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META-ANALYSIS

Association of serum C-reactive protein (CRP) and D-dimer concentration on the severity of COVID-19 cases with or without diabetes: a systematic review and meta-analysis

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ABSTRACT

Introduction: Coronavirus disease (COVID-19) is a highly contagious disease that poses major public health risks. Fewer studies link high CRP and D-dimer levels to severe COVID-19 infection. Therefore, this study investigates the association of serum CRP and D-dimer concentration with COVID-19 severity in diabetic and non-diabetic patients.

Areas covered: Relevant published articles were identified using electronic search engines, such as Google Scholar, PubMed, Springer, Science Direct, and Researchgate. A total of 29 articles reporting on 15,282 patients (4,733 diabetes and 10,549 non-diabetes) were included in this systematic review and meta-analysis. RevMan V5.4, STATA V14 software, and SPSS V25 were used for the meta-analysis. Egger's regression and Begg-Mazumdar's test were used for assessing publication bias. The pooled result of all studies revealed that serum CRP (Standard mean difference (SMD) 0.41 mg/L; $P < 0.0001$; I^2 93%) and D-dimer (SMD 0.32 mg/L; $P < 0.0001$; I^2 83%) concentration was significantly higher in COVID-19 diabetic patients. The prevalence of COVID-19 infection was comparatively higher in male diabetic patients (OR 2.41; $P < 0.00001$; I^2 88%). There was no publication bias. CRP and D-dimer rose with age in COVID-19 diabetic and non-diabetic patients.

Expert opinion: Overall, the serum CRP and D-dimer concentration in COVID-19 diabetic patients was significantly higher than non-diabetic patients indicating severe illness.

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KEYWORDS
CRP; COVID-19; D-Dimer; diabetes; non-diabetes; meta-analysis

1. Introduction

The novel coronavirus pandemic is the most significant global health challenge we have faced in this century [1]. The Chinese Center for Disease Control and Prevention first isolated a new coronavirus strain, officially called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), from three patients with COVID-19, related to a cluster of acute respiratory illness cases in Wuhan, China, in December 2019 [2,3]. As of 22 May 2021, 166 M cases of COVID-19 had been confirmed Worldwide, with 3.4 M patients dying from the disease and 1489 M people were vaccinated, according to the World Health Organization (WHO) [4]. Despite the implementation of extensive lockdown and social isolation measures, these statistics continue to rise, notably in North America, Eastern Asia, and Europe [5].

For both clinicians and researchers, this prevalence was a challenge. COVID-19 infection can cause a wide variety of clinical consequences. A recent study found that cough, sore throat, sputum formation, diarrhea, nausea, vomiting, chest pain, conjunctivitis, shortness of breath was reported as more common clinical phenotypes in critical or non-survived COVID-19 patients, whereas fever and headache were less common [6,7]. Among them, fever, dyspnea, dry cough, and tiredness are reported as major symptoms of COVID-19. On the other hand, gastrointestinal symptoms, skin lesion, anosmia, headache, sore throat are considered as minor symptoms [8,9]. Age, diabetes, cardiovascular disease (CVD), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), malignancy, and stroke are considered risk factors that have been linked to severe illness and poor outcomes [10–12].

Severe disease is a clinical condition, which include diabetes, CVD, pneumonia, COPD, multi-organ failure, etc., and the patient requires immediate hospitalization, intensive care unit (ICU), invasive mechanical ventilation (IMV) and oxygen support. Inflammatory biomarkers such as CRP and D-Dimer are higher in those type of patients. There is also a high risk of mortality that can negatively affect the quality of life and daily function [13–15].

Among them, diabetes has been identified as one of the significant comorbidities linked with a poor COVID-19 prognosis that was firstly reported by Chinese researchers [16]. In addition, previous studies have found that the incidence of diabetes in intensive care unit (ICU) patients has been two to threefold greater than in less severe cases,

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and the death rate in diabetic patients has been dramatically higher [16–18]. Other comorbidities such as obesity, hypertension, chronic kidney disease, and cardiovascular disease are frequently associated with diabetes, and they have all been linked to an increased chance of COVID-19 catastrophic consequences [19–21]. The most common COVID-19 comorbidity was hypertension (16.9%), followed by diabetes (8.2%), and this study drew significant attention to comorbid COVID-19 conditions of patients [22].

Moreover, multiple-host factors influence the pathogenesis of diseases. COVID-19 critical patients had higher high-sensitive cardiac troponin, creatinine, aspartate aminotransferase (AST), procalcitonin, lactate dehydrogenase, CRP, lymphocyte count, interleukin 6 (IL-6), and D-Dimer than non-severely infected patients [6,8,12]. Of these clinical parameters, serum CRP has been identified as a critical marker that dramatically changes COVID-19 patients with severe diseases [23]. In infection and inflammation, CRP, a protein produced by the liver, is a remarkable biomarker [24]. The average level of CRP in the blood is <10 mg/L; nevertheless, it rises promptly within 6–8 hours at the initial stage and reaches its most significant peak within 48 hours after the onset of diseases [25]. In COVID-19, some researchers observed that diabetes patients also had a higher D-Dimer level than persons without diabetes [26]. Higher blood glucose levels are associated with a poorer prognosis for COVID-19. Interestingly, D-Dimer levels have been higher in patients with hyperglycemia and COVID-19 [27,28]. It is well accepted as a thromboembolism biomarker and a prognostic biomarker for severely ill patients [26]. Primarily some home remedies are used for COVID-19 patients who are not in severe condition. But for severe patients staying in hospital, therapies are developed to reduce the risk. Remdesivir was the first FDA approved drug that is being used for the treatment of COVID-19. The patients who need oxygen therapy, steroids (dexamethasone, baricitinib, tocilizumab) are used along with remdesivir. But large doses of steroids are avoided because steroids develop hyperglycemia in large doses [29].

Since only a few published studies have directly compared the clinical outcomes of diabetic or non-diabetic COVID-19 patients, and to our knowledge, no previous studies have been performed to assess the potential association between the inflammatory markers, such as CRP; coagulation indicators such as D-Dimer and COVID-19 patients with or without diabetes. Therefore, the present study aims to perform a meta-analysis of included studies to investigate the ability of laboratory biomarkers (serum CRP and D-Dimer) to predict the severe outcomes of COVID-19 diseases in diabetic and non-diabetic patients.

