Treatment of Coagulopathy in COVID-19 Patients: A scoping review

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Systematic Review

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Abstract

Background: Coagulopathy, including disseminated intravascular coagulation, is frequently noted in patients with coronavirus infection disease 2019 (COVID-19). Recently, a number of articles on this topic have been reported.

Objective: The aim of this study is to identify existing gaps where further research on anticoagulants in COVID-19 patients with coagulopathy needs to be done.

Methods: We used the PRISMA Extension for Scoping Reviews. The protocol was registered on May 21, 2020, before conducting this review. MEDLINE, CENTRAL, WHO-ICTRP, ClinicalTrial.gov and PROSPERO were used.

Result: Eight studies were included; six studies were already published and two are ongoing. The reported results for three publications were from case series, three were from retrospective cohorts and two were from randomized controlled trials. Eight studies examined the effectiveness of low molecular weight heparin (LMWH), of which seven studies used a prophylactic dose and four studies used a therapeutic dose of LMWH. A prophylactic or therapeutic dose of unfractionated heparin was investigated in four and three studies, respectively. No recombinant human soluble thrombomodulin was investigated.

Conclusion: The anticoagulants are limited to heparinoids, and the study designs were of low quality. Further studies with an improved design are needed to compare other available anticoagulants.

Background

One of the major clinical manifestations noted in coronavirus disease 2019 (COVID-19) patients is coagulopathy, including disseminated intravascular coagulation (DIC) and thrombosis that is triggered, at least in part, by cytokines produced by inflammatory cells[1]. In addition, the endothelial cell derangement caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the pathogen that causes COVID-19, may contribute to the development of coagulopathy; SARS-CoV-2 exploits the angiotensin-converting enzyme 2 (ACE2) receptor expressed on the cell surface of vascular endothelial cells and induces diffuse endothelial inflammation, so-called endotheliitis [2], resulting in thrombotic microangiopathies [3]. This complex process plays a role in the development of the coagulopathy induced by SARS-CoV-2. A previous observational study found that the presence of coagulopathy, as evidenced by an increase in plasma levels of D-dimer, is associated with poor prognosis in COVID-19 patients [4]. Currently, many papers are focusing on the treatment of COVID-19-associated coagulopathy; however, there is no scoping review on this topic. The scoping review is a useful method to review evidence in rapidly emerging topics. The identification and analysis of knowledge gaps are valuable indications for conducting a scoping review [5]. The objective of this review is to conduct a scoping review to systematically map the anticoagulants used in this area and to identify the existing gaps where further research needs to be performed.

Methods

Protocol and Registration

We conducted this scoping review after the a priori protocol was registered in Protocols.io. Link: <https://dx.doi.org/10.17504/protocols.io.bgrpjv5n> in which the inclusion and exclusion criteria were described. The methodology to conduct scoping reviews by the Joanna Briggs Institute was followed [6], and the results are presented using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Extension for Scoping Reviews (PRISMA-ScR) [7].

Results

The results of the checklist [7] are described in Table 1.

Selection of sources of evidence

A total of 238 articles (MEDLINE, 155; CENTRAL, 1; ClinicalTrial.gov, 79; WHO-ICTRP, 11; PROSPERO, 7) regarding the treatment of coagulopathy in COVID-19 patients were identified, and 38 studies were selected according to the title and abstract for further full-text review after the removal of duplicates (Fig. 1). Among them, seven articles fulfilled the inclusion criteria, and one article was assessed after reviewing the references of another study. Thus, eight studies were analyzed in the scoping review [8-15]. The results of the literature search strategy are described in Table 2. There is no previous scoping review on this topic.

Characteristics of the sources of evidence

The author, status, publication or registration data, location, study design, patient conditions, interventions, and outcomes of all the included studies are summarized in Map 1.

Status, publication or registration data, and location

Regarding the status of the studies, seven studies have been published and two clinical studies are ongoing. The first study was published in March 2020 [8], followed by studies in April (n = 4) [9-12] and May (n = 1) [13]. The ongoing studies were registered in March [14] and April [15]. The studies were conducted in China (n = 2) [8, 12], France (n = 2) [11, 13], Ireland (n = 1) [9], the Netherlands (n = 1) [10], Canada (n = 1) [15], and the USA (n = 1) [14].

