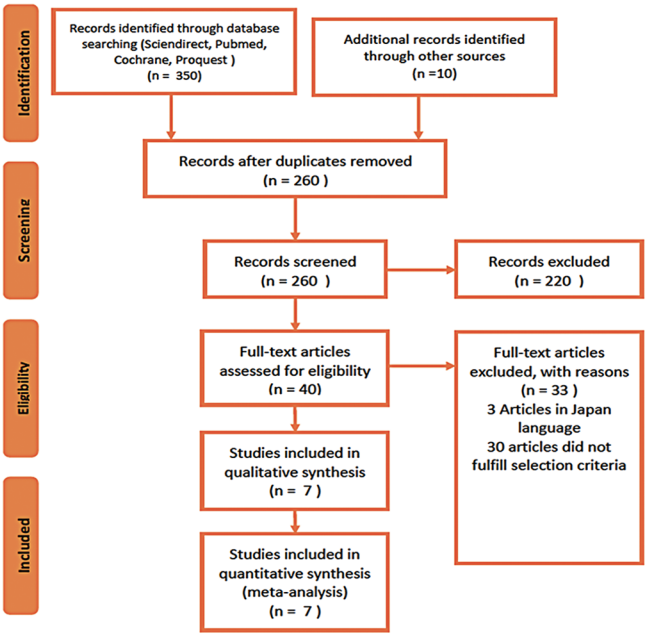

Figure 1: Flowchart of the study the selection process of included studies

Study selection and eligibility criteria

We conducted a systematic review and meta-analysis guidelines (PRISMA) [11]. The inclusion criteria of this study were reported patients with primary outcome mechanical ventilation, bleeding, and mortality. We included all articles study about randomized controlled trial and retrospective and prospective studies. We excluded articles with one or more theses following criteria: (1) Duplications; (2) published not in the English language; (3) irrelevant titles and/or abstracts, reviews, comments, and dissertations case report, and (4) outcome of interest not reported.

Data extraction

Data extraction was conducted to get important information about articles. The data information is (1) first author; (2) publication year; (3) country of center study; (4) duration; (5) time followed; (6) sample population; and (7) NOS.

Data synthesis and quality assessment

We performed data analysis using Review Manager 5.4.1 (Cochrane, Copenhagen, Denmark). Mantel-Haenzel statistical technique used for categorical data to calculate the risk ratio (RR) and 95% confident interval (CI). We use a random-effect analysis model if P for heterogeneity (pHet < 0.1) and a fixed-effect analysis model if pHet ≥ 0.1 [12]. The quality of the article was determined using the Newcastle-Ottawa quality assessment scale (NOS) tool. The NOS consisted of three components: Patient selection, comparability, and exposition [13], [14], [15]. The authors evaluated the quality of paper severely by (YY and MFRS).

Results

The selection of studies for inclusion in the systematic review is shown in Figure 1. A preliminary search of Embase, ProQuest, and PubMed retrieved 360 articles. After removing duplicates, we discovered a total of 260 records and 40 articles that remained after title and abstract screening. After screening

Table 1: Characteristics study included in study

Serial number	Author , yeasr	Country	Design study	Sample	Duration	Followed	Sample population and additional information	NOS
1	Andrew, 2020	USA	Observational cohort study	324	30 days	30 days	COVID (+) ICU admitted	8
2	Albani, 2020	Italy	Observational cohort study	278	7–21 days	7–21 days	COVID (+)	7
3	Roomi *et al*., 2021	USA	Retrospective cohort study	176	7 days	7 days	COVID (+)	7
4	Lopes *et al*.,2021	Iran	Multicenter randomized trial	562	30 days	30 days	COVID (+) ICU admitted	8
5	Yu *et al*., 2021	USA	Retrospective cohort study	973	Not mentioned	Not mentioned	COVID (+)	6
6	Elmelhat *et al*., 2021	UAE	Retrospective cohort study	59	4 months	30 days	COVID (+)	8
7	Kuno *et al*., 2021	USA	Retrospective cohort study	2533	30 days	30 days	COVID (+)	8

NOS: Newcastle-Ottawa quality assessment scale, USA : United States of America, UAE: United Arab Emirates

