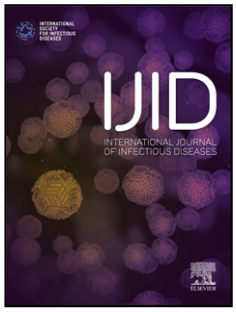
# Journal Pre-proof




Meta-Analysis of coagulation parameters associated with disease severity and poor prognosis of COVID-19

Aining Zhang, Yan Leng, Yi Zhang, Kefan Wu, Yelong Ji, Shaoqing Lei, Zhongyuan Xia

PII: S1201-9712(20)30737-2

DOI: https://doi.org/10.1016/j.ijid.2020.09.021

Reference: IJID 4604

To appear in: *International Journal of Infectious Diseases*

Received Date: 18 May 2020

Revised Date: 5 September 2020

Accepted Date: 10 September 2020

Please cite this article as: Zhang A, Leng Y, Zhang Y, Wu K, Ji Y, Lei S, Xia Z, Meta-Analysis of coagulation parameters associated with disease severity and poor prognosis of COVID-19, *International Journal of Infectious Diseases* (2020), doi: https://doi.org/10.1016/j.ijid.2020.09.021

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2020 Published by Elsevier.

Journal Pre-proof

# Meta-Analysis of coagulation parameters associated with disease severity and poor prognosis of COVID-19

Aining Zhang [1], Yan Leng [1], Yi Zhang [1], Kefan Wu [1], Yelong Ji [1], Shaoqing Lei [1], Zhongyuan Xia [1※]

Drs.Aining Zhang and Yan Leng contributed equally to the article.

[1] Department of anesthesiology, Renmin Hospital of Wuhan University, Wuhan, Hubei, China

※Corresponding author:

Zhongyuan Xia, Department of anesthesiology, Renmin Hospital of Wuhan University, Wuhan, Hubei Province, 430060, China.

Tel: +86-13808628560.

E-mail: xiazhongyuan2005@aliyun.com (Z.-Y. Xia).

## Highlights

- COVID-19 spread rapidly around the world.
- Assessed the abnormal coagulation parameters in infected patients.
- Coagulopathy could be considered as a risk factor for disease severity and mortality of COVID-19.
- Help clinicians to identify the incidence of poor outcomes in COVID-19 patients.

Journal Pre-proof

Journal Pre-proof

**Abstract**

**Background:** To figure out whether abnormal coagulation parameters are associated with disease severity and poor prognosis in patients with 2019 Corona Virus Disease (COVID-19).

**Methods:** A systematic literature search was conducted using the databases PubMed, Embase, and Web of sciences until April 25, 2020. We included a total of 15 studies with 2277 patients. Platelet count (PLT), prothrombin time (PT), activated partial thromboplastin time (APTT), D-dimer (D-D) and fibrinogen (FIB) were collected and analyzed. The statistical results were expressed the effect measure by mean difference (MD) with the related 95% confidence interval (CI).

**Results:** The PLT level of severe patients was lower than that of mild patients, while the levels of PT, D-D and FIB were higher than those of mild patients ($P$ <0.05). The level of APTT had no statistical difference between two groups ($P$ >0.05). Compared to Non-ICU patients, PT of ICU patients was significantly longer ($P$ <0.05). In Non-survivors, PT and D-D were higher, yet PLT was lower than survivors ($P$ <0.05). There was no significant difference in APTT between survivors and Non-survivors ($P$ >0.05). The funnel plot and Egger's Regression test demonstrated that there was no publication bias.

**Conclusions:** Our data support the notion that coagulopathy could be considered as a risk factor for disease severity and mortality of COVID-19, which may help clinicians to identify the incidence of poor outcomes in COVID-19 patients.

**Key words:** COVID-19, Coagulation parameters, Coagulopathy, Laboratory,

Journal Pre-proof

Prognosis

## 1 Introduction

In early December 2019, a new coronavirus named severe acute respiratory syndrome coronavirus 2(SARS-COV-2) caused a catastrophic international phenomenon of the respiratory disease COVID-19[1]. This is the third serious coronavirus outbreak in less than 20 years, following SARS in 2002 and MERS in 2012[2]. Since the outbreak, this innovative type of pneumonia, far more contagious than SARS, has spread rapidly around the world, posing a serious threat to human life and health[3]. Confirmed cases have been reported in 216 countries, areas or territories. As of 23 July 2020, a total of 15,012,731 cases, including 619,150 deaths, have been reported worldwide[4]. Although about 15% of cases caused by human coronavirus strains are the common cold, SARS-COV-2 infection can have a variety of manifestations ranging in severity from influenza to death[2]. Therefore, the identification of certain laboratory parameters that could distinguish between severe and non-severe cases, or between high and low risk of death, will help to improve the understanding of the clinical situation[5].

