D-dimer is associated with the risk of mortality in Coronavirus Disease 2019 patients

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Abstract. – This study aims to investigate the association between D-dimer and the risk of mortality in coronavirus disease 2019 (COVID-19) patients using a meta-analysis. We found that the D-dimer levels in non-survival patients were significantly higher than those in survival patients (SMD = 0.91, 95% CI = 0.79 to 1.03). In conclusion, the elevated D-dimer levels were associated with an increased risk of mortality in COVID-19 patients.

Key Words:
    COVID-19, D-dimer, Mortality.

Short Report

We read with great interest the recent article titled "Changes in Blood Coagulation in Patients with Severe Coronavirus Disease 2019 (COVID-19): a Meta-Analysis" by Xiong et al[1], which was published online in the British Journal of Haematology. This paper revealed that the elevated D-dimer levels were positively associated with the severity of COVID-19 patients based on a systematic meta-analysis[1]. To our knowledge, several individual studies have reported that the D-dimer levels in non-survival COVID-19 patients were higher than those in survival COVID-19 patients[2-4]. Generally, individual studies with relatively small sample size lack the ability to provide confirmed evidence. Thus, it is required to conduct a quantitative meta-analysis to systematically evaluate the association between D-dimer and the risk of mortality in COVID-19 patients. This study will provide useful information for predicting the risk of mortality in COVID-19 patients.

The databases of PubMed, Chinese National Knowledge Infrastructure (CNKI) and Web of Science were searched for eligible literature until April 26, 2020. The keywords included "clinical" OR "laboratory" AND "SARS-CoV-2" OR "COVID-19" OR "coronavirus 2019" OR "2019-nCoV" AND "mortality" OR "outcome". Studies exploring the D-dimer levels in survivors and non-survivors with COVID-19 were included. The references of the included studies and relevant reviews were screened for additional eligible studies. The combined standardized mean difference (SMD) with 95% confidence interval (CI) was calculated using a fixed-effects model. We estimated the mean and standard deviation by using sample size, median and interquartile range[5]. Sensitivity analysis was conducted to test the stability of results. Furthermore, Egger's test and Begg's test were carried out to detect publication bias. All statistical analyses were performed with STATA software (version 11.2, Stata Corp, College Station, TX, USA). $p < 0.05$ was considered to be statistically significant.

Briefly, 986 related studies were yielded during the process of initial literature retrieval. After removing duplicates, scanning titles and abstracts, and subsequently reading full texts, six studies met the inclusion criteria, bringing together with a total of 1,379 patients for further analysis[2-4,6-8]. All the included patients were from China. Five of the six studies were used to calculate the SMD with 95% CI of D-dimer values. The standard deviation of one paper in survival patients was zero and thus was not included in the calculation of the SMD. The basic characteristics of the eligible studies are summarized in Table I.

As shown in Figure 1A, the D-dimer levels in non-survival patients were significantly higher than that in survival patients (SMD = 0.91, 95% CI = 0.79 to 1.03, $I^2 = 0.0\%$). We observed no significant impact of any single research on the combined SMD based on the sensitivity anal-

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Table I. Characteristics of the included studies.

Author	Location	Case	Non-survival patients				Survival patients			
			N	Age, years	Male	D-dimer	N	Age, years	Male	D-dimer
Zhou et al[4]	China	191	54	69.0 (63.0-76.0)	38 (70.4)	5.2 (1.5-21.1) µg/L	137	52.0 (45.0-58.0)	81 (59.1)	0.6 (0.3-1.0) µg/L[a]
Tang et al[6]	China	449	134	68.7 ± 11.4	90 (67.2)	4.70 (1.42-21.00) µg/mL	315	63.7 ± 12.2	178 (56.5)	1.47 (0.78-4.16) µg/mL
Luo et al[2]	China	298	84	71 (64-80)	51 (60.7)	4.59 (0.95-17.14) mg/L	214	51 (37-63)	99 (46.3)	0.50 (0.29-1.10) mg/L
Wang et al[7]	China	344	133	70 (62-77)	74 (55.6)	5.1 (1.7-31.5) µg/mL	211	57 (47-69)	105 (49.8)	0.7 (0.4-1.5) µg/mL
Wu et al[3]	China	84	44	68.5 (59.3-75.0)	29 (65.9)	3.95 (1.15-10.96) µg/mL	40	50.0 (40.3-56.8)	31 (77.5)	0.49 (0.31-1.18) µg/mL
He et al[8]	China	13	8	39 (22-54)	5 (62.5)	1.3 (0.8-2.4) mg/L	5	35 (26-37)	2 (40.0)	0.6 (0.6-0.6) mg/L

