Systematic Review

Diagnosis and Treatment of Coagulopathy Caused by the New Coronavirus: A Systematic Review and Meta-Analysis Protocol

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Abstract

Background: The new coronavirus is an agent of respiratory infections associated with thrombosis in vital organs. This study aimed to propose a better diagnosis and treatment of coagulation disorders caused by the new coronavirus (Covid-19).

Materials and Methods: Search in Cochrane central, Web of Science, PubMed, Scopus, and Ovid will be done. Also, according to the inclusion criteria, cross-sectional studies, cohort, clinical trial, and case-control will be included without gender and language restriction. Participants will also be Covid-19 patients with coagulation disorders. Any disagreement in the stages of screening, selection, and extraction of data between the two reviewers will be resolved by discussion, then if not resolved, the opinion of expert reviewers will be used. The risk of bias will be assessed using the NOS **(**Newcastle–Ottawa scale**)** tool for cross-sectional study, cohort and case-control, and the Cochrane checklist for clinical trials study. Metaanalysis of included studies that are similar based on the methodology will be done. Also, a fixed or random-effect model will be used for this it. Heterogeneity indices (I2), odds ratio (OR), risk ratio (RR), mean difference, and %95 confidence interval will also be calculated by Stata V.13.0 (Corporation, College Station TX).

Results: Treatment with anticoagulants will reduce the severity of thrombosis and lung disease in patients. D-dimer measurement will also be a diagnosis indicator of thrombosis.

Conclusions: Simultaneous study of coagulation disorders and thrombosis in patients and development of a Godliness based on it will play a treatment role in the follow-up of the coronavirus disease.

Keywords: Coronavirus, diagnosis, treatment

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Introduction

Coronavirus disease of 2019 (COVID-19) is a respiratory viral infection that increases the risk of prothrombotic coagulation abnormalities.[1,2] The thrombotic consequences are significantly associated with COVID-19 mortality and morbidity.[3,4] A handful of literature review studies have examined patients for the prevalence of thromboembolism.[5-8] It is reported that half of the expired patients may have undetected thromboembolism.[9] The body organs where thrombosis occurs are cephalic, cerebral, cervical, aortic, and carotid arteries, with thrombosis in the cerebral arteries being higher than others.[10] However, 90% of patients suffering from the severe stage of disease have been reported with pulmonary thrombosis, which was more common than cerebral thrombosis.[10,11]

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In COVID-19 patients the risk of coagulation abnormalities triggers by comorbidities like obesity, pregnancy, diabetes.[12,13] In addition, it has been shown that corticosteroid therapy is involved in worsening venous thrombosis and is associated with a poor prognosis in patients.[14] The comorbidity, severity of the disease, and where a patient is examined, e.g., ward versus intensive care unit (ICU), are considered the main risk factors for thrombosis as several studies reported a higher incidence of thrombosis in the ICU.[15-18] In addition, these factors will determine the amount of anticoagulation a patient may receive, which in turn may affect subsequent thrombosis. Therefore, the evaluation of risk factors in COVID-19 patients is critical for the prevention and treatment of thrombosis.

The diagnosis of thrombosis is based on clinical findings and the narrow therapeutic window makes it difficult to provide reasonable and effective treatment.[19] Moreover, the potential benefits of anticoagulation administration as prophylaxis need to be weighed against the risk of bleeding. Therefore, thrombosis must be confirmed with appropriate laboratory tests. One of the confirmatory diagnostic tests for thrombosis is the D-dimer blood test. The cut-off value for diagnosis varies between 1000 and 5000 ng/mL from study to study for viral thromboembolism (VTE).[20] Thus, it can be used as a screening tool for patients with VTE, which includes deep vein thrombosis and pulmonary embolism. In addition, prothrombin time (PT), viscoelastic methods including rotational thromboelastometry (ROTEM), thromboelastography (TEG), and ClotPro thromboelastography have also been used to diagnose hypercoagulopathy, fibrinolysis, coagulation dysfunctions and predict thrombosis.[21-23]

After diagnosis of coagulation disorder, it is essential to find the best therapy procedure. One study shows that different doses of low molecular weight heparin could be effective in the treatment and prevention of thromboembolism in patients. Moreover, the injection of high doses had preventive role in thrombosis in patients.[24] In another study, it was concluded that standard, therapeutic, and moderate doses of thrombosis prevention drugs have been effective in reducing patient mortality.[25]

Therefore, given the nature of review studies, which provide researchers with a wide view of the results of controversial studies, a comprehensive literature review of coagulation disorders is required. The advantage of this study over other studies is that it will provide a guideline for clinical professionals and healthcare system policymakers with the latest information about the prevalence, diagnosis, and treatment of thrombosis in COVID-19 patients.