Study design

The study design included case series (n = 3) [9, 10, 13], retrospective cohort studies (n = 3) [8, 11, 12], and randomized control trials (RCTs) (n = 2) [14, 15]. None of the studies followed case report, case-control or prospective cohort studies.

Patients' conditions

Coagulopathy was assessed using several scales, such as the International Society on Thrombosis and Hemostasis (ISTH) DIC score [16](n = 3) [9, 13, 14], Japanese Association for Acute Medicine (JAAM) DIC score [17] (n = 1) [13], sepsis-induced coagulopathy (SIC) DIC score [18] (n = 2) [8, 13], D-dimer level (n = 6) [8, 9, 11-13, 15] and other blood coagulation tests (n = 2) [10, 11]. Seven studies described patient severity [8-14], of which one study [13] used the simplified acute physiology score (SAPS) II [19]. The DIC diagnostic criteria released from the Japanese Society on Thrombosis and Hemostasis (JSTH) DIC score [20] or Japanese Ministry of Health and Welfare (JMHW) DIC score [21] were not used.

Anticoagulants

The anticoagulants therapies used in the studies were a prophylactic dose of unfractionated heparin (UFH) (n = 3, mainly 1000 – 15000 U/day) [8, 11-13], therapeutic dose of UFH (n = 3, detail of dose not reported) [11, 13, 15], prophylactic dose of low molecular weight heparin (LMWH) (n = 7, mainly enoxaparin 40 - 60 mg/day) [8-14], therapeutic dose of LMWH (n = 4, mainly enoxaparin 1 - 1.5 mg/kg/day) [11, 13-15], and the other (n = 1) [9].

Outcomes

The survival of patients, incidence of venous thromboembolism (VTE), incidence of MOF, results of blood coagulation tests, and other outcomes were assessed in 7 [8-12, 14, 15], five [10, 11, 13-15], one [11], one [15], and three studies [11, 14, 15], respectively. The side effects caused by the anticoagulant therapy were reported in one study [13].

Results of the individual sources of evidence

Tang et al [8]

Data and location: In March 2020 from China

Study design: a retrospective cohort study

Patients: 449 severe COVID-19 patients

Coagulopathy and severity condition: Ninety-seven out of 449 patients (21.6%) met the SIC criteria (total score ≥ 4). Plasma levels of D-dimer exceeding 3.0 $\mu\text{g/mL}$ were noted in 161 patients (32.2%).

Interventions: Ninety-nine (22.0%) patients received heparin treatment for at least 7 days, and 94 of those patients received LMWH (enoxaparin 40-60 mg/day) and 5 patients received UFH (10000 - 15000 U/day).

Comparisons: 350 patients did not receive any anticoagulant.

Outcome: No statistically significant difference in 28-day mortality was found between patients who received heparin and those who did not receive heparin (30.3% vs. 29.7%, $p = 0.910$). The 28-day mortality

of heparin users was lower than that of nonusers in patients with severe coagulopathy with an SIC score ≥ 4 (40.0% vs. 64.2%, $p = 0.029$) and D-dimer values $>3.0 \mu\text{g/mL}$ (32.8% vs. 52.4%, $p = 0.017$).

Note: The number of heparin users and nonusers with SIC scores ≥ 4 and D-dimer values $>3.0 \mu\text{g/mL}$, respectively, were not reported. Neither therapy-related side effects nor the study design was reported.

Fogarty et al [9]

Data and location: April 2020 from Ireland

Study design: case series

Patients: 83 hospitalized COVID-19 patients

Coagulopathy and severity condition: The median and quantile D-dimer levels were 732 ng/ml (200 - 10,000 ng/ml), and none of the patients met the diagnostic criteria of DIC as defined according to the ISTH DIC score on admission.

Interventions: The dose of LMWH was based on a prophylactic dose and adjusted according to body weight and renal function (enoxaparin 20 mg OD if $< 50 \text{ kg}$; enoxaparin 40 mg OD if 50-100 kg; 40 mg BD if 101-150 kg; 60 mg BD if $>150 \text{ kg}$). Eight patients had renal impairment on admission and were therefore treated with enoxaparin 20 mg OD. Four patients were on therapeutic anticoagulation (2 patients on apixaban, 1 on edoxaban and 1 on warfarin).