The most common manifestations of COVID-19 infection are fever, cough, and progressive dyspnea caused by respiratory infection[6]. Emerging evidence suggested that severe COVID-19 may be complicated with coagulopathy, and even severe cases may cause disseminated intravascular coagulation (DIC)[7]. Research report by Tang[8] et al. showed that 71.4% of patients who died of coronavirus met ISTH criteria for DIC. However, a recent study suggested that the characteristics of COVID-19-associated

Journal Pre-proof

coagulopathy(CAC) are different from clotting disorders caused by bacterial infections and other diseases. CAC usually presents with elevated D-dimer and fibrinogen levels, but there are few abnormalities in the prothrombin time and platelet count during the initial course of the disease[9]. In order to explore the relationship between coagulopathy and the severity and prognosis of the disease, we conducted this meta-analysis to compare the difference in blood coagulation parameters among COVID-19 patients.

## 2 Methods

### 2.1 Information sources and search strategy

We conducted a systematic review using PubMed, Embase, and Web of Science databases with the keywords “laboratory” in all fields AND “COVID-19” OR “2019 novel coronavirus disease” OR “COVID-19 pandemic” OR “2019 novel coronavirus infection” OR “2019-nCoV infection” OR “2019-nCoV disease” OR “COVID-19 virus infection” OR “wuhan coronavirus”, between 2019 and present time (i.e., April 25, 2020), with no language restrictions. The reference lists of selected studies were also checked for identifying additional eligible studies. All included studies were managed by EndNoteX9.2 software and duplicates were removed.

### 2.2 Study selection

Our inclusion criteria included (1) study population: adult patients (>18 years of age) who were laboratory- confirmed or clinically diagnosed as COVID-19; (2) study design: cross-sectional study, prospective/retrospective cohort study, case-control study, and randomized controlled trials. Our exclusion criteria included (1) asymptomatic patients;

Journal Pre-proof

(2) studies without reporting coagulation parameters; (3) systematic reviews, meta-analyses, editorials and other forms not presenting original data. The results of the initial search strategy were first screened by title and abstract to exclude apparently irrelevant articles. Remainings were delivered the full text to further screen based on inclusion and exclusion criteria. Two reviewers independently examined the literature, and when there was any disagreement, the opinion of a third researcher was sought to resolve it through discussion.

**2.3 Data extraction and analysis**

Two reviewers independently extracted the following data from the included references: patient basic characteristics (age and sex), clinical classification or clinical outcome and coagulation parameters. There were five coagulation parameters included: PLT, PT, APTT, D-D and FIB. A third researcher checked the data extraction to ensure compliance with our inclusion criteria and the accuracy of the data. Continuous variables were presented as mean ± standard deviation (SD). If variables were represented by median and interquartile range (IQR), we used Excel software to convert them to the form of mean ±SD. The data was meta-analyzed using Revman5.3 software provided by the Cochrane collaboration. The statistical results were expressed the effect measure by mean difference (MD) with the related 95% confidence interval (CI). Heterogeneity analysis of the included studies was carried out by $I^{2,}$, an indicator in percentages used to determine whether the fixed effect model or random effect model was applied. "$I^2 > 50\%$" considered the heterogeneity to be statistically significant that the random effect model was adopted for analysis; otherwise, the fixed effect model

Journal Pre-proof

was selected. The level of meta-analysis was equal to 0.05.

### 2.4 Assessment of methodological quality and risk of bias

The AXIS tool[10] was used to score the methodological quality of included studies, which is a critical appraisal tool to assess study design, reporting quality and the risk of bias in cross-sectional studies[11]. The components of the AXIS tool consist 20 questions, each of which could be answered “yes” (1 point) or “no or don't know/comment” (0 point). A funnel plot was developed using Stata12.0 software to assess publication bias. Meanwhile, Egger’s regression test was applied to make a quantitative analysis of publication bias.

## 3 Results

### 3.1 Study selection and characteristics

The initial search identified 1209 potentially relevant citations through PubMed database and 43 through other sources (Fig. 1). After eliminating the duplicated literature as well as reading titles and abstracts, 39 articles were screened out for full-text assessment. Of these, 28 were excluded for reasons listed in Fig. 1. Four additional studies were identified by reading the reference lists of the selected documents, thus, the pooled analysis finally included 15 studies[8, 12-25]. We listed the basic characteristics and quality score of each study included in Table 1. All the studies were cross-sectional studies conducted in China, involving a total of 2277 patients with sample sizes ranging from 30 to 449. Among them, 7 studies were included to evaluate differences in coagulation function between mild and severe patients, 4 between ICU and Non-ICU

Journal Pre-proof

patients and 5 between survivors and Non-survivors. All the statistical results were presented in Table 2, as well as visually displayed through the forest plots.