Objective

Primary objective

The primary objective of the present systematic review and metaanalysis is to determine the diagnosis and treatment of coagulation disorders in the new coronavirus with no limitation in gender, language, and geographical regions.

Secondary objective

1. Estimating the prevalence and incidence of different types of coagulation disorder by age, gender, ethnicity, and comorbidities.
2. Evaluating the efficacy of treatment in different age groups, gender, ethnicity, and comorbidities.
3. Evaluating the relationship between the severity of lung disease and the type of coagulation disorder.
4. Evaluating the relationship between the strain of the virus and the severity of the coagulation disorder.
5. Evaluating the relationship between the type of coagulation disorder and the mortality rate
6. Assessing the relationship between the type of treatment and virus strain, mortality rate.

Materials and Methods

Details of the protocol for this systematic review and meta-analysis were registered on PROSPERO (CRD42021262137). The selection process of the studies will be reported according to the Preferred Reporting Items for Systematic review and Meta-Analysis-Protocols (PRISMA-P). The design steps of the study will be as follows:

1. Initial formulation of search strategy based on PICO (patient, intervention, comparison, outcome).
2. Final development of search strategy based on preliminary search and pilot study.
3. Screening studies by title and abstract.
4. Screening studies by full text.
5. Selection of studies based on inclusion criteria.
6. Data extraction based on a check list.
7. Risk of bias assessment.
8. Selection of homogeneous studies for metaanalysis.

Intervention and outcome

Receiving different regimens of anticoagulant drugs as a treatment for thrombosis in COVID-19 infection (e.g., drug type, dosage, and route). Bleeding disorders and thrombosis in various organs are the main outcome. Prevention of bleeding and thrombosis due to the use of coagulation drugs are secondary outcome.

Study eligibility criteria

Cross-sectional studies, cohort, clinical trial, and case--control, without gender and age restrictions for patients will be included in the study based on the main objectives, which include information about treatment and coagulation disorders. Studies with incomplete data are excluded from the study. To do this, the authors will first be contacted by email or phone. If they do not respond after three calls or answer that they do not have access to the data, these studies will be excluded.

Types of participants

All patients with new coronavirus who have been diagnosed with coagulation disorders will be included in the study. Also, Patients under 18 years of age or with underlying coagulation disorders will be excluded from the study. The study will be

conducted without restrictions on gender, race, region, and language.

Search strategy and literature sources

The search will be conducted in the electronic databases of Cochrane central, Web of Science, PubMed, Scopus, and Ovid by research syntax between December 2019 to June 2021. References List will also be searched. Both human recommended and/or automated MeSH terms and Emtree keywords were used for the literature search. The search syntax is based on PICO and will be finalized after the preliminary search [Table 1]. The systematic search steps will be performed in the following, respectively:

1. The studies will be searched based on the developed search strategy in the electronic database and other sources.
2. All studies will be transferred to EndNote X9 software and at this stage duplicate studies will be removed.
3. Screening will be done by two reviewers based on the title and abstract.
4. Screening will be continued by two reviewers based on the Full-text.
5. The selection of studies will be made based on the inclusion criteria by two reviewers. An expert reviewer will also be used to resolve the discrepancy between the two reviewers.
6. Data extraction will be done by two reviewers based on the checklist. At this stage, if a study is incomplete data, the author of the study will be contacted by email or phone to collect data. If again the data is incomplete, the study will be removed. Also, in case of any conflict between the two reviewers, an expert browser will be consulted for resolve.
7. Risk bias assessment will be done by an expert reviewer.
8. Homogeneous studies will be selected for meta-analysis.

Screening and selection process

The pilot phase of the selection process will be initially conducted on a sample of study. In the pilot phase, after the initial search, if there are between 5 and 7 articles in every 100 studies, the syntax will be finalized. Then, the studies will be screened and selected by two reviewers. Contradictions will also be resolved in the form of discussions with each other, and if not resolved, the expert reviewer will be asked to interfere.

Study quality and risk of bias assessment

The risk of bias will be assessed using the NOS (Newcastle–Ottawa scale) tool for cross-sectional study, cohort, and case--control and the Cochrane checklist for clinical trials. Using these tools, studies will be divided into three categories: high risk, low risk, and unspecified.