Outcome: 50 patients (60.2%) had fully recovered and were discharged from the hospital without requiring ICU admission, while 20 remained in the hospital and 13 had died. Among the patients, 23 were transferred to the ICU during treatment.

Note: The study design was reported as a cohort, but this study did not compare the clinical outcomes among anticoagulants. Side effects were not reported.

Klok et al [10]

Data and location: April 2020 from the Netherlands

Study design: case series in multiple centers

Patients: 184 patients admitted to the ICU

Coagulopathy and severity condition: Prolongation of the prothrombin time (PT) > 3 seconds or activated partial thromboplastin time (APTT) > 5 seconds was noted in 70 patients.

Interventions: The standard dose of nadroparin differed between hospitals: 2850 IU subcutaneous injection (sc) per day or 5700 IU per day if bodyweight > 100 kg; 5700 IU per day; 5700 IU sc twice daily; 2850 IU sc per day or 5700 IU per day if bodyweight > 100 kg; and 5700 IU sc per day.

Outcome: Twenty-two patients were discharged alive (12%), 139 (76%) were still in the ICU, and 23 died (13%). The number of patients with the composite outcome was 31, and ultrasonography confirmed DVT in 3 patients and arterial thrombotic events in 3 patients. Pulmonary embolism (n = 25) was the most frequent thrombotic complication. Coagulopathy defined as above was an independent predictor of thrombotic complications (adjusted HR 4.1, 95% CI 1.9 - 9.1).

Note: Neither therapy-related side effects nor the study design was reported.

Llitjos et al [11]

Data and location: April 2020 from France

Study design: retrospective cohort study

Patients: 26 patients with severe COVID-19 received mechanical ventilation.

Coagulopathy and severity condition: The median and quantile SOFA score and concentrations of D-dimers and fibrinogen were 2.5 (2 - 3.2), 2330 ng/mL (1495 - 3165) and 7.1 g/L (6.9 - 8.3) in the therapeutic anticoagulation group and 3.5 (3 - 5), 1750 ng/mL (1245 - 2850) and 6.8 g/L (6.4 - 7.3) in the prophylactic anticoagulation group, respectively.

Interventions: Eight patients (31%) were treated with the prophylactic dose of the anticoagulant such as LMWH or UFH. The details of the prophylactic doses were not reported.

Comparisons: Eighteen patients (69%) were treated with the therapeutic dose of anticoagulant such as LMWH or UFH. The details of the therapeutic doses were not reported.

Outcome: The overall rate of VTE at day 7 after ICU admission was 69%. The proportion of VTE was significantly higher in patients treated with prophylactic anticoagulation than in the therapeutic group (100% vs. 56%, respectively, p=0.03). The numbers of patients who developed ARDS, pulmonary embolism, acute kidney injury, and liver dysfunction or who died were 7, 0, 2, 1, and 1, respectively, in the prophylactic group and 14, 6, 7, 3, and 2 in the therapeutic group.

Note: Neither therapy-related side effects nor the study design was reported.

Yin et al [12]

Data and location: April 2020 from China

Study design: retrospective cohort study

Patients: hospitalized COVID-19 patients

Coagulopathy and severity condition: patients with D-dimer levels $\geq 3.0 \mu\text{g/mL}$.

Interventions: Ninety-four patients received LMWH (enoxaparin 40 – 60 mg/day), 5 received UFH (10000 – 15000 U/day) for at least 7 days.

Comparisons: 350 received no anticoagulants.

Outcome: The 28-day mortality of heparin users was significantly lower than that of nonusers (32.8% vs. 52.4%, $p = 0.017$).

Note: Side effects were not reported.

Helms et al [13]

Data and location: May 2020 from France

study design: a case series

Patients: 150 COVID-19 ARDS patients admitted to the ICU

Coagulopathy and severity condition: The median quantile levels of D-dimer and fibrinogen were 2.27 mg/L (1.16 - 20) and 6.99 g/L (6.08 - 7.73), respectively. A total of 144 patients (96%) were diagnosed with non-JAAM-DIC (< 4 points), none of the patients were diagnosed with DIC by the ISTH criterion (< 5 points), and 22 patients (14.7%) had a positive SIC score. The median SAPS II score was 49 (37 – 64) points.