2. Materials and methods

2.1. Registration

The study protocol is registered to PROSPERO, and the registration number is CRD42021257841.

2.2. Literature search strategy

We performed a meta-analysis on diabetic and non-diabetic COVID-19 patients according to PRISMA guidelines [30]. Seven different search engines, such as Google Scholar, PubMed, Springer, Science direct, ResearchGate, Web of Science, and Wiley online library, were used to find relevant articles. The following keywords were applied throughout the search: 'Novel coronavirus,' 'COVID-19,' 'SARS-CoV-2,' 'coronavirus infection,' 'CRP,' 'serum C-reactive protein,' 'serum D-Dimer,' 'type-2 diabetes,' 'diabetes mellitus.' Only articles written in English were selected for this study, and the search was restricted to humans. However, the study was not limited to a single country.

2.3. Data extraction

The data extraction was done based on the inclusion and exclusion criteria. Extracted data include: a) articles containing continual data on serum CRP and D-Dimer concentration in COVID-19 patients, b) studies including diabetic patients, c) there were no geographical restriction, d) study with human sample e) articles reporting case-control studies, retrospective cohort studies and observational studies f) articles published in English g) collecting data from the original article that were published between 1 January 2020 to 20 May 2021.

The exclusion criteria were: a) insufficient information (not contain laboratory findings or CT imaging result) for data extraction b) overlapping or duplicate publication, c) review article, d) did not report serum CRP or D-Dimer concentration as mean/median, standard deviation (SD) or IQR values, e) unpublished studies.

2.4. Quality assessment

The quality assessment of detailed studies was done through Newcastle-Ottawa Scale (NOS) [31]. The NOS was described as follows: a) score 7–9 indicates that the paper is in high-quality b) score 4–6 indicates high-risk c) score 0–3 indicates the very high risk of bias. Two independent reviewers were involved in the quality assessment. Any kind of disagreements were solved by the team.

2.5. Statistical analysis, heterogeneity, and publication bias

Collected data were entered into MS Excel-2010, sorted out, and exported to Review Manager 5.4 (RevMan 5.4, the Cochrane Collaboration, Oxford, United Kingdom) software and Stata 14 (STATA Corp., College Station, TX, USA) for statistical meta-analysis. Review manager 5.4 was used to estimate the standard mean difference (SMD) in serum CRP and D-Dimer concentrations between diabetic and non-diabetic COVID-19 patients and the odds ratio (OR). The data were integrated using forest plots, and a 95% confidence interval (CI) was utilized to estimate the prediction. The Mantel-Haenszel fixed-effects or DerSimonian-Laird ran-

dom-effects models were used, depending on the sample's heterogeneity [32]. The *p-value* <0.05 indicates the statistical significance. According to Wan et al. [33], and Luo et al. [34], the median and interquartile range (IQR) were used to calculate the mean and SD. The I^2 values of 25%, 50%, and 75% indicate low, medium, and high heterogeneity. The random-effect model was performed throughout the analysis. The funnel plot, Begg-Mazumdar's rank correlation test, and Egger's regression test were done through STATA. The *P-values* >0.05 are expected to not have any publication bias [35,36]. SPSS V25 was used to analyze the Pearson correlation.

3. Results

3.1. Selection of studies

A total of 105 articles were obtained from multiple databases, such as PubMed, Google Scholar, Science Direct, Springer, ResearchGate, Wiley online library, and Web of science based on the search strategies. After the removal of 57 articles due to duplication (45 articles), language restriction (3 articles published in the Arabic language, 2 articles in Chinese), and full-text article access ineligibility (7 articles), 48 articles were selected for eligibility in the study. Then, 19 articles were excluded due to insufficient data, and review articles did not report serum CRP or D-Dimer value as mean/median, SD, or IQR values, a total of 29 studies were confirmed for CRP and 18 studies were for D-dimer. All of the papers have a NOS score of not less than 7 which indicates that all papers have maintained high quality. The searching procedure is represented in Figure 1.

3.2. Baseline characteristics

Tables 1 and 2 summarize the key aspects of the studies that were considered. A retrospective study design was adopted in most of the research, and observational and case-control studies were adopted. A total of 2855 diabetes and 6457 non-diabetes patient from 29 studies on CRP [37–64]; 1878 diabetes and 4114 non-diabetes patient from 18 studies on D-dimer [41–44,46–48,51,52,54–56,59,60,62–65] were included in our study. The majority of the experiment (n = 20) were administered in Asia (Singapore n = 1; China, n = 14; India, n = 1; Kuwait, n = 1; Qatar, n = 1; Iran, n = 1) where three studies were in North America (UK, N = 1; USA, n = 2) and six studies in Europe (Italy, n = 3; Belgium, n = 1; France, n = 2). Among the studies, the largest sample size was 1206 conducted in France [59], and the smallest sample size was 39 conducted in India [60].

3.3. Analysis of SMD of CRP in COVID-19 patients (diabetic and non-diabetic)

Figure 2 represents the SMD in CRP concentrations between diabetic and non-diabetic COVID-19 patients in selected 29 studies. The pooled result of CRP of all studies revealed that the