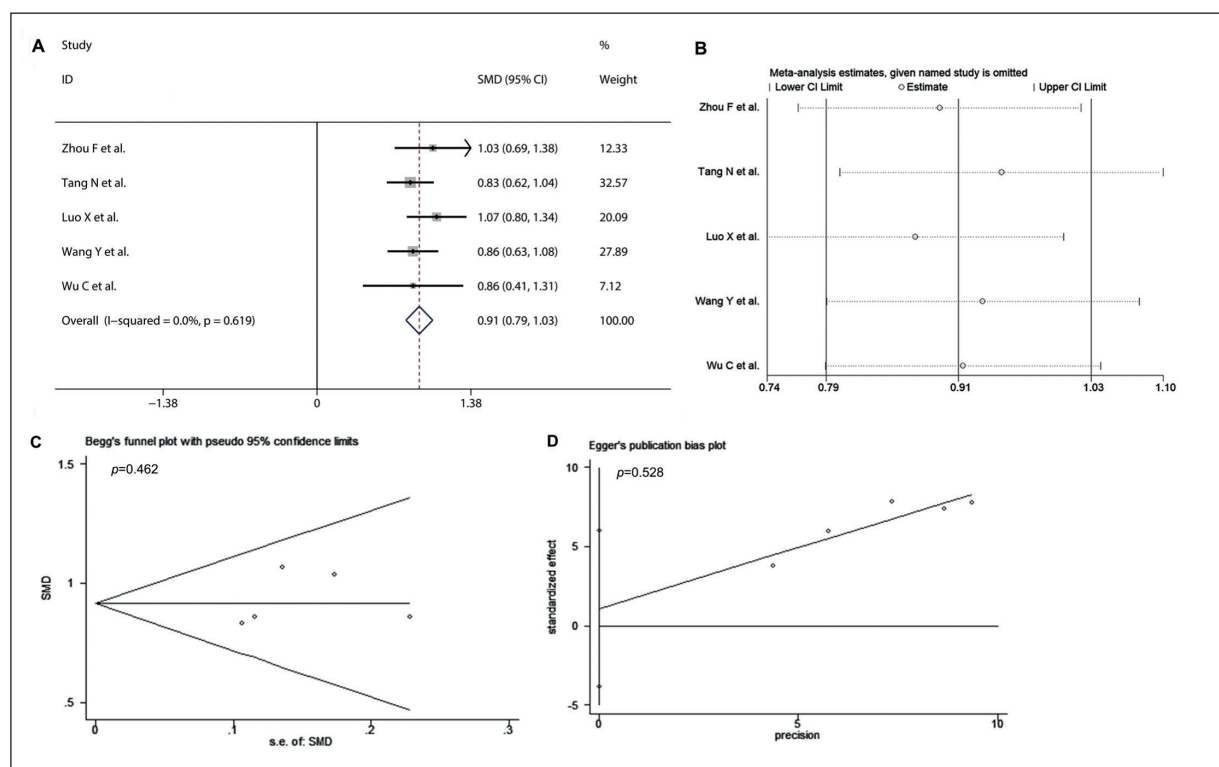All values are n (%), median (IQR), or mean ± SD. a, Data missing for 19 patients.

Figure 1. Forest plot (**A**), sensitivity analysis (**B**), Begg's funnel plot (**C**), and Egger's test (**D**) of D-dimer levels in non-survival COVID-19 patients vs. survival COVID-19 patients.

ysis. This suggests that the conclusion of this meta-analysis was stable and accurate (Figure 1B). *p*-values of Begg's tests and Egger's tests were 0.462 and 0.528, respectively, suggesting no publication bias was tested in our study (Figure 1C and 1D).

D-dimer molecule, a soluble fibrin degradation product, predicts intravascular coagulation[9,10]. Also, it is considered to be one of the most valuable indicators for diagnosing disseminated intravascular coagulation (DIC). Sepsis syndrome can be caused by viral infection[4] and elevated D-dimer levels are associated with the 28-day mortality in patients with infection or sepsis[11]. As we all know, sepsis is one of the most common causes of DIC and DIC has occurred in most of the deaths of COVID-19 patients[6]. 71.4% of non-survival COVID-19 patients fulfilled the clinical criteria for DIC during the course of disease[6,12]. Our meta-analysis indicated that COVID-19 patients with elevated D-dimer levels had a high mortality risk. To our knowledge, a previous meta-analysis has reported that elevated D-dimer levels were associated with the severity of COVID-19 patients[1]. Taken together, the levels of D-dimer

are not only considered as a predictor for the progression of COVID-19, but also for the clinical outcome.

Limitations

The limitations of this study should be acknowledged. First, all the included studies were from China. Second, the number of the included studies and the sample size were limited. Therefore, large-scale and well-designed studies are still needed to verify our findings.

Conclusions

The elevated D-dimer levels were associated with an increased risk of mortality in COVID-19 patients. Thus, clinicians should pay more attention to the alterations of this hematological marker in the clinical management for COVID-19 patients.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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