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RESEARCH LETTER

Markers of coagulation dysfunction and inflammation in diabetic and non-diabetic COVID-19

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Abstract

Coagulation dysfunction and inflammatory status were compared between diabetic and non-diabetic COVID-19 patients. The standardized mean difference (SMD) and its 95% confidence interval (CI) was computed for the difference of inflammatory and hypercoagulability markers. The levels of serum ferritin (standardized mean difference-SMD: 0.47, CI 0.17–0.77, p = 0.002), C-reactive protein (SMD = 0.53, CI 0.20–0.86, p = 0.002), interleukin-6 (SMD = 0.31, CI 0.09–0.52, p = 0.005), fibrinogen (SMD = 0.31, CI 0.09–0.54, p = 0.007) and D-dimers (SMD = 0.54, CI 0.16–0.91, p = 0.005) were significantly higher in diabetic COVID-19 cases as compared to non-diabetic COVID-19 patients, suggesting more susceptibility of diabetic COVID-19 patients to coagulation dysfunction and inflammatory storm.

Keywords COVID-19 · Diabetes · D-dimer · Inflammation

Highlights

- The markers of coagulation dysfunction and inflammation were studied between diabetic and non-diabetic COVID-19 patients by meta-analysis.
- COVID-19 patients with diabetes have a significantly higher levels of coagulation dysfunction markers such as Fibrinogen (SMD = 0.31, CI 0.09–0.54, p = 0.007) and D-dimers (SMD = 0.54, CI 0.16–0.91, p = 0.005) than the non-diabetic COVID-19 cases.
- COVID-19 patients with diabetes have a significantly higher inflammatory markers such as C-reactive protein (SMD = 0.53, CI 0.20–0.86, p = 0.002), Interleukin-6 (