Interventions: The prophylactic dose was 4000 UI/day for LMWH or 5–8 U/kg/h for UFH. The therapeutic dose was not described.

Outcome: Sixty-four clinically relevant thrombotic complications were diagnosed, with pulmonary embolisms being the most frequent event (16.7%). The reported side effects included hematoma in 4 patients (2.7%).

Note: The study design was reported as a cohort; however, the outcomes were not reported based on anticoagulants, and the study was judged as a case series.

Usha et al [14]

Data and location: in April 2020 from the U.S.A.

study design: single-center, randomized, open-label study

Patients: 170 hospitalized COVID-19 patients

Coagulopathy and severity condition: ISTH Overt DIC scores ≥ 3 .

Interventions: the prophylactic dose of enoxaparin (40 mg SC daily or 30 mg SC twice daily if BMI ≥ 40 ; standard of care arm).

Comparison: intermediate-dose enoxaparin (1 mg/kg sc daily or 0.5 mg/kg sc twice daily if BMI ≥ 40 ; intervention arm).

Outcome: the outcome measures were all-cause mortality, major bleeding, arterial thrombosis, venous thromboembolism, and ICU admission.

Note: ongoing

Sholzberg et al [15]

Data and location: in April 2020 from Canada

Study design: multicenter open-label randomized controlled trial

Patients: hospitalized patients with COVID-19

Coagulopathy and severity condition: D-dimer (≥ 2 -fold of the upper limit of normal)

Interventions: therapeutic anticoagulation including the LMWH used in this study includes tinzaparin 175 U/kg once per day, enoxaparin 1.5 mg/kg once per day or 1 mg/kg twice per day or dalteparin 200 U/kg once per day or 100 U/kg twice per day. UFH will be administered using a bodyweight-based nomogram according to the center-specific institutional protocol.

Comparison: the standard care

Outcome: The primary outcome is the composite outcome of ICU admission, noninvasive positive pressure ventilation, invasive mechanical ventilation, or all-cause death up to 28 days.

Note: ongoing

Protocol versus overview

Our planned search strategy registered in protocol.io was compared with the final reported review methods. There was a difference between the study designs reported by original articles and those judged by our reviews. We chose to report the study design based on our judgment.

Discussion

This study is the first scoping review that summarizes the available evidence on the treatment of coagulopathy in COVID-19 patients. Our results provide insights into the gap that exists among anticoagulants recommended by current therapeutic strategies.

Some patterns were found after the scoping review. Most reviewed studies were related to heparin, especially the prophylactic dose and therapeutic dose of LMWH, and no published research evaluating the efficacy of recombinant human soluble thrombomodulin (rTM) was identified. A prophylactic dose of UFH or LMWH is not one of the therapeutic strategies to treat DIC or coagulopathy caused by severe underlying diseases [22]. However, the prophylactic dose of those anticoagulants was used in seven studies including for severe patients. A randomized control trial to compare the prophylactic dose to the therapeutic dose of LMWH is ongoing [14]. Compared with UFH, the use of rTM improved the DIC resolution rate in patients with DIC caused by hematological malignancies or infectious diseases [23], and rTM is approved only in Japan for use in daily clinical practice, which could explain why, currently, no study has reported the rTM treatment of COVID-19-induced coagulopathy. However, an international randomized trial to assess the effect of rTM on sepsis-associated coagulopathy was conducted [24], and it is the rationale to register a clinical trial comparing rTM with other anticoagulants.

The ISTH DIC score as well as D-dimer levels were utilized to assess coagulopathy in most studies. Given that COVID-19 patients showed a high level of interleukin-6 [25], which promotes the production of fibrinogen [26], the criteria released from JAAM or JSTH may be more suitable to evaluate the coagulopathy induced by COVID-19, as these criteria do not evaluate serum levels of fibrinogen. The serum levels of fibrinogen were higher in COVID-19 patients than in non-COVID-related acute respiratory distress syndrome patients [13] [27]. In addition to coagulopathy, the severity of the underlying disease is related to morbidity and mortality. Therefore, it is necessary to precisely evaluate the severity of COVID-19. Only one study [13] assessed the severity of the general condition of patients using SAPS II, and the others used clinical factors such as admission to the ICU.