### 3.2 Meta analysis results

#### 3.2.1 Coagulation parameters between mild and severe patients

Five indicators of PLT, PT, APTT, D-D and FIB were compared between mild and severe patients, included 2, 5, 4, 7, 2 studies respectively. According to the $I^2$ value, the fixed effect model was adopted for the statistical analysis of PLT and FIB (both $I^2$=0), and the random effect model was adopted for the statistical analysis of PT, APTT and D-D ($I^2$=82%, 75%, 84%, respectively). The results showed that PLT of mild patients was higher than that of severe patients [MD=16.63, 95%CI=(0.39, 32.86), *P* <0.05]. PT, D-D and FIB of mild patients were all lower than those of severe patients [MD=-0.50, 95%CI=(-0.97, -0.03), *P* <0.05; MD=-0.83, 95%CI=(-1.31, -0.34), *P* <0.05; MD=-0.76, 95%CI=(-1.20, -0.32), *P* <0.01; separately]. There was no significant difference in APTT between the two groups [MD=-1.15, 95%CI=(-3.59, 1.30), *P* >0.05] (Fig. 2).

#### 3.2.2 Coagulation parameters between ICU and Non-ICU patients

Four parameters of PLT, PT, APTT and D-D were carried out quantitative synthesis between ICU and Non-ICU patients, separately involved 3, 4, 4, 3 researches. We used the fixed effect model to calculate the differences of PLT, PT and APTT between the two groups (all $I^2$=0) and the random effect model to calculate D-D difference between the two groups (I=85%). We found that PLT, APTT and D-D between ICU and Non-ICU patients had no statistical difference [MD=-0.19, 95%CI=(-20.22, 19.85), *P* >0.05; MD=-0.59, 95%CI=(-1.84, 0.67), *P* >0.05; MD=3.51, 95%CI=(-7.40, 14.41), *P* >0.05;

Journal Pre-proof

respectively]. While PT of ICU patients was higher than that of Non-ICU patients [MD=0.54, 95%CI=(0.13, 0.95), *P* <0.05] (Fig. 3).

### 3.2.3 Coagulation parameters between survivors and Non-survivors

We evaluated four indicators of PLT, PT, APTT and D-D to investigate coagulation function between survivors and Non-survivors, included 3, 5, 2, 5 studies respectively. Referred to the $I^2$ value, We used the fixed effect model to compare the differences of PLT and PT between the two groups ($I^2$=0, 38%, separately) and the random effect model to compare APTT and D-D between the two groups (I=70%, 81%, separately). The statistics showed that PLT of survivors was higher than that of Non-survivors [MD=51.47, 95%CI=(38.41, 64.54), *P* <0.001]. PT and D-D of survivors were both lower than those of Non-survivors [MD=-1.10, 95%CI=(-1.37, -0.83), *P* <0.001; MD=-6.01, 95%CI=(-8.99, -3.03), *P* <0.001; separately]. There was no significant difference in APTT between survivors and Non-survivors [MD=-2.42, 95%CI=(-5.84, 1.01), *P* >0.05] (Fig. 4).

### 3.3 Publication Bias

Studies comparing D-D indicator were used to draw a funnel plot (Fig. 5) for the analysis of publication bias. The selected researches were distributed in the plot in a basically symmetrical way, indicating that the possible bias was small. For further quantitative analysis, we conducted Egger's regression test (*P*=0.923) and confirmed that there was no significant statistically evidence of publication bias (Table 3).

## 4 Discussion

Journal Pre-proof

Although the mortality rate of this novel coronary pneumonia is lower than that of SARS and MERS, the risk of severe and critically ill patients progressing to ARDS and being admitted to ICU still remains fairly high[26]. There is an urgent need to identify a few indicators for early diagnosis of disease progression and prognosis in order to provide more appropriate treatment options. Studies have shown that the cytokines IL-6 and procalcitonin can be used to predict the severity of COVID-19[9, 27]. Currently, emerging researches from Wuhan, China, suggest that severe or critically ill COVID-19 patients may develop coagulation disorders and increase the risk of thromboembolic events[28-30]. Professor Taisheng Li[31], pointed out that COVID-19 patients showed obvious abnormal coagulation function. The study of Zhai[32] et al. similarly demonstrated that nearly 20% of patients with COVID-19 had severe coagulation abnormalities, which clinical types were all severe or critical.

Some researchers concluded that COVID-19 can activate the coagulation cascade through a variety of mechanisms, resulting in a severe hypercoagulable state and secondary DIC[33]. The current view is that SARS-COV-2 enters host cells through cell surface receptor, ACE2. This process leads to local inflammation, endothelial activation, tissue damage, and cytokine release changes that lead to coagulation activation[34, 35]. Another perspective is that the virus interferes, directly or indirectly, with the clotting pathways. The susceptibility of these two pathways to coagulation disorders is mainly related to host factors such as age, comorbidities, and degree of lung injury[36]. However, when the coagulation function is excessively activated and a large amount of coagulation factors are over-consumed, it will stimulate secondarily severe DIC, cause

Journal Pre-proof

a fatal threat to the body, and have a significant negative impact on prognosis[37]. Recently, it was found that with the aggravation of clinical symptoms and chest imaging, PLT gradually decreased, D-D gradually increased and PT gradually prolonged. These changes are consistent with the pathological process of DIC[31]. Most of the current studies only use D-D as an indicator of disease progression[8, 25, 38]. Yet our quantitative synthesis showed that the coagulation status of critically ill or dead patients was worse than that of lightly infected patients, including increased D-D, decreased PLT, and prolonged PT. This suggests that attention should be paid to anticoagulation therapy for COVID-19 patients.