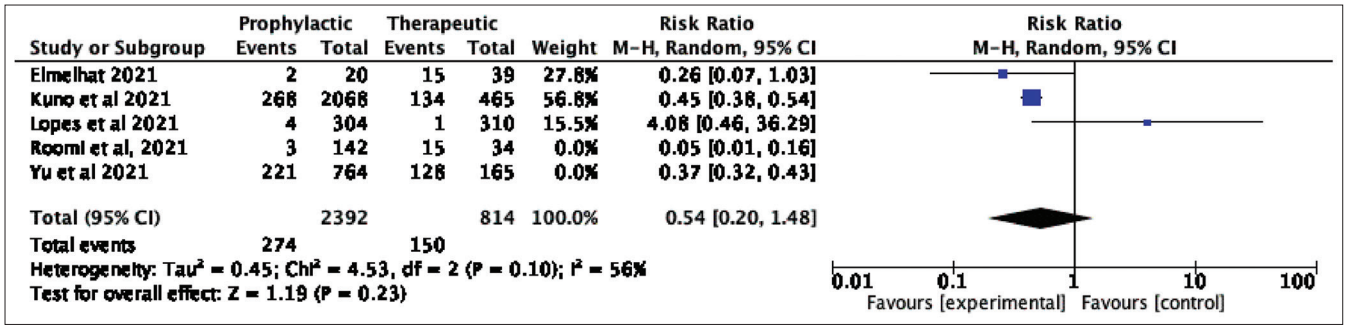

Figure 2: Comparison prophylactic and therapeutic anticoagulant for ventilator necessity

the title and abstract, a total of 220 records were eliminated. After determining the eligibility of seven publications, we excluded 30, because the studies did not describe the criteria outcome, and three articles in Japan language. Seven publications satisfied the inclusion criteria for the systematic review and meta-analysis.

We analyzed the general characteristics of 3432 patients from seven study included in this meta-analysis for necessity of definitive airway or oxygen in COVID-19 patients that used prophylactic and therapeutic anticoagulants (Table 1). Prophylactic dose of anticoagulant showed no difference for the need for definitive airway for COVID-19 patients (RR = 0.54; 95% CI = 0.20-1.48; p = 0.23) relative to prophylactic dose as shown in Figure 2.

Several studies included in the meta-analysis reported prophylactic dose given a higher dose of anticoagulant rather than the therapeutic group. Our result showed prophylactic anticoagulant more safe for bleeding incidence (RR = 0.27; 95% CI = 0.18-0.39; p = <0.00001) in Figure 3a. While, we found that there is a significant difference between prophylactic and therapeutic doses of anticoagulants on the mortality rate of COVID-19 patients, and prophylactic anticoagulants have more protective ability than therapeutic doses of anticoagulants in preventing the risk of mortality as visualized in Figure 3b (RR = 0.52; 95% CI=0.46-0.58; p = <0.00001).

Discussion

We compared the use of prophylactic and therapeutic anticoagulants that result in the need for definitive airway in COVID-19 patients in this meta-analysis study. Our study revealed that therapeutic anticoagulants were not associated with a lower need for mechanical ventilation compared to the prophylactic anticoagulant. Tremblay *et al*. demonstrated that there was no difference in the need for mechanical ventilation

