INTRODUCTION

The ongoing pandemic of COVID-19 caused by the novel coronavirus Syndrome-Coronavirus-2 (SARS-CoV-2) is an emerging, rapidly evolving situation. Coronaviruses (CoV) are enveloped viruses with a positive single-stranded RNA virus, which are widely distributed in humans and animals and cause respiratory infections in humans. Study reported that SARS-CoV-2 enters the cells through its predicated receptor angiotensin converting enzyme 2 (ACE2). Unfortunately, until now, there are no specific/targeted drugs or vaccines, and in many parts of the world, the number of SARS-CoV-2-positive patients are increasing. As of 20 April 2020, in total, 2 486 597 cases and 170 582 deaths have been confirmed around the world, suggesting that the overall death rate of COVID-19 was 6.86%. D-dimer is a specific degradation product produced by fibrin monomer cross-linking with activated factor XIII and then hydrolysed by plasmin, and is a specific marker of fibrinolysis process. Excluded typical manifestation of pneumonia and acute respiratory symptoms, COVID-19 patients also have abnormal D-dimer concentration in the serum, but the results are controversial.
study indicated that D-dimer greater than 2.0 μg/mL at admission can effectively predict the hospital mortality of COVID-19 patients, with a sensitivity of 92.3% and a specificity of 83.3%. However, Lei et al found that D-dimer levels were not significant between intensive care unit (ICU) and non-ICU COVID-19 patients (P = .99). Therefore, this meta-analysis aims to explore the possible clinical severity between D-dimer concentration and COVID-19, and analysis if infected patients with abnormal D-dimer are particularly likely to have the worst clinical prognostic risk and to evaluate the strength of the evidence.

2 | METHODS

2.1 | Search strategy

The preferred describing items for meta-analyses (PRISMA) guidelines were used. We determined to include studies involving in COVID-19 or SARS-CoV-2 or D-dimer. To find relevant primitive articles, we performed a comprehensive search in databases, involving Medline via PubMed, EMBASE and Web of Science applying the following terms: ‘COVID-19’, ‘SARS-CoV-2’, ‘Wuhan virus’, ‘Chinese virus’, ‘Novel coronavirus’, ‘Novel coronavirus 2019’, ‘2019 nCoV’, ‘Wuhan coronavirus’, ‘Wuhan pneumonia’, ‘The 2019 coronavirus’, ‘D-dimer’, ‘feature’ and ‘Characteristics’. Papers were searched in the databases up to 18 April 2020, and off restrict of language. We also reviewed reference lists based on the recognised literature to find additional eligible studied. We first screened both the titles and abstracts of the articles, and publications which may involve in data concerning COVID-19 or SARS-CoV-2 and D-dimer.

2.2 | Inclusion and exclusion standard, data extraction

Primitive studies were carefully examined, and there were no nation restrictions in our study. The inclusion standard was as follows: (a) all studies reporting data on COVID-19 and laboratory-confirmed COVID-19 patients; and (b) studies were limited to mankind, contained original data, published in English and appeared in either abstract form or full-text. The exclusion standard was as follows: (a) duplicate studies, letters, case reports, abstracts, and reviews; (b) patients that may affect the fibrinolytic system, such as severe blood diseases. We collected the following information from each study: publication year, first author’s name, sample size, age and D-dimer for both severe group and non-severe group.

2.3 | Statistical analysis

We assessed the quality of each involved research by the Newcastle-Ottawa Scale. Meta-analysis was conducted via Review Manager 5.3. We calculated the $I^2$ index to evaluate the heterogeneity. An $I^2$ value of <25%, 25%-50%, 50%-75% and 75-100% was considered as homogeneous, low, moderate and high heterogeneity level respectively. If the $I^2$ value >50%, the random effects model (REM) was applied and if the $I^2$ value was <50% the fixed effects model (FEM) was applied. The pooled weighted mean difference (WMD) of different studies and corresponding 95% confidence intervals (CIs) were used to estimate the relationship between D-dimer and COVID-19. Subgroup analysis was applied to determine the source of heterogeneity. According to the method of Hozo et al, when continuous variables not available, the mean and standard are inferred from the sample size, median and interquartile range (IQR).

3 | RESULTS

3.1 | Study processing

Overall 623 potentially relevant articles identified using our search strategy from databases and 2 from reference lists. A total of 514 studies remained after ruling out duplicates. After screening the titles and abstracts led us to rule out 466 researches that did not satisfied the inclusion criteria. After scanning the whole main body of the reserving 48 records, another 38 articles were excluded. Finally, 10 qualified articles met the eligibility criteria. The steps of document retrieval are shown in Figure 1, meanwhile, the characteristic of included studies is listed in Table 1. The meta-analysis involved overall 1430 cases (378 severe and 1052 non-severe) and all published in 2020.
The clinical severity was defined as the composite of ICU admission in three studies. Four studies defined clinical severity as the non-survivors. All articles are of high quality because of NOS score no less than 6.