COVID- 19 usually does not cause PT to be prolonged for more than 3 seconds, PLT to<$100\times10^9$/L or FIB to<1 gm/L. Therefore, COVID-19 coagulopathy does not lead to a bleeding state, but to a thrombotic state[38]. Although the role of anticoagulant therapy in inhibiting progression of disease and reducing death is not yet clear, most hospitals have begun to use preventive medium doses or even therapeutic doses of anticoagulant therapy for specific patients to prevent potential thrombosis complications[28, 39, 40]. The study by Jian[41] et al. demonstrated when treated with heparin molecules, not only did heparin act as an anticoagulant, it also bound to the SARS-COV-2 spike protein, preventing the virus from binding to the receptor cells. A notable problem is that patients with severe COVID-19 are more likely to show gastrointestinal abnormalities[24, 42]. Anticoagulant therapy increases the risk of gastrointestinal bleeding and exacerbates the underlying bleeding condition in COVID-19 patients[43, 44]. Therefore, we recommend screening for coagulation tests at the time of patients admitted to hospital

Journal Pre-proof

or early in the course of the disease. At the same time, the dynamic changes of coagulation parameters should always be paid attention to during the treatment process, so as to adjust the patients' anticoagulation treatment plan in real time. If PT, D-D as well as other indicators are increased, it may warn patients to get worse and have a poor prognosis.

Our research has several limitations that included articles are biased in the nature of observation during statistical analysis. Second, few studies on SARS-CoV-2 infection have divided the cohort into ICU and Non-ICU patients, as well as survivors and Non-survivors, which limited the number of studies and related patients included in our meta-analysis. Next, we could not exclude patients with basic coagulopathy from the study.

In conclusion, this study demonstrated beneficial of screening abnormal coagulation parameters, such as decreased PLT, elevated PT, D-D and FIB for predicting the severity and prognosis of COVID-19. We suggest clinicians to pay attention to changes in blood coagulation of COVID-19 patients and explore their potential guidance for therapy.

**Funding Source**

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Ethics**



Journal Pre-proof

Journal Pre-proof

The study does not require ethical approval because the meta-analysis are based on published research and the original data are anonymous.

**Conflict of interest**

The authors declared that they have no conflicts of interest to this work.

## Conflict of Interest Statement

We declare that there are no potential conflicts of interest.

**Declaration of interests**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Declaration of interests
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

**Contributions**

Aining Zhang: Study design, Data collection, Data analysis, Writing

Yi Zhang: Data collection, Data analysis

Yan Leng: Data collection, Data analysis

Shaoqing Lei: Paper modification

Zhongyuan Xia: Research guidance, Paper modification

Journal Pre-proof

**Figure Legend**

**Fig. 1.** Study selection and characteristics.

**Fig. 2.** Coagulation parameters PLT (A), PT (B), APTT (C), D-D (D) and FIB (E) between mild and severe patients.

**Fig. 3.** Coagulation parameters PLT (A), PT (B), APTT (C) and D-D (D) between ICU and Non-ICU patients.

**Fig. 4.** Coagulation parameters PLT (A), PT (B), APTT (C) and D-D (D) between survivors and Non-survivors.

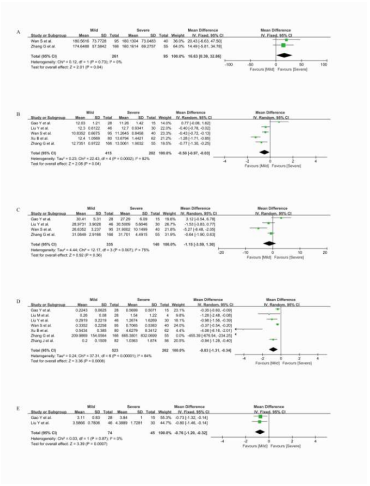
**Fig. 5.** Funnel plot comparing the level of D-D indicator among parents.