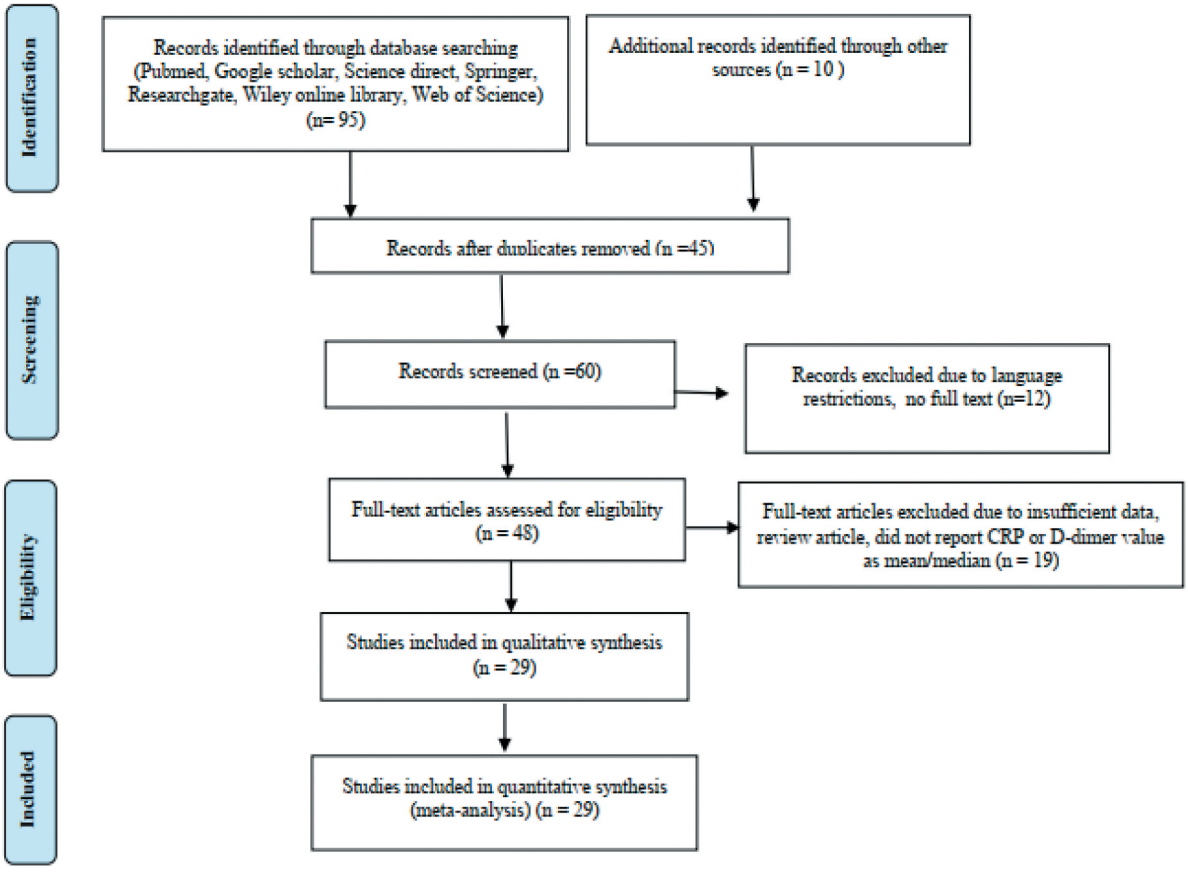

Figure 1. Flow-chart illustrating the electronic search strategy and results.

Table 1. Baseline characteristics of the COVID-19 patients with or without diabetes and CRP concentration.

References	NOS Score	Year of data collection	Location	Sample size	Study design	Diabetics/ Non-diabetics	CRP Concentration (mg/L)		*P* value
							Diabetics	Non-diabetics	
Akbariqomi et al. 2020 [37]	8	2020	Iran	595	Single-center retrospective study	148/447	27(15–59)	21(11–45)	0.01
Alguwaihes et al. 2020 [38]	8	2020	Saudi Arabia	439	Single-center retrospective study	300/139	107.9 ± 4.4	97.3 ± 7.3	NA
Al-salameh et al. 2021 [39]	7	2020	France	432	Observational cohort study	115/317	83.1(32.6–162.7)	87(35.1–152)	0.87
Alshukry et al. 2021 [40]	8	2020	Kuwait	82	Retrospective study	45/37	195.12 ± 109.55	110.75 ± 90.61	0.003
Chen et al. 2020 [41]	8	2020	China	563	Retrospective study	87/476	2.86(0.55–5.39)	0.49(0.08–2.81)	<0.001
Chen et al., 2020 [42]	8	2020	China	208	Retrospective study	96/112	3.11(2.40–20.30)	3.11(3.11–31.70)	0.469
Cheng et al. 2021 [43]	7	2020	China	407	Multicentral retrospective study	50/357	29.29(5.00–50.30)	9.71(4.20–24.50)	0.007
Ciardullo et al. 2021 [44]	8	2020	Italy	373	Single-center retrospective study	69/304	98 ± 74	104 ± 84	0.73
Conway et al. 2020 [45]	7	2020	UK	71	Single-center retrospective study	16/55	12 ± 75	45 ± 81.8	NA
Fadini et al. 2020 [46]	8	2020	Italy	413	Retrospective study	107/306	7.8(3.3–14.8)	5.5(2.2–11.4)	0.123
Fox et al. 2021 [47]	7	2020	USA	355	Single-center retrospective study	166/189	143(65–230)	125(50–192)	0.091
Guo et al. 2020 [48]	8	2020	China	174	Retrospective study	37/137	32.8(11.3–93)	16.3(7.17–43.9)	0.06
Koh et al. 2021 [49]	7	2020	Singapore	949	Retrospective cohort study	140/809	10.1(2.5–34.2)	3.3(1.1–7.7)	<0.001
Liang et al. 2020 [50]	8	2020	China	131	Retrospective study	55/76	2.9(1.4–11.9)	2(0.9–5.8)	<0.05
Liu et al. 2020 [51]	7	2020	China	192	Retrospective cohort study	64/128	39.3(2.9–72.3)	7.6(1.6–31.6)	0.006
Mirani et al. 2021 [52]	7	2020	Italy	385	Case series study	90/295	11 ± 7.5	9.4 ± 7.7	0.9
Orioli et al.2021 [53]	7	2020	Belgium	192	Monocentric retrospective study	64/128	91(49–152)	85(54–147)	0.614
Shang et al. 2020 [54]	8	2020	China	584	Retrospective cohort study	84/500	33.5(6.1–84.3)	15.45(2.0,51.7)	0.008
Shi et al. 2020 [55]	7	2020	China	306	Double-center retrospective study	153/153	23.3(5–85.2)	16.8(5–62.8)	0.178
Shrestha et al. 2021 [56]	8	2020	USA	147	Single-center retrospective cohort study	73/74	102.5(43–170.2)	100(51–139.5)	0.392
Soliman et al. 2020 [57]	8	2020	Qatar	303	Retrospective study	59/244	67.9 ± 86.89	24.60 ± 55.37	<0.05
Sun et al. 2020 [58]	7	2020	China	60	Case-control study	13/47	10.61 ± 22.96	13.65 ± 28.64	NA
Sutter et al. 2021 [59]	8	2020	France	1206	Multi-center retrospective observational study	603/603	75.7(34.0–128)	77(38.1,138)	0.629
Tomar et al. 2021 [60]	8	2020	India	39	Single-center observational study	24/15	17.5(6–30.2)	46(20–60)	0.017
Wu et al. 2020 [61]	7	2020	China	66	Retrospective study	22/44	43.31(23.93–87.77)	10.42(4.24–34.20)	0.001
Yan et al. 2020 [62]	7	2020	China	193	Single-center retrospective, Observational study	48/145	75.5(49.9–150.5)	43.3(11–116.5)	0.004
Zhang et al. 2021 [63]	8	2020	China	131	Single-center retrospective cohort study	50/81	36.48(5.77–87.72)	7.12(1.86–36.03)	0.002
Zhang et al. 2020 [65]	8	2020	China	258	Retrospective cohort study	63/195	30.75(4.53–81.72)	30.68 (5.75,67.37)	0.765
Zhou et al. 2020 [64]	7	2020	China	58	Retrospective study	14/44	7.5(2.67–11.94)	1(0.069–2.5)	0.00
Total				9,312					