### 3.2 Pooled analysis

The forest plot outcome for the connection between D-dimer and the severity of patients with COVID-19 can be found in Figure 2. Our results showed a significant relationship between D-dimer and COVID-19, with a pooled odds ratio (OR) of 1.90 (95% CI: 1.32-2.48; \( P < .001 \)). The pooled data were calculated with the REM as a high heterogeneity within the studies.

### 3.3 Subgroup analysis and sensitivity analysis

Meanwhile, our study demonstrated high heterogeneity, so we next used subgroup analysis to determine the sources of heterogeneity. We found some potential sources of heterogeneity involved in age and the number of non-severe/severe; the detailed information is shown in Table 2. Since our data are insufficient, more on the impact of age stratification should be carried out. The sensitivity analysis results showed that the WMD ranged from 1.69 (95% CI: 1.15 to 2.23) to 2.06 (95% CI: 1.51 to 2.62). The risk of publication bias was analysed by Begg's test (\( P = .19 \)) and Egger's regression test (\( P = .26 \)) indicates no significant publication bias in our meta-analysis.

### 4 DISCUSSION

Our meta-analysis suggests that patients with COVID-19 was significantly related to D-dimer concentration (OR = 1.90, 95% CI: 1.32-2.48; \( P < .001 \)). However, our study indicates that a high heterogeneity exists within the studies. Therefore, we conducted subgroup analyses to find the sources of heterogeneity. In addition, sensitivity analysis revealed that when any single study was excluded or after REM was converted into FEM, the total outcomes yet held. So, we are confident in the data obtained in our study showing that a powerful correlation exists between D-dimer and the severity of patients with COVID-19.

According to reports, among COVID-19 patients requiring hospitalisation, elevated D-dimer is one of the most common laboratory

### TABLE 1 Description of included studies

| Study, y       | Setting        | Country | Sample (severe/non-severe), n | Age (severe/non-severe), y | D-dimer (All), mg/L | D-dimer (severe/non-severe), mg/L | Female gender | NOS |
|----------------|----------------|---------|------------------------------|---------------------------|-------------------|-----------------------------------|---------------|-----|
| Zhou et al     | Isolation ward | China   | 54/135                       | 69.0 (63.0-76.0)/52.0 (45.0-58.0) | 0.8 (0.4-3.2)     | 5.2 (1.5-21.1)/0.6 (0.3-1.0)     | 11/6          | 7   |
| Wang et al     | Isolation ward | China   | 65/274                       | 76 (70-83)/68 (64-74)      | 1.20 (0.62-3.25)   | 4.38 (1.32-17.01)/1.08 (0.52-2.05) | 26/147        | 7   |
| Chen et al     | Isolation ward | China   | 113/161                      | 68.0 (62.0-77.0)/51.0 (37.0-66.0) | 1.1 (0.5-3.2)      | 4.6 (1.3-21.0)/0.6 (0.3-1.3)     | 30/73         | 8   |
| Wang et al     | ICU            | China   | 36/102                       | 66 (57-78)/51 (37-62)      | 203 (121-403)      | 414 (191-1324)/166 (101-285)     | 14/49         | 7   |
| Wan et al      | Isolation ward | China   | 40/95                        | 56 (52-73)/44 (33-49)      | 0.4(0.2-0.6)       | 0.6 (0.4-1.1)/0.3 (0.2-0.5)      | 19/43         | 7   |
| Chen et al     | Isolation ward | China   | 11/10                        | 61.0 (56.5-66.0)/52.0 (42.8-56.0) | 0.5 (0.4-1.8)      | 2.6 (0.6-18.7)/0.3 (0.3-0.4)     | 3/1           | 7   |
| Liu et al      | Isolation ward | China   | 11/67                        | 66 (51-70)/37 (32-41)      | 0.42 (0.20, 1.08)  | 0.56 (0.21-6.84)/0.39 (0.20-1.07) | 4/35          | 7   |
| Huang et al    | ICU            | China   | 13/28                        | 49.0 (41.0-60.0)/49.0 (40.1-57.5) | 0.5 (0.3-1.3)      | 2.4 (0.6-14.4)/0.5 (0.3-0.8)     | 2/9           | 8   |
| Lei et al      | ICU            | China   | 15/19                        | 55 (44-74)/47 (29-58)      | 1.8 (0.6-2.8)      | 1.9 (1.2-3.1)/1.5 (0.4-2.9)      | 10/10         | 6   |
| Du et al       | Isolation ward | China   | 21/158                       | 70.2 (7.7)/56.0 (13.5)     | 0.5 (0.3-1.7)      | 1.1 (0.4-10.5)/0.5 (0.3-1.2)      | 11/71         | 7   |

Note: Data expressed by median (IQR).
Abbreviation: ICU, intensive care unit.
test results. Chen et al.\(^{10}\) conducted a retrospective study and found the D-dimer concentration of the deceased (4.6 μg/mL) was significantly higher than that of the recovered patients (0.6 μg/mL). Similarly, Guan et al.\(^{17}\) analysed 1099 laboratory-confirmed COVID-19 patients from more than 550 hospitals in China and found that the D-dimer of non-survivors was significantly higher than that of survivors. Elevated D-dimer indicates that COVID-19 patients are in a hypercoagulable state, but the real pathophysiology is still unclear.