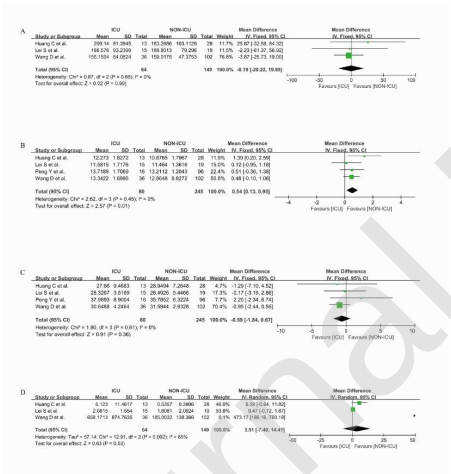
Journal Pre-proof

Journal Pre-proof

Journal Pre-proof

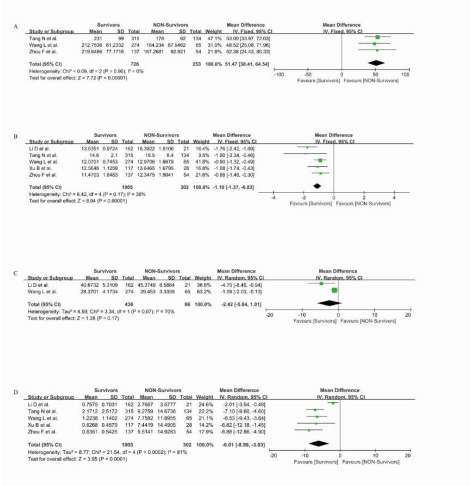
Journal Pre-proof

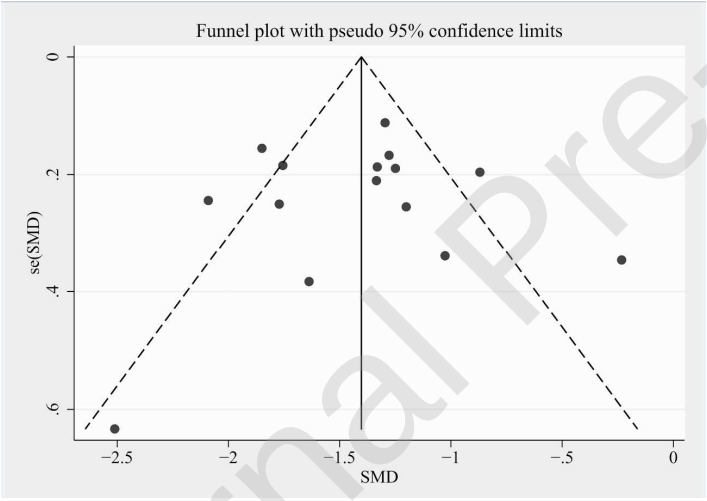




Journal Pre-proof

Journal Pre-proof






## References

1. Chan, J. F.; Yuan, S.; Kok, K. H.; To, K. K.; Chu, H.; Yang, J.; Xing, F.; Liu, J.; Yip, C. C.; Poon, R. W.; Tsoi, H. W.; Lo, S. K.; Chan, K. H.; Poon, V. K.; Chan, W. M.; Ip, J. D.; Cai, J. P.; Cheng, V. C.; Chen, H.; Hui, C. K.; Yuen, K. Y., A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet* **2020,** *395* (10223), 514-523.

2. Yang, Y.; Peng, F.; Wang, R.; Yange, M.; Guan, K.; Jiang, T.; Xu, G.; Sun, J.; Chang, C., The deadly coronaviruses: The 2003 SARS pandemic and the 2020 novel coronavirus epidemic in China. *J Autoimmun* **2020,** *109*, 102434.

3. Ungaro, R. C.; Sullivan, T.; Colombel, J. F.; Patel, G., What Should Gastroenterologists and Patients Know About COVID-19? *Clin Gastroenterol Hepatol* **2020,** *18* (7), 1409-1411.

4. World Health Organization. Coronavirus disease (COVID-19) outbreak situation. [cited

Journal Pre-proof

2020 July 25]. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019 .

5. Henry, B. M.; de Oliveira, M. H. S.; Benoit, S.; Plebani, M.; Lippi, G., Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. *Clin Chem Lab Med* **2020,** *58* (7), 1021-1028.

6. Wang, D.; Hu, B.; Hu, C.; Zhu, F.; Liu, X.; Zhang, J.; Wang, B.; Xiang, H.; Cheng, Z.; Xiong, Y.; Zhao, Y.; Li, Y.; Wang, X.; Peng, Z., Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *Jama* **2020,** *323* (11), 1061-9.

7. Kollias, A.; Kyriakoulis, K. G.; Dimakakos, E.; Poulakou, G.; Stergiou, G. S.; Syrigos, K., Thromboembolic risk and anticoagulant therapy in COVID-19 patients: Emerging evidence and call for action. *Br J Haematol* **2020**.

8. Tang, N.; Li, D.; Wang, X.; Sun, Z., Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost* **2020,** *18* (4), 844-847.

9. Iba, T.; Levy, J. H.; Connors, J. M.; Warkentin, T. E.; Thachil, J.; Levi, M., The unique characteristics of COVID-19 coagulopathy. *Crit Care* **2020,** *24* (1), 360.

10. Downes, M. J.; Brennan, M. L.; Williams, H. C.; Dean, R. S., Development of a critical appraisal tool to assess the quality of cross-sectional studies (AXIS). *BMJ Open* **2016,** *6* (12), e011458.