NOS- Newcastle Ottawa scale (Score 7–9 = high quality; 4–6 = high risk; 0–3 = very high risk); NA: Not available
*Data were represented as Mean ± SD; Median (IQR values)

diabetic patients showed higher levels of CRP than the non-diabetic patients [SMD 0.41 mg/L, 95% CI (0.21–0.60) mg/L, *p-value* <0.0001]. The heterogeneity was significantly higher (I^2 = 93%). The funnel plots were symmetric overall , and the Egger regression test (*p-value* = 0.73) and Begg-Mazumdar's rank correlation test (*p-value* = 0.51) did not find any publication bias.

3.4. Analysis of SMD of serum D-Dimer in COVID-19 patients (diabetic and non-diabetic)

Figure-3 represents the SMD in D-Dimer concentrations between diabetic and non-diabetic COVID-19 patients in selected 18 studies. The overall result observed that, the concentration of D-Dimer level was comparatively higher on

Table 2. Baseline characteristics of the COVID-19 patients with or without diabetes and D-Dimer concentration.

References	NOS Score	Year of data collection	Location	Sample size	Study design	Diabetics/ Non-diabetics	D dimer Concentration (mg/L)		P-value
							Diabetics	Non-Diabetics	
Chen et al.2020 [36]	7	2020	China	208	Retrospective study	96/112	0.52(0.32–1.32)	0.47(0.34–1.07)	0.729
Chen et al. 2020 [37]	8	2020	China	563	Retrospective study	87/476	0.98(0.42–2.39)	0.50(0.23–1.22)	<0.001
Cheng et al.2021 [38]	7	2020	China	407	Multicentral retrospective study	50/357	0.14(0.03–0.40)	0.20(0.09–0.35)	0.61
Ciardullo et al.2021 [39]	8	2020	Italy	373	Single-center retrospective study	69/304	3.76 ± 10.60	2.37 ± 7.69	0.233
Fadini et al. 2020 [41]	8	2020	Italy	413	Retrospective study	107/306	0.28(0.169–0.58)	0.21(0.15–0.38)	0.669
Fox et al. 2021 [42]	7	2020	USA	355	Single-center retrospective study	166/189	2.035(1.06–3.49)	1.6(0.82–3.1)	0.187
Guo et al. 2020 [43]	8	2020	China	174	Retrospective study	37/137	1.15(0.83–2.11)	0.54(0.25–1.1)	<0.01
Liu et al.2020 [46]	7	2020	China	192	Retrospective cohort study	64/128	0.8(0.4–1.7)	0.7(0.3–1.5)	0.422
Mirani et al.2020 [47]	7	2020	Italy	385	Case series study	90/295	0.928 ± 1.68	1.09 ± 2.72	0.621
Shang et al.2020 [49]	8	2020	China	584	Retrospective cohort study	84/500	0.31(0.13–1.06)	0.19(0.09–0.52)	0.033
Shi et al.2020 [50]	7	2020	China	306	Retrospective	153/153	0.68(0.27–2.34)	0.57(0.27–1.54)	0.551
Shrestha et al.2021 [51]	8	2020	USA	147	Single-center retrospective cohort study	73/74	1.3(0.82–5.075)	0.914(0.445–1.98)	0.033
Sutter et al.2021 [54]	8	2020	France	1206	Multi-center retrospective observational study	603/603	0.96(0.36–1.75)	0.98(0.47–1.91)	0.314
Tomar et al.2021 [55]	8	2020	India	39	Single-center observational study	24/15	0.82(0.28–2.06)	0.81(0.37–1.98)	0.77
Yan et al. 2020 [57]	7	2020	China	193	Single-center retrospective, observational study	48/145	2.6(1–21)	1.2(0.4–10.7)	0.012
Zhang et al. 2021 [58]	8	2020	China	131	Single-center retrospective cohort study	50/81	2.57(0.83–3.88)	0.85(0.43–2.57)	0.001
Zhang et al.2020 [59]	8	2020	China	258	Retrospective cohort study	63/195	0.87(0.35–2.46)	0.54(0.25–1.51)	0.046
Zhou et al.2020 [60]	7	2020	China	58	Retrospective study	14/44	0.37(0.19–0.67)	0.21(0.10–0.43)	0.189
Total				5,992					

NOS- Newcastle Ottawa scale (Score 7–9 = high quality; 4–6 = high risk; 0–3 = very high risk); NA- Not available
*Data were represented as Mean ± SD; Median (IQR values)

diabetic patients suffering from COVID-19 [SMD 0.32 mg/L, 95% CI (0.17–0.47) mg/L, *p-value* <0.0001]. The heterogeneity was significantly higher (I^2 = 83%). The funnel plots were symmetric overall , and the Egger regression test (p = 0.41) and Begg-Mazumdar's rank correlation testFigure 3 (p = 0.59) did not find any publication bias.(Figure 4)