As we all know, SARS-CoV-2 is closely related to SARS-CoV, and they share the same receptor, ACE2, however, until now, there was no relevant study that explored about the role of ACE2 in COVID-19 patients about high D-dimer concentration. The over-activated immune response in SARS-CoV-2 infection and systemic inflammation associated with cytokine storms may lead to blood hypercoagulable. In addition, stress (such as shock, acute respiratory distress syndrome, septic) or drug toxicity might be associated with hypoxia reoxygenation, oxidative stress, imbalance of acid-base and thus contributed to very high D-dimer concentrations. Until now, no meta-analysis explored the possible connection between COVID-19 and D-dimer concentrations and may contribute to better clinical management of patients with COVID-19.

Compared with younger patients, patients aged 65 and over have higher initial comorbidities, more severe symptoms and are more prone to multiple organ involvement and death.\(^{18}\) Study suggests older people’s suspicion and detection threshold for SARS-CoV-2 should be lower, such as temperature, the decline function in cough and shortness of breath.\(^{19}\) Severe COVID-19 patients are more prone to be of older age and are risk factors for hypercoagulation or thrombosis. Management begins with the diagnosis and classification of the elderly in order to achieve an appropriate level of care becomes more important. In our age subgroup analysis results indicated that there was significant regard age > 55 subgroup. However, more researches on the impact of age stratification should be carried out.

Until now, this is the first attempt to use the meta-analysis to prove whether the severity of patients with COVID-19 related to D-dimer concentrations. At the same time, our study has limitations. First, because of the inadequate data, we do not have information such as drug use, nutritional levels, invasive treatment, underlying conditions, etc. Second, we only got the information with regard to COVID-19 patients’ age and gender, but other factor may influence the accuracy of results, such as BMI, measurement ways and instruments to detect D-dimer. Finally, the patients are who diagnosed with COVID-19 may have multiple chronic diseases simultaneously, such as cardiovascular disease, cerebrovascular disease and COPD and this may affect the accuracy of the results. Meanwhile, sample was quite not enough and more large-scale researches are needed.

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**TABLE 2** Results of subgroup analysis among included studies

| Subgroup subgroup | Studies included (N) | Sample size (study/control) | Chi square (df) | P value | Pooled overall WMD (95% CI) | Heterogeneity (I²) |
|-------------------|---------------------|-----------------------------|----------------|--------|-----------------------------|------------------|
| ICU               | 3                   | 64/149                      | 12.51 (2)      | .001   | 1.69 (0.76-2.62)            | 84               |
| Isolation ward    | 7                   | 314/903                     | 111.1 (6)      | .001   | 1.98 (1.24-2.72)            | 95               |
| Age >55           | 8                   | 350/1005                    | 112.85 (7)     | .001   | 2.05 (1.40-2.70)            | 94               |
| Age ≤55           | 2                   | 28/47                       | 0.66 (1)       | .001   | 1.24 (0.72-1.76)            | 0                |
| N <30 in non-severe| 3                   | 38/58                       | 0.77 (2)       | .001   | 1.20 (0.75-1.65)            | 0                |
| N <30 in severe   | 5                   | 70/283                      | 4.94 (4)       | .001   | 0.97 (0.64-1.30)            | 19               |
| Female >10 in non-severe | 3       | 77/176                      | 14.05 (2)      | .001   | 1.78 (0.75-2.81)            | 86               |
| Total N <100      | 4                   | 49/125                      | 4.84 (3)       | .001   | 0.95 (0.48-1.43)            | 38               |

**FIGURE 2** The forest plot outcome for the connection between D-dimer and the severe of patients with COVID-19
5 | CONCLUSION

Our meta-analysis showed that the severity of patients with COVID-19 significance related to D-dimer concentrations. Meanwhile, the severe COVID-19 patients tend to have a higher concentration of D-dimer when compared with non-severe patients.

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DISCLOSURE

There are no conflicts of interest.

AUTHORS’ CONTRIBUTIONS

YY and YZ designed and analyzed the research study; YY and W-ND wrote and revised the manuscript, R-MZ collected the data and all authors have read and approved the manuscript.

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