11. Ma, L. L.; Wang, Y. Y.; Yang, Z. H.; Huang, D.; Weng, H.; Zeng, X. T., Methodological quality (risk of bias) assessment tools for primary and secondary medical studies: what are they and which is better? *Mil Med Res* **2020,** *7* (1), 7.

12. Gao, Y.; Li, T.; Han, M.; Li, X.; Wu, D.; Xu, Y.; Zhu, Y.; Liu, Y.; Wang, X.; Wang, L., Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19. *J Med Virol* **2020**.

13. Liu, M.; He, P.; Liu, H. G.; Wang, X. J.; Li, F. J.; Chen, S.; Lin, J.; Chen, P.; Liu, J. H.; Li, C. H., [Clinical characteristics of 30 medical workers infected with new coronavirus pneumonia]. *Zhonghua Jie He He Hu Xi Za Zhi* **2020,** *43* (3), 209-214.

14. Liu, Y.; Liao, W.; Wan, L.; Xiang, T.; Zhang, W., Correlation Between Relative Nasopharyngeal Virus RNA Load and Lymphocyte Count Disease Severity in Patients with COVID-19. *Viral Immunol* **2020**.

15. Wan, S.; Xiang, Y.; Fang, W.; Zheng, Y.; Li, B.; Hu, Y.; Lang, C.; Huang, D.; Sun, Q.; Xiong, Y.; Huang, X.; Lv, J.; Luo, Y.; Shen, L.; Yang, H.; Huang, G.; Yang, R., Clinical features and treatment of COVID-19 patients in northeast Chongqing. *J Med Virol* **2020**.

16. Xu, B.; Fan, C. Y.; Wang, A. L.; Zou, Y. L.; Yu, Y. H.; He, C.; Xia, W. G.; Zhang, J. X.; Miao, Q., Suppressed T cell-mediated immunity in patients with COVID-19: a clinical retrospective study in Wuhan, China. *J Infect* **2020**.

17. Zhang, G.; Hu, C.; Luo, L.; Fang, F.; Chen, Y.; Li, J.; Peng, Z.; Pan, H., Clinical features and short-term outcomes of 221 patients with COVID-19 in Wuhan, China. *J Clin Virol* **2020,** *127*, 104364.

18. Zhang, J. J.; Dong, X.; Cao, Y. Y.; Yuan, Y. D.; Yang, Y. B.; Yan, Y. Q.; Akdis, C. A.; Gao, Y. D., Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy* **2020**.

Journal Pre-proof

19. Huang, C.; Wang, Y.; Li, X.; Ren, L.; Zhao, J.; Hu, Y.; Zhang, L.; Fan, G.; Xu, J.; Gu, X.; Cheng, Z.; Yu, T.; Xia, J.; Wei, Y.; Wu, W.; Xie, X.; Yin, W.; Li, H.; Liu, M.; Xiao, Y.; Gao, H.; Guo, L.; Xie, J.; Wang, G.; Jiang, R.; Gao, Z.; Jin, Q.; Wang, J.; Cao, B., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* **2020,** *395* (10223), 497-506.

20. Lei, S.; Jiang, F.; Su, W.; Chen, C.; Chen, J.; Mei, W.; Zhan, L. Y.; Jia, Y.; Zhang, L.; Liu, D.; Xia, Z. Y.; Xia, Z., Clinical characteristics and outcomes of patients undergoing surgeries during the incubation period of COVID-19 infection. *EClinicalMedicine* **2020**, 100331.

21. Peng, Y. D.; Meng, K.; Guan, H. Q.; Leng, L.; Zhu, R. R.; Wang, B. Y.; He, M. A.; Cheng, L. X.; Huang, K.; Zeng, Q. T., [Clinical characteristics and outcomes of 112 cardiovascular disease patients infected by 2019-nCoV]. *Zhonghua Xin Xue Guan Bing Za Zhi* **2020,** *48* (0), E004.

22. Wang, D.; Hu, B.; Hu, C.; Zhu, F.; Liu, X.; Zhang, J.; Wang, B.; Xiang, H.; Cheng, Z.; Xiong, Y.; Zhao, Y.; Li, Y.; Wang, X.; Peng, Z., Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *Jama* **2020**.

23. Tang, N.; Bai, H.; Chen, X.; Gong, J.; Li, D.; Sun, Z., Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost* **2020**.

24. Jin, X.; Lian, J. S.; Hu, J. H.; Gao, J.; Zheng, L.; Zhang, Y. M.; Hao, S. R.; Jia, H. Y.; Cai, H.; Zhang, X. L.; Yu, G. D.; Xu, K. J.; Wang, X. Y.; Gu, J. Q.; Zhang, S. Y.; Ye, C. Y.; Jin, C. L.; Lu, Y. F.; Yu, X.; Yu, X. P.; Huang, J. R.; Xu, K. L.; Ni, Q.; Yu, C. B.; Zhu, B.; Li, Y. T.; Liu, J.; Zhao, H.; Zhang, X.; Yu, L.; Guo, Y. Z.; Su, J. W.; Tao, J. J.; Lang, G. J.; Wu, X. X.; Wu, W. R.; Qv, T. T.; Xiang, D. R.; Yi, P.; Shi, D.; Chen, Y.; Ren, Y.; Qiu, Y. Q.; Li, L. J.; Sheng, J.; Yang, Y., Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. *Gut* **2020,** *69* (6), 1002-1009.