3.5. Effect of sex on diseases severity of diabetic patients

Among the 2327 diabetic patients, 1417 patients were male, and 910 patients were female. Meta-analysis results revealed that male patients were predominantly with higher heterogeneity (I^2 = 88%) than female patients. In addition, male patients had 2.48 times more risk of severity of illness than the female patients (OR = 2.48; 95% CI: 1.70–3.61, p < 0.00001). The funnel plots were symmetric overall (Figure-5), and Egger's regression test (p value = 0.29)(Figure 5)and Begg-Mazumdar's rank correlation test (p value = 0.34) indicate there is no publication bias.(Figure 5)

3.6. Correlation coefficient between different variables

Table 3 represents the correlation coefficient (r) between age, CRP and D-Dimer. The current study revealed that the serum CRP (r = 0.25 for diabetic and r = 0.37 for non-diabetic patients) and D-Dimer (r = 0.44 for diabetic and r = 0.30 for non-diabetic patients) concentration were positively correlated with the age of COVID-19 patients. No significant correlation was found when compared the prevalence of COVID-19 diseases based on different geographical region (Table 4).

4. Discussion

In this meta-analysis, we retrospectively evaluated clinical data from individuals with COVID-19. We identified 29 independent articles from January 2020 to May 2021, which reported the effect of coagulation indicators such as D-dimer and inflammatory biomarkers such as CRP on 15,304 persons with diabetes and non-diabetic COVID-19 patients.

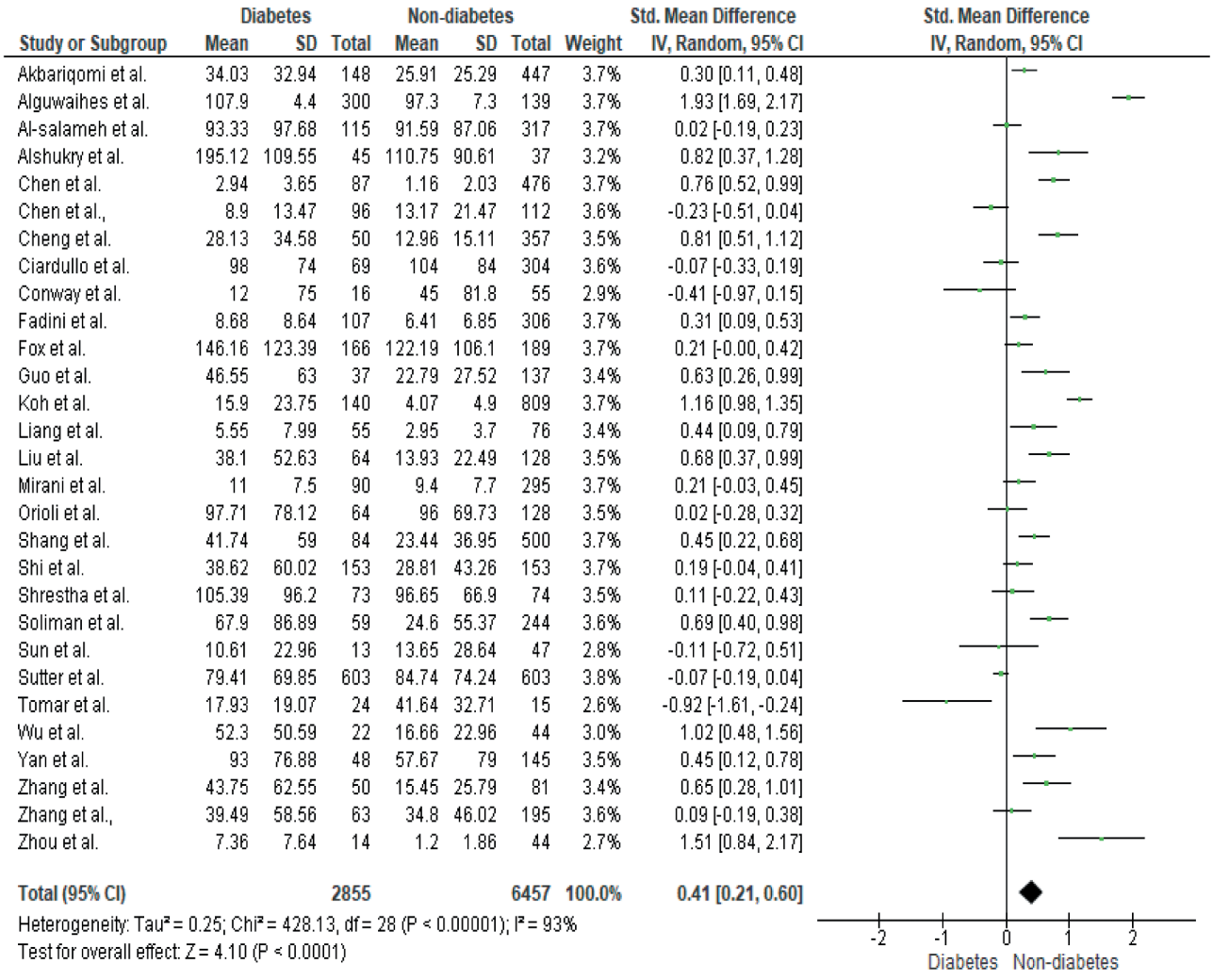

Figure 2. Forest plot illustrating CRP standardized mean differences (SMD) between two group of patients (Diabetes and Non-diabetes).