Data extraction

To extract the data, a checklist is used that includes information about the study date, author name, type of study (including: cross-sectional, cohort, clinical trial, case--control), type of coagulation disorder (including: DIC or thrombosis), type

Table 1: The search strategy used in from December 2019 to June 2021

	syntax
PubMed	(“2019 Novel Coronavirus Disease”[tiab] OR “2019 Novel Coronavirus Infection”[tiab] OR “2019-nCoV Disease”[tiab] OR “2019-nCoV Infection”[tiab] OR “COVID-19 Pandemic”[tiab] OR “COVID-19 Pandemics”[tiab] OR “COVID-19 Virus Disease”[tiab] OR “COVID-19 Virus Infection”[tiab] OR “COVID19”[tiab] OR “Coronavirus Disease 2019”[tiab] OR “Coronavirus Disease-19”[tiab] OR “SARS Coronavirus 2 Infection”[tiab] OR “SARS-CoV-2 Infection”[tiab] OR “COVID-19”[tiab]) AND ((“Coagulation Disorders” AND Blood)[tiab] OR (Disorders AND “Blood Coagulation”)[tiab] OR “Blood Coagulation Factor Deficiencies” [tiab] OR “Coagulation Proteins Disorders”[tiab] OR Coagulation[tiab] AND “Disseminated Intravascular”)[tiab] OR (“Disseminated Coagulation”AND Intravascular)[tiab] OR (“Intravascular Coagulation” AND Disseminated)[tiab] OR “Intravascular Disseminated Coagulation”[tiab] OR “Coagulation dysfunction”[tiab] OR Thrombosis[tiab] OR “Blood Clot”[tiab] OR Thrombus[tiab]) AND 2019/12/01:2021/06/01[dp]
Scopus	(ALL (“2019 Novel Coronavirus Disease”) OR ALL (“2019 Novel Coronavirus Infection”) OR ALL (“2019-nov disease”) OR ALL (“2019-nov infection”) OR ALL (“cvid-19 pandemic”) OR ALL (“cvid-19 pandemics”) OR ALL (“cvid-19 virus disease”) OR ALL (“cvid-19 virus infection”) OR ALL (“corvidae”) OR ALL (“Coronavirus Disease 2019”) OR ALL (“Coronavirus Disease-19”) OR ALL (“SARS Coronavirus 2 Infection”) OR ALL (“SARS-CoV-2 Infection”) OR ALL (“cvid-19”)) AND (ALL (“Coagulation Disorders”) AND (ALL (blood)) OR (ALL (disorders) AND ALL (“Blood Coagulation”)) OR ALL (“Blood Coagulation Factor Deficiencies”) OR ALL (“Coagulation Proteins Disorders”) OR (ALL (coagulation) AND ALL (“Disseminated Intravascular”)) OR (ALL (“Disseminated Coagulation”) AND ALL (intravascular)) OR (ALL (“Intravascular Coagulation”) AND ALL (disseminated)) OR ALL (“Intravascular Disseminated Coagulation”) OR ALL (“Coagulation dysfunction”) OR ALL (thrombosis) OR ALL (“Blood Clot”) OR ALL (thrombus)) AND (PUBYEAR>2019 AND PUBYEAR<2022)
WOS	(ALL = (“2019 Novel Coronavirus Disease”) OR ALL = (“2019 Novel Coronavirus Infection”) OR ALL = (“2019-nov disease”) OR ALL = (“2019-nov infection”) OR ALL = (“cvid-19 pandemic”) OR ALL = (“cvid-19 pandemics”) OR ALL = (“cvid-19 virus disease”) OR ALL = (“cvid-19 virus infection”) OR ALL = (“corvidae”) OR ALL = (“Coronavirus Disease 2019”) OR ALL = (“Coronavirus Disease-19”) OR ALL = (“SARS Coronavirus 2 Infection”) OR ALL = (“SARS-CoV-2 Infection”) OR ALL = (“cvid-19”)) AND (ALL = (“Coagulation Disorders”) AND (ALL = (blood)) OR (ALL = (disorders) AND ALL = (“Blood Coagulation”)) OR ALL = (“Blood Coagulation Factor Deficiencies”) OR ALL = (“Coagulation Proteins Disorders”) OR (ALL = (coagulation) AND ALL = (“Disseminated Intravascular”)) OR (ALL = (“Disseminated Coagulation”) AND ALL = (intravascular)) OR (ALL = (“Intravascular Coagulation”) AND ALL = (disseminated)) OR ALL = (“Intravascular Disseminated Coagulation”) OR ALL = (“Coagulation dysfunction”) OR ALL = (thrombosis) OR ALL = (“Blood Clot”) OR ALL = (thrombus)) AND (PY=2019-2022)

Contd...