25. Zhou, F.; Yu, T.; Du, R.; Fan, G.; Liu, Y.; Liu, Z.; Xiang, J.; Wang, Y.; Song, B.; Gu, X.; Guan, L.; Wei, Y.; Li, H.; Wu, X.; Xu, J.; Tu, S.; Zhang, Y.; Chen, H.; Cao, B., Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* **2020,** *395* (10229), 1054-1062.

26. Han, H.; Yang, L.; Liu, R.; Liu, F.; Wu, K. L.; Li, J.; Liu, X. H.; Zhu, C. L., Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. *Clin Chem Lab Med* **2020**.

27. Lippi, G.; Plebani, M., Procalcitonin in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis. *Clinica Chimica Acta* **2020,** *505*.

28. Patel, P.; Sengupta, N., PPIs and Beyond: A Framework for Managing Anticoagulation-Related Gastrointestinal Bleeding in the Era of COVID-19. *Dig Dis Sci* **2020,** *65* (8), 2181-2186.

29. Chen, N.; Zhou, M.; Dong, X.; Qu, J.; Gong, F.; Han, Y.; Qiu, Y.; Wang, J.; Liu, Y.; Wei, Y.; Xia, J.; Yu, T.; Zhang, X.; Zhang, L., Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* **2020,** *395* (10223), 507-513.

30. Yin, S.; Huang, M.; Li, D.; Tang, N., Difference of coagulation features between severe pneumonia induced by SARS-CoV2 and non-SARS-CoV2. *J Thromb Thrombolysis* **2020**.

31. Li, T.; Lu, H.; Zhang, W., Clinical observation and management of COVID-19 patients. *Emerg Microbes Infect* **2020,** *9* (1), 687-690.

Journal Pre-proof

32. Zhai, Z.; Li, C.; Chen, Y.; Gerotziafas, G.; Zhang, Z.; Wan, J.; Liu, P.; Elalamy, I.; Wang, C., Prevention and Treatment of Venous Thromboembolism Associated with Coronavirus Disease 2019 Infection: A Consensus Statement before Guidelines. *Thromb Haemost* **2020**.

33. Lin, L.; Lu, L.; Cao, W.; Li, T., Hypothesis for potential pathogenesis of SARS-CoV-2 infection-a review of immune changes in patients with viral pneumonia. *Emerg Microbes Infect* **2020,** *9* (1), 727-732.

34. Connors, J. M.; Levy, J. H., COVID-19 and its implications for thrombosis and anticoagulation. *Blood* **2020,** *135* (23), 2033-2040.

35. Leisman, D. E.; Deutschman, C. S.; Legrand, M., Facing COVID-19 in the ICU: vascular dysfunction, thrombosis, and dysregulated inflammation. *Intensive Care Med* **2020,** *46* (6), 1105-1108.

36. Marchandot, B.; Trimaille, A.; Curtiaud, A.; Matsushita, K.; Jesel, L.; Morel, O., Thromboprophylaxis: balancing evidence and experience during the COVID-19 pandemic. *J Thromb Thrombolysis* **2020**, 1-10.

37. Kawano, N.; Wada, H.; Uchiyama, T.; Kawasugi, K.; Madoiwa, S.; Takezako, N.; Suzuki, K.; Seki, Y.; Ikezoe, T.; Hattori, T.; Okamoto, K., Analysis of the association between resolution of disseminated intravascular coagulation (DIC) and treatment outcomes in post-marketing surveillance of thrombomodulin alpha for DIC with infectious disease and with hematological malignancy by organ failure. *Thromb J* **2020,** *18*, 2.

38. Pryzdial, E. L. G.; Sutherland, M. R.; Lin, B. H.; Horwitz, M., Antiviral anticoagulation. *Res Pract Thromb Haemost* **2020,** *4* (5), 774-788.

39. Proctor, E. A.; Dineen, S. M.; Van Nostrand, S. C.; Kuhn, M. K.; Barrett, C. D.; Brubaker, D. K.; Yaffe, M. B.; Lauffenburger, D. A.; Leon, L. R., Coagulopathy signature precedes and predicts severity of end-organ heat stroke pathology in a mouse model. *J Thromb Haemost* **2020**.

40. Yin, S.; Huang, M.; Li, D.; Tang, N., Difference of coagulation features between severe pneumonia induced by SARS-CoV2 and non-SARS-CoV2. *J Thromb Thrombolysis* **2020**, 1-4.