This study is the first systematic review to summarize the effect of CRP and D-Dimer on diabetic and non-diabetic COVID-19 patients. Our observation found that diabetic patients compared to non-diabetic patients had higher CRP concentration (SMD 0.41 mg/L, $P < 0.0001$, 95 CI%: 0.21–0.60). This might have happened due to inflammatory reactions and related tissue destruction. Oxygen saturation (SpO2 < 90%) is significantly decreased in these types of patients indicating that CRP levels are increased in severe lung injury patients [66]. Increased CRP were reported in 13 studies [37,38,40,43,47–49,51,54,61–64], where patients were separated into two groups: diabetic and non-diabetic. This result showed that increased CRP was highly associated with severe conditions of diabetic patients. Compared with a recent meta-analysis of six studies where 1260 severe COVID-19 patients have participated, the SMD value was partially higher, 0.73 mg/L, and 95% CI was 0.60–0.85 mg/L [67]. Furthermore, in the current meta-analysis, significantly higher heterogeneity was observed, and the I^2 value was 93% which showed similarities in some other studies. For example, Saha et al [68]. revealed that, in hospitalized diabetes mellitus (DM) patients (20.0%, 95% CI: 15.0–26.0; $I^2 = 96.8\%$), the weighted death rate was 1.822 times greater than in non-diabetic mellitus (non-DM) patients (11.0%, 95% CI: 6.0–16.0; $I^2 = 99.32\%$). The mortality rate in COVID-19 diabetic patients was higher in France, Italy, and United Kingdom (28%, 95% CI: 14.0–44.0) than in the United States (20%, 95% CI: 11.0–32.0) and Asia (17%, 95% CI: 8.0–28.0). Severe COVID-19 DM and non-DM patients exhibited 37% and 19% greater mortality rates, respectively, compared to less severe patients [69,70].

The COVID-19 ICU patients with diabetes mellitus had a greater mortality rate (26%) than non-ICU patients (19%). The death ICU patients with DM showed greater severity of COVID-19 infection (81%, 95% CI: 67.0–91.0) [68]. For this reason, DM is considered one of the major comorbidities that might influence the survival of infected patients. The severity of COVID-19 illness worsens in individuals with high glucose levels due to a strong pro-inflammatory cytokine response, weakened innate immunity, and downregulated angiotensin 2-converting enzyme (ACE-2) [71]. COVID-19 infects the lungs via binding to the ACE-2 inhibitor. Diabetes patients have a higher ACE-2 level. ACE inhibitors, statin, and GLP-1 agonists are the medications that can further increase ACE-2 levels. Increased glucose levels aid SARS-CoV-2 replication. COVID-19 severity

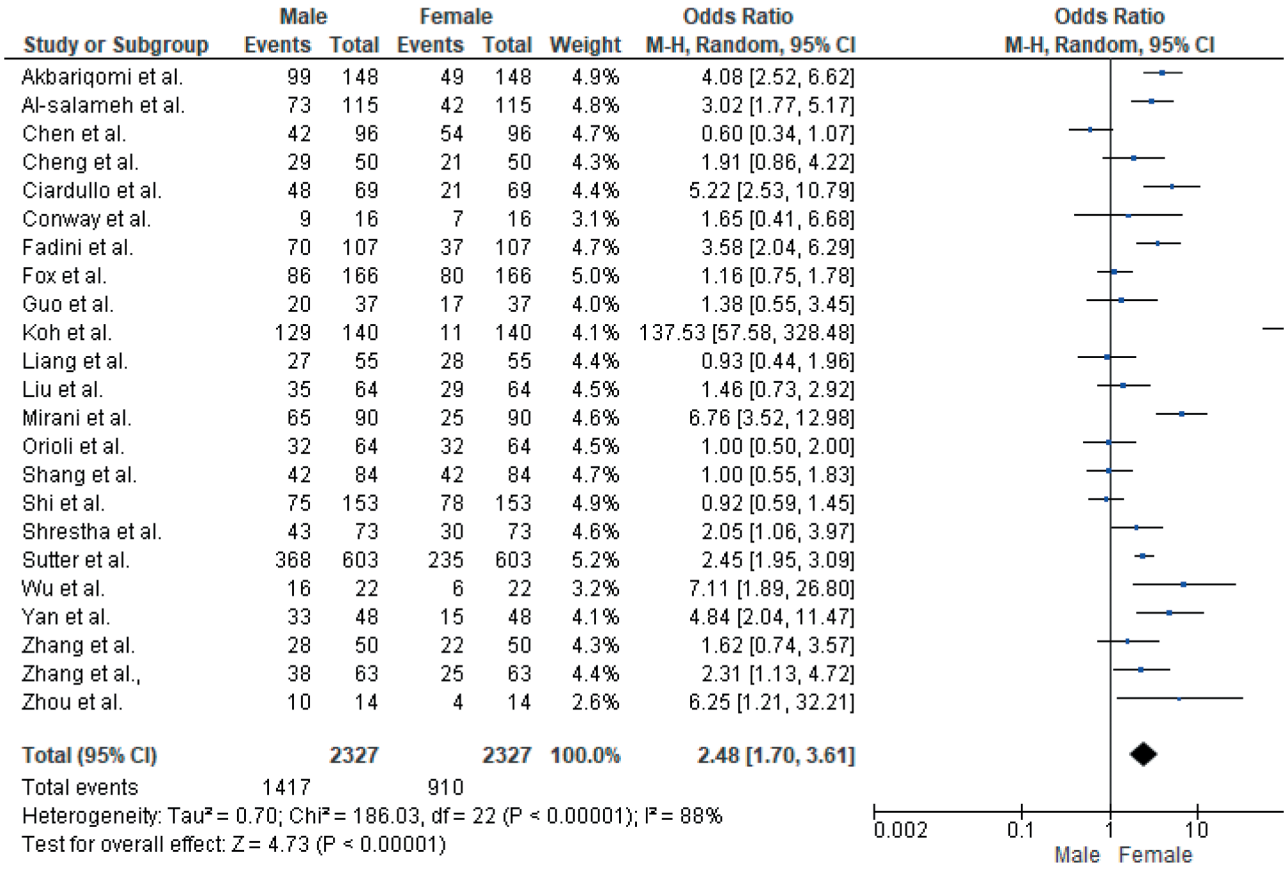

Figure 3. Forest plot representing SMD of D-Dimer between two groups of patients (Diabetes and Non-diabetes).