There is also a gap in the study design. Most of the reviewed studies were observational, starting with low-quality evidence, according to the GRADE system for grading the quality of evidence [28], which likely limits the validity and reproducibility of the results. In addition to this gap, three studies did not report the study design, and one reported the design incorrectly and was judged by our reviewers to be a case series because of not comparing the results of anticoagulant use. Therefore, future studies that could apply to clinical practice should focus on improving study quality.

Strengths and limitations

Our review was conducted systematically according to the methodology after registration of a prior protocol. Performance was based on the recommendations from the PRISMA Extension for Scoping Reviews. We believe that this review followed a robust method. However, due to the urgent need for evidence on this topic and limited time, we did not contact authors to clarify the details of primary data when necessary. We did not search as many databases as possible. Because studies on this topic are rapidly being conducted, there may be other studies that were not examined in this review when the results are published.

Conclusion

Evidence on the treatment of coagulopathy in COVID-19 patients is accumulating but is still mainly focused on the use of heparinoids, observational study designs, and the assessment of coagulopathy by the ISTH DIC score. Further clinical trials are needed to compare other anticoagulants and may provide more accurate results by improving their study design.

Recently, ISTH has released the interim guidance on recognition and management of coagulopathy in COVID-19; it recommends the physicians to measure D-dimer, PT, and the platelet count to determine the patients requiring admission. Based on the reports by Tang et al [8], the prophylactic dose of LMWH is recommended for all admitted patients [29]. This guidance should be modified after the accumulation of more solid evidences.

Declarations

Contributions

HM conceived this study and designed the protocol. HM and HO developed and conducted the literature search strategy. HM, HO, RT, MR, YS and TI drafted and revised the manuscript.

Conflict of interest

All of authors declare that they have no conflicts of interests.

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Tables

Section	Item	PRISMA-ScR Checklist Item	Reported on page # or section
Title	1	Identify the report as a scoping review.	Front page
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	Introduction
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	Introduction
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	Method
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	p.3 in protocol
Information sources	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	p.3-4 in protocol
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	p.4-5 in protocol
Selection of sources of evidence	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	p.6 in protocol
Data charting process	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	p.6 in protocol
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	p.7 in protocol

Critical appraisal of individual sources of evidence	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	Not applicable
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	p.7 in protocol
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	Table 1 in review
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	Map 1 in review
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	Not applicable
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	Result in review
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	Mapping study in review
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	Discussion in review
Limitations	20	Discuss the limitations of the scoping review process.	Discussion in review
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	Conclusion in review
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	p.8 in protocol

Table 1. PRISMA-ScR check list

PRISMA-ScR : Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

Table 2. The results of the literature search strategy MEDLINE		No.
1	"disseminated intravascular coagulation"[MeSH Terms]	10964
2	"disseminated intravascular coagulation"[Title/Abstract]	9895
3	"disseminated intravascular coagulations"[Title/Abstract]	9
4	"coagulopathy"[Title/Abstract]	13108
5	"coagulopathies"[Title/Abstract]	1516
6	"Anticoagulants"[MeSH Terms]	81731
7	"anticoagulants"[Title/Abstract]	27550
8	"anticoagulant"[Title/Abstract]	45879
9	"anticoagulation"[Title/Abstract]	41159
10	"anticoagulations"[Title/Abstract]	13
11	#1 - #10/OR	156004
12	"Coronavirus"[MeSH Terms]	14401
13	"coronavirus"[Title/Abstract]	16580
14	"Coronavirus Infections"[MeSH Terms]	13237
15	"COVID"[Title/Abstract]	13558
16	"cov 2" [Title/Abstract]	4250
17	#7 - #11/OR	33421
18	#10 AND #17	155