41. Liu, J.; Li, J.; Arnold, K.; Pawlinski, R.; Key, N. S., Using heparin molecules to manage COVID-2019. *Res Pract Thromb Haemost* **2020,** *4* (4), 518-523.

42. Iba, T.; Levy, J. H.; Levi, M.; Thachil, J., Coagulopathy in COVID-19. *J Thromb Haemost* **2020**.

43. Schelleman, H.; Brensinger, C. M.; Bilker, W. B.; Hennessy, S., Antidepressant-warfarin interaction and associated gastrointestinal bleeding risk in a case-control study. *PLoS One* **2011,** *6* (6), e21447.

44. Hansen, M. L.; Sørensen, R.; Clausen, M. T.; Fog-Petersen, M. L.; Raunsø, J.; Gadsbøll, N.; Gislason, G. H.; Folke, F.; Andersen, S. S.; Schramm, T. K.; Abildstrøm, S. Z.; Poulsen, H. E.; Køber, L.; Torp-Pedersen, C., Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. *Arch Intern Med* **2010,** *170* (16), 1433-41.

Journal Pre-proof

**Table 1** Characteristics of the included studies on COVID-19, 2020.

Journal Pre-proof

Journal Pre-proof

-, Not available, not reported.

| Author | N | Males [N (%)] | Mean age | Quality score | Country |
|---|---|---|---|---|---|
| Gao Y et al. | 43 | 26(60.5) | - | 17 | China |
| Liu M et al. | 30 | - | - | 14 | China |
| Liu Y et al. | 76 | 49(64.5) | 45 | 17 | China |
| Wan S et al. | 135 | 72(53.3) | 46 | 18 | China |
| Xu B et al. | 145 | 76(52.4) | - | 18 | China |
| Zhang G et al. | 221 | 108(48.9) | 53 | 16 | China |
| Zhang J et al. | 140 | 71(50.7) | 56 | 16 | China |
| Huang C et al. | 41 | 30(73.2) | 49 | 19 | China |
| Lei S et al. | 34 | 14(41.2) | 54 | 18 | China |
| Peng Y et al. | 112 | 53(47.3) | 61 | 16 | China |
| Wang D et al. | 138 | 75(54.3) | 55 | 19 | China |
| Li D et al. | 183 | 98(53.6) | 54 | 17 | China |
| Tang N et al. | 449 | 268(59.7) | 65 | 18 | China |
| Wang L et al. | 339 | 166(49.0) | 70 | 19 | China |
| Zhou F et al. | 191 | 119(62.3) | 56 | 16 | China |

**Table 2** Results of meta-analysis comparing coagulopathy in COVID-19 patients with

Journal Pre-proof

and without severe illness or mortality.

| Coagulation parameters | Mild vs severe | | | | Non-ICU vs ICU | | | | Survival vs Non-survival | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | #of studies (# of pts*) | MD (95% CI) | $I^2$ | Cochran's Q *P*-value | #of studies (# of pts*) | MD (95% CI) | $I^2$ | Cochran's Q *P*-value | #of studies (# of pts*) | MD (95% CI) | $I^2$ | Cochran's Q *P*-value |
| PLT(×109/L) | 2 (356) | 16.63 (0.39, 32.86) | 0% | 0.04 | 3 (213) | -0.19 (-20.22,19.85) | 0% | 0.99 | 3 (979) | 51.47 (38.41,64.54) | 0% | <0.001 |
| PT(s) | 5 (620) | -0.50 (-0.97,-0.03) | 82% | 0.04 | 4 (325) | 0.54 (0.13, 0.95) | 0% | 0.01 | 5 (1307) | -1.10 (-1.37,-0.83) | 38% | <0.001 |
| APTT(s) | 4 (475) | -1.15 (-3.59, 1.30) | 75% | 0.36 | 4 (325) | -0.59 (-1.84, 0.67) | 0% | 0.36 | 2 (522) | -2.42 (-5.84,1.01) | 70% | 0.17 |
| D-D(mg/L) | 7 (790) | -0.83 (-1.31,-0.34) | 84% | <0.001 | 3 (213) | 3.51 (-7.40, 14.41) | 85% | 0.53 | 5 (1307) | -6.01 (-8.99,-3.03) | 81% | <0.001 |
| FIB(g/L) | 2 (119) | -0.76 (-1.20,-0.32) | 0% | <0.001 | - | - | - | - | - | - | - | - |

* pts: patients.

-, Not available, not reported.

**Table 3** Egger's test.

| Std-Eff | Coef. | Std. Err. | t | P>\| t \| | [95% Conf. | Interval] |
|---|---|---|---|---|---|---|

Journal Pre-proof

| | | | | | | |
|---|---|---|---|---|---|---|
| slope | -1.376091 | 0.2850025 | -4.83 | 0.000 | -1.991801 | -0.7603804 |
| bias | -0.138335 | 1.408603 | -0.10 | 0.923 | -3.181437 | 2.904767 |

Journal Pre-proof