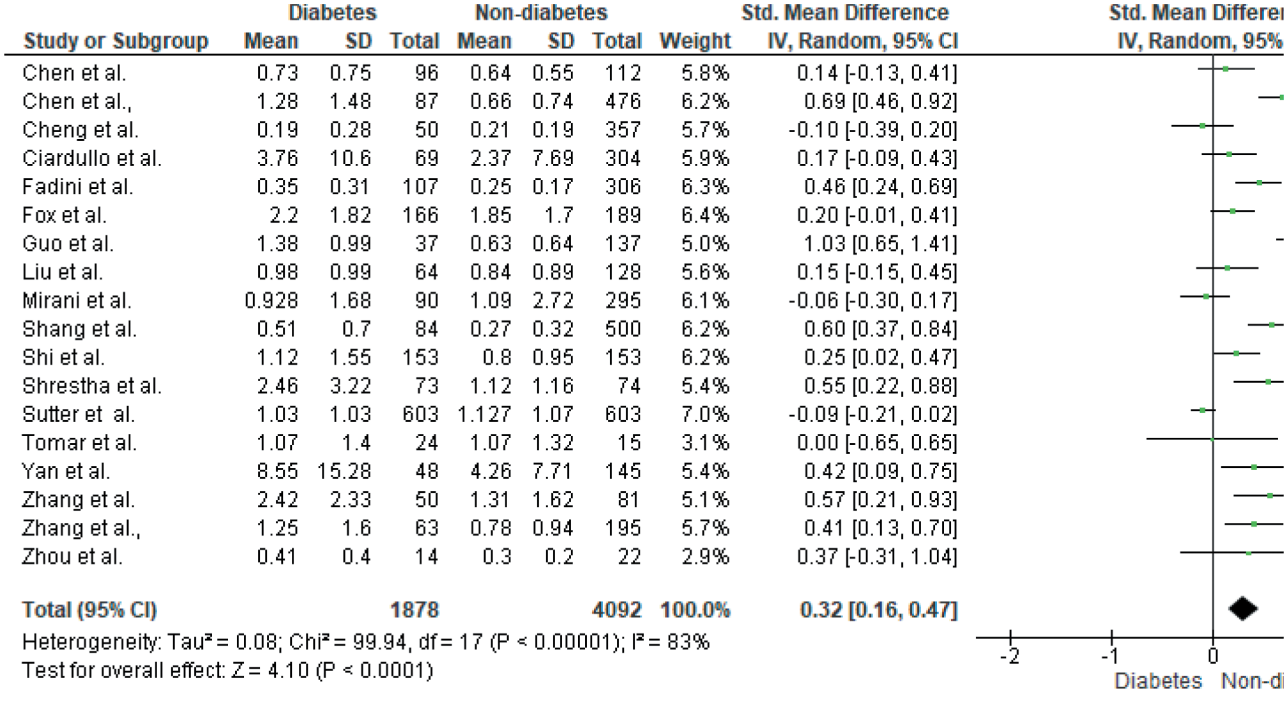

Figure 4. Forest plot compares the effect of sex on the severity of COVID-19 cases in diabetes patients.

may be increased due to increased expression of ACE-2 receptors in several tissues in diabetes [72]. ACE inhibitors and Angiotensin II Receptor blockers can decrease the level of ACE-2, and the use of those inhibitors is safe for patients [73]. Diabetes mellitus patients had a higher reduction of lymphocyte counts and increment of neutrophil counts, also

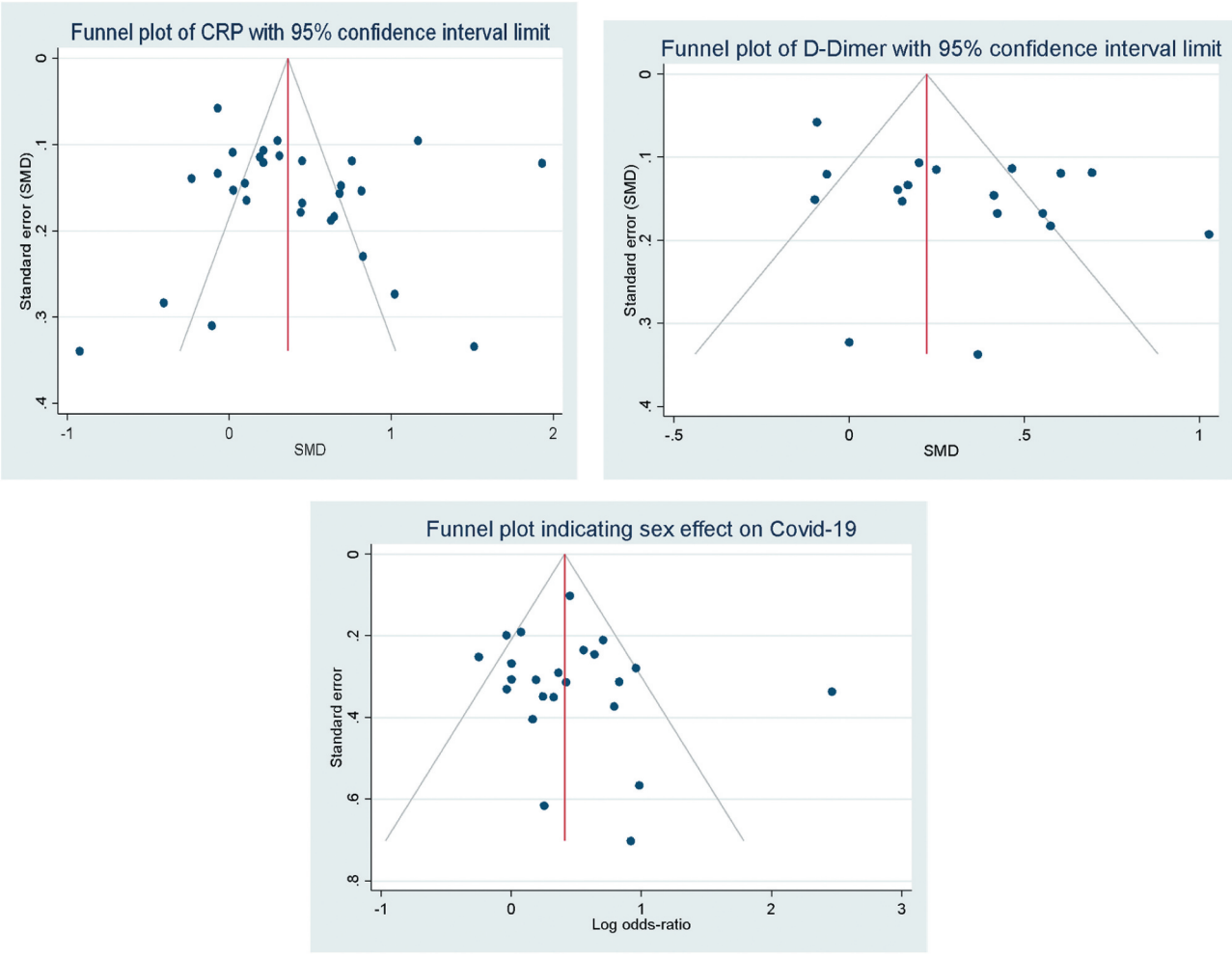

Figure 5. Funnel plots for the assessment of publication bias.