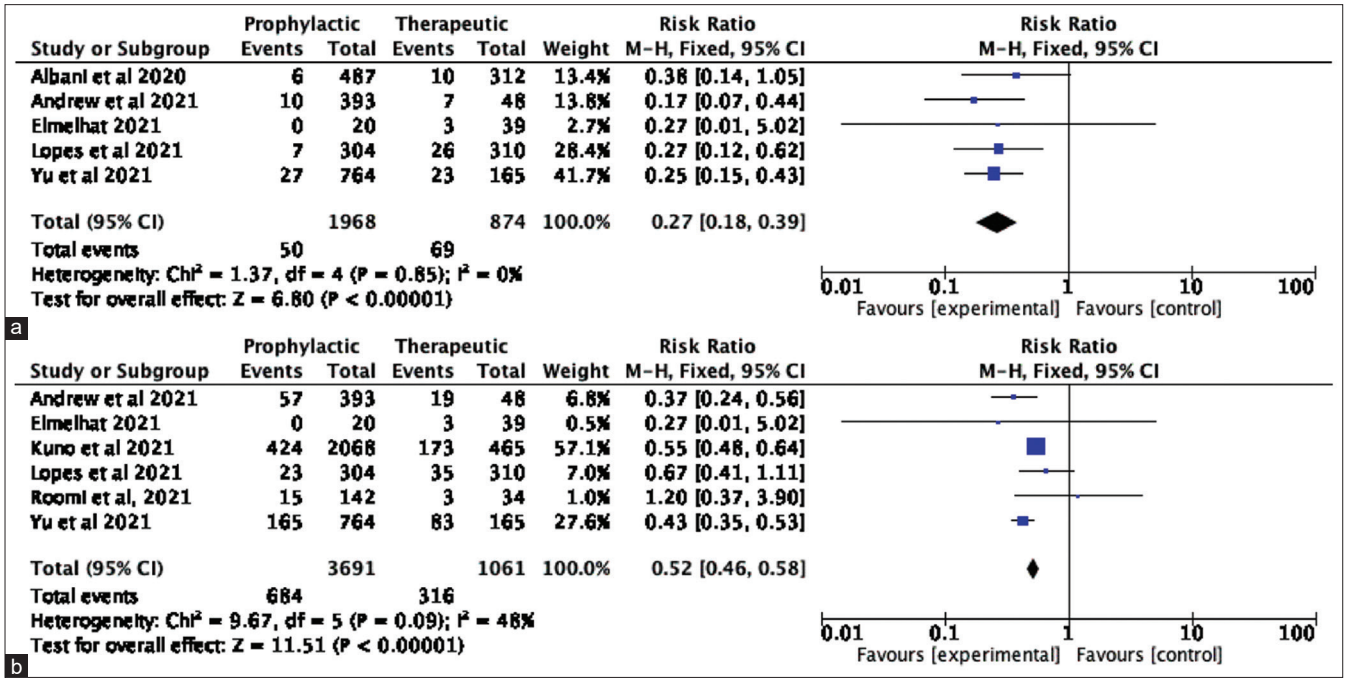

Figure 3: Comparison of prophylactic and therapeutic of anticogulant for risk of bleeding (a) and mortality (b)

between those who received anticoagulant therapy, those who did not receive it, and those who had previously received anticoagulant therapy. While therapeutic dose does not benefit non-critical COVID-19 patients, it may benefit those in a critical state [16]. It is consistent with the American Society of Hematology's recommendation that therapeutic doses of anticoagulants are ineffective in non-critical areas. However, in the case of moderate-to-severe COVID-19, the clinical judgment regarding the use of therapeutic anticoagulants is the most critical factor to consider. Clinicians must conduct a thorough assessment before administering it due to the risk of bleeding for patients [17].

Our investigation discovered a difference significant in mortality and bleeding result between prophylactic and therapeutic anticoagulation. Prophylactic anticoagulants have a lower risk of death (27%) and bleeding (52%) than therapeutic doses as shown in Figure 3. This result was consistent with National Institutes of Health (NIH) recommendations, which urge that hospitalized patients with SARS-CoV-2 infection get a prophylactic dosage of anticoagulants (level of evidence AIII), with LMWH, unless contraindicated [18]. Prophylactic is also more safe for reducing bleeding risk than therapeutic use [19]. The American Society of Hematology (ASH) also recommended prophylactic anticoagulation over intermediate and therapeutic anticoagulation in patients with COVID-19-associated acute illness who do not have established or suspected VTE [20]. This is also confirmed by our study's findings that prophylactic anticoagulant reduced the risk of bleeding and mortality.

Due to the fact that the pathophysiology of COVID-19 remains unknown, the established regiment therapy continues to evolve dynamically. According to some, COVID-19 may induce procoagulation in the body. In the majority of patients who died as a result of COVID-19, postmortem examinations revealed microthrombi in the pulmonary circulation, increased new vessel growth, and diffuse alveolar damage [21], [22]. These conditions can lead to compromised gas exchange and contribute to hypoxemia in patients. A study conducted in severe COVID-19 patients who need mechanical ventilation showed that therapeutic anticoagulants could improve gas exchange over time, decreased D-dimer level, and increased the liberation of mechanical ventilation use after the patients suffered from respiratory failure [23]. Other suggestions of pulmonary thrombi in COVID-19 are perhaps due to the viral infection and severe inflammation leads to vascular damage, to contribute as well by several interactions from platelet, vascular wall, white blood cells, XIIA factor, von Willebrand factor, complement, and other factors in thrombin inflammation [24].

However, this research shown that although prophylactic anticoagulants are not more efficient in reducing mechanical ventilation, it is more effective and safe at reducing mortality and bleeding associated with the use of LMWH anticoagulants.

Conclusion

In sum, the anticoagulant LMWH dosage did not correlate with the lower mechanical ventilation necessity, but it associated with the risk of bleeding and mortality. Prophylactic anticoagulant dose was advised in this research due to their decreased risk of bleeding and mortality. Additional study is necessary to determine the efficacy of various kinds of anticoagulants.

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