Cochrane CENTRAL	No.
⊠1 MeSH descriptor: [disseminated intravascular coagulation] explode all trees	107
⊠2 "disseminated intravascular coagulation":ti,ab	295
⊠3 "disseminated intravascular coagulations":ti,ab	0
⊠4 coagulopathy:ti,ab	1189
⊠5 coagulopaties:ti,ab	137
⊠6 MeSH descriptor [Anticoagulants] explode all trees	4533
⊠7 anticoagulants:ti,ab	2389
⊠8 anticoagulant:ti,ab	4469
⊠9 anticoagulations:ti,ab	5
⊠10 anticoagulation:ti,ab	5319
⊠11 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10	13458
⊠12 MeSH descriptor [Coronavirus] explode all trees	13
⊠13 coronavirus:ti,ab	187
⊠14 MeSH descriptor [Coronavirus Infections] explode all trees	131
⊠15 COVID:ti,ab	294
⊠16 "cov 2":ti,ab	24
⊠17 #12 - #16	382
⊠18 #11 AND #17	1

ClinicalTrial.gov	
COVID-19	1673
other terms: coagulation OR DIC OR coagulopathy OR anticoagulants OR anticoagulation	
Total after duplication elimination	79

PROSPERO	No.
#1 (((coronavirus or corona-virus) AND (wuhan or beijing or shanghai or Italy or South-Korea or korea or China or Chinese or 2019-nCoV or nCoV or COVID-19 or Covid19 or SARS-CoV* or SARSCov2 or ncov)) OR (pneumonia AND Wuhan) or "COVID-19" or "2019-nCoV" or "SARS-CoV" or SARSCOV2 or 2019-nCov or "2019 coronavirus" or "2019 corona virus" or covid19 or ncov OR "novel corona virus" or "new corona virus" or "nouveau corona virus" or "2019 corona virus" OR "novel coronavirus" or "new coronavirus" or "nouveau coronavirus" or "2019 coronavirus" OR (MeSH DESCRIPTOR Coronavirus Infections EXPLODE ALL TREES) OR ((MeSH DESCRIPTOR Coronavirus EXPLODE ALL TREES) AND (wuhan or beijing or shanghai or Italy or South-Korea or korea or China or Chinese or 2019-nCoV or nCoV or COVID-19 or Covid19 or SARS-CoV* or SARSCov2 or ncov)))	860
#2 disseminated intravascular coagulation" or "coagulation" or "DIC" or "coagulopathy" or "coagulopathy" or "anticoagulant"	
#3 #1 AND #3	7

WHO-ICTRP	No.
We used the WHO-ICTRP providing all COVID-19 trials from the ICTRP database	2370
Other terms: coagulation OR coagulations OR coagulopathy OT coagulopathy OR coagulants OR anticoagulation	
Total	10

Figures

Figure 1

PRISMA flow diagram

status	author	data	location	Study design						Patients' conditions						Interventions						Outcomes						details of others			
				cohort						D IC																					
				CR	CS	CC	pros.	retro.	RCTs	ISTH	JAM	ASTH	JMHW	SIC	D-dimer	others	Severity	P-UFH	T-UFH	P-LMWH	T-LMWH	rTM	others	mortality	DOAC	VTE	MOF		CLD	others	SE
published	Tang et al [8]	2020.3	China																												
	Fogarty et al [9]	2020.4	Ireland																												
	Klok et al [10]	2020.4	Netherland																												
	Litips et al [11]	2020.4	France																												
	Yin et al [12]	2020.4	China																												
	Helm et al [13]	2020.5	France																												
ongoing	Usha et al [14]	2020.3	U.S.A																												
	Sholzberg et al [15]	2020.4	Canada																												
Total No.				0	3	0	0	3	2	3	1	0	0	2	6	2	6	4	3	7	4	0	1	7	0	5	1	1	3	1	

Map 1. CR: case report, CS: case series, CC: case control, pros: prospective cohort, retro: retrospective cohort, ISTH: International Society on Thrombosis and Haemostasis, JAAM: Japanese Association for acute medicine, JMHW: Japanese Ministry of Health and Welfare, SIC: sepsis-induced coagulopathy, P-UFH: prophylactic dose of unfractionated heparin, T-UFH: therapeutic dose of unfractionated heparin, P-LMWH: prophylactic dose of low molecular weight heparin, T-LMWH: therapeutic dose of low molecular weight heparin, rTM: recombinant thrombomodulin, VTE: venous thromboembolism, MOF: multiple organ failure, CLD: coagulation laboratory data, DOAC: direct oral anticoagulation, No: number

Figure 2

Map 1. Map caption in figure.