Table 3. Correlation coefficient (r) among different variables (Age, CRP, and D-Dimer).

	CRP (Diabetes)	Age (Diabetes)	CRP(Non-diabetes)	Age (Non-diabetes)
CRP (Diabetes)	1	NS	**	NS
Age (Diabetes)	.255	1	NS	**
CRP(Non-diabetes)	.895	.230	1	NS
Age (Non-diabetes)	.166	.729	.370	1
	D-Dimer (Diabetes)	Age	(Diabetes)	D-Dimer (Non-diabetes)
Age (Non-diabetes)				
D-Dimer (Diabetes)	1	NS	**	NS
Age (Diabetes)	.435	1	*	**
D-Dimer (Non-diabetes)	.966	.536	1	NS
Age (Non-diabetes)	.208	.835	.304	1

Table 4. Comparison of prevalence of diseases based on different geographical region.

Region	Diabetes	Non-diabetes
Asia	77.6 ± 67	209.3 ± 206.6
Europe	174.67 ± 210.8	325.5 ± 153.53
North America	85 ± 75.72	106 ± 72.5

Data are presented as mean ± SD; Asia (Singapore, China, India, Kuwait, Qatar, Iran); Europe (Italy, Belgium, France) and North America (UK, USA).
*Indicates the comparison between Asia group and Europe/ North America group by independent sample t-test, $p < 0.05$ is labeled as * and $p < 0.01$ is labeled as **
#Indicates the comparison between Europe and North America by independent sample t-test, $p < 0.05$ is labeled as # and $p < 0.01$ is labeled as ##

had a higher level of serum IL-6, CRP, and Lactic Dehydrogenase (LDH), and higher blood glucose levels than non-diabetic patients. Hyperglycemia hinders the management of viremia and inflammation, worsening mortality and morbidity to a wide range of patients; therefore, the link between diabetes and a poor prognosis in viral infection was unexpected [74]. Moreover, hyperglycemia is responsible for osmosis diuresis, which as a result decreases the volume of circulatory blood. This also causes fluid shift from intracellular space and causes cellular dehydration [75].

The development of COVID-19 diseases has been linked to an irregular coagulation activity with elevated D-Dimer [76,77]. In the current meta-analysis, we observed that the D-Dimer concentration in diabetic patients (SMD 0.32 mg/L; *P-value* <0.0001, 95% CI: 0.17–0.47) was notably higher than non-

diabetic patients and the heterogeneity (I^2 = 83%) was also higher. Comparing the meta-analysis which included six studies between two groups of patients (severe and non-severe), the SMD value was significantly higher, 1.07 mg/L; 95% CI was 0.73–1.42 mg/L and I^2 = 95% [78]. In another meta-analysis, a total of 13 studies was conducted on 1,807 severe and non-severe patients and observed that the D-Dimer value was significantly higher (SMD 0.91; 95% CI: 0.75–1.07 and I^2 = 46.5%) on severe COVID-19 patients [79]. A recent analysis documented that the D-Dimer level was shown to be upward in COVID-19 patients admitted to the ICU. Intense COVID-19 patients who were frequently bedfast and had irregular coagulation activity should be given special care in terms of venous thromboembolism risk [14]. In this case, D-Dimer may be a sign of serious virus infection along with thrombosis and pulmonary embolism. A virus infection can cause sepsis and coagulation problems which are also frequent in the development of severe diseases. Furthermore, the increment of D-Dimer may be considered as an indirect expression of an inflammatory response, as inflammatory cytokine may induce an imbalance in coagulation and fibrinolysis in the alveoli which can stimulate the fibrinolysis mechanism and raise D-Dimer levels [80]. In case of poor prognosis of COVID-19 patients, D-Dimer levels of >1 mg/L were considered as a risk factor [16]. Abnormal D-Dimer levels were also linked to 28-days mortality in COVID-19 patients and low molecular weight heparin treatment can benefit COVID-19 patients with higher D-dimer level (i.e. more than 3 mg/L) by lowering the mortality rate [80].

In the present study, we observed that male diabetic patients were more infected with COVID-19 diseases than the female patients (OR = 2.48; 95% CI: 1.70–3.61, $p < 0.00001$). Almost seven studies [37,39,44,46,49,52,65] reported that the COVID-19 severity was significantly higher in male diabetic patients where patients were classified into two groups: male and female. A study conducted in Bangladesh reported that males were more susceptible to COVID-19 than the female and developed severe symptoms (OR = 2.41, $p < 0.00001$) [81]. Another study that was conducted in Spain observed that males are more exposed than females because of their careless attitude concerning the potential of a COVID-19 pandemic [82]. Moreover, males are at more risk of viral infections because of differences in innate immunity, steroid hormones, and variables associated with sex chromosomes. Antibodies were detected in large concentrations in female's bloodstream and these antibodies stay longer in females than in males [83]. Pearson correlation analysis observed a positive correlation between the CRP, D-Dimer and age of COVID-19 diabetic and non-diabetic patients which showed similarities with Qu et al. [84], and Zhao et al. [85]. The author also stated that more serious conditions had a higher value of CRP and D-Dimer, as well as a longer disease-elevating time, a faster rate of increase, and a slower recovery and the inflammatory reaction was more intense as people became older. In the current study, we did not found any significant correlation between the prevalence of diseases and geographical region which is in agreement with the findings of Tini et al. [86].

5. Conclusion

We conclude that serum CRP and D-Dimer concentration that was used to diagnose the lung lesion and the existence of a prothrombotic condition was remarkably higher in COVID-19 diabetic patients. RT-PCR is the gold standard for early detection of SARS-COV-2. The severity of COVID-19 might be detected by early serum CRP and D-Dimer and provide cause for physicians to begin early initiation of treatment.

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