Table 1: Contd...

	syntax
Ovid	((“2019 Novel Coronavirus Disease” or “2019 Novel Coronavirus Infection” or “2019-nCoV Disease” or “2019-nCoV Infection” or “COVID-19 Pandemic” or “COVID-19 Pandemics” or “COVID-19 Virus Disease” or “COVID-19 Virus Infection” or “COVID19” or “Coronavirus Disease 2019” or “Coronavirus Disease-19” or “SARS Coronavirus 2 Infection” or “SARS-CoV-2 Infection” or “COVID-19”) and ((“Coagulation Disorders” and Blood) or (Disorders and Blood Coagulation) or “Blood Coagulation Factor Deficiencies” or “Coagulation Proteins Disorders” or (Coagulation and “Disseminated Intravascular”) or (“Disseminated Coagulation” and Intravascular) or (“Intravascular Coagulatio” and Disseminated) or “Intravascular Disseminated Coagulation” or “Coagulation dysfunction” or Thrombosis or “Blood Clot” or Thrombus)).af.
Cochrane central	((“2019 Novel Coronavirus Disease” or “2019 Novel Coronavirus Infection” or “2019-nCoV Disease” or “2019-nCoV Infection” or “COVID-19 Pandemic” or “COVID-19 Pandemics” or “COVID-19 Virus Disease” or “COVID-19 Virus Infection” or “COVID19” or “Coronavirus Disease 2019” or “Coronavirus Disease-19” or “SARS Coronavirus 2 Infection” or “SARS-CoV-2 Infection” or “COVID-19”) AND (“Coagulation Disorders” AND Blood) OR (Disorders AND “Blood Coagulation”) OR “Blood Coagulation Factor Deficiencies” OR “Coagulation Proteins Disorders” OR (Coagulation AND “Disseminated Intravascular”) OR (“Disseminated Coagulation” AND Intravascular) OR (“Intravascular Coagulatio” AND Disseminated) OR “Intravascular Disseminated Coagulation” OR “Coagulation dysfunction” OR Thrombosis OR “Blood Clot” OR Thrombus) AND 2019/12/01:2021/06/01[dp]

of treatment (including: heparin, aspirin), age (more than 18 years to be tested), sex (to be studied in both sexes), clinical signs (including: bleeding, pulmonary, cerebral disorders), and ethnicity and severity of disease (mild-severe-moderate). Data will be extracted by two reviewers. If there is a discrepancy in the data extraction between the two reviewers, this will be resolved by an expert reviewer.

Data analysis

The level of heterogeneity between studies will be assessed and homogeneous studies will be selected for statistical analysis. The minimum number of studies required to perform a meta-analysis will be 10 studies. Subgroup analysis will be performed based on the existing level of heterogeneity, if appropriate. Also, subgroup analysis will be performed by the type of studies (cohort or clinical trial study). The selected model (Random Effect Model) will be based on the percentage of heterogeneity of the studies. The effect size for the studies includes OR (Odds Ratio), RR (Risk Ratio), MD (Mean Difference) and r^2, with CI (Confidence interval). Stata V.13.0 (Corporation, College Station TX). software will be used for metaanalysis.

Discussion

This systematic review and metaanalysis study will estimate the pooled incidence and prevalence of coagulopathy due to COVID-19 infection and the best diagnostic tool and therapeutic intervention. Coronavirus is associated with severe, moderate, and mild clinical conditions in patients involved. Coagulopathy and thrombosis are important because they can be life-threatening.[26] Patients with severe clinical symptoms are prone to thrombosis in vital organs such as the lungs and brain, whereas hemorrhagic events are less frequent.[27-29] Several review studies have examined the cause of death among severe coronavirus cases.[30,31] One of the most common causes of mortality is deep vein thrombosis, which is one of the consequences of thromboembolism in COVID-19 patients.[32]

Despite studies on the cause of coagulation disorders caused by this virus, there is still no clear reason for its cause. Furthermore, the indirect effect of the systematic inflammation due to the cytokine storm should be considered for thrombotic events.[29,33] It has been reported that chronic oral anticoagulation reduces all-cause mortality in COVID-19 patients.[34] In a review conducted by Gómez-Mesa *et al*.[33] on 1,099 patients, thrombocytopenia and elevation of D-dimer were reported to be the most consistent hemostatic alterations in COVID-19 infection, associated with a higher requirement for mechanical ventilation, admission to intensive care, and death. Initial anticoagulant treatment with low molecular weight heparin reduced mortality by 48% at 7 days and 37% at 28 days and significant improvement in the arterial oxygen pressure/inspired fraction of O2 (PaO2/FiO2) by mitigating the formation of microthrombi and pulmonary coagulopathy. These finding were in concordant with Meisbach *et al*.,[35] and Kollias *et al*.[5,35,36] On the other hand, different treatment methods for thrombosis caused by this virus have been mentioned.[37] Other therapeutic interventions (anti-inflammatory, antiviral, antiparasitic, antibody and antibiotic) may interact with antiplatelets and/or anticoagulants.[38]

Given the high rate of thrombosis in COVID-19 patients and its direct and indirect effect on high mortality and morbidity, the information gathered from this study can be widely used as a guideline for physicians and health policymakers for the prevention and treatment.

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Ethical approval and consent to participant

The authors confirm that they are accountable for all aspects of the work (including full data access, the integrity of the data, and the accuracy of the data analysis) in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflicts of interest

There are no conflicts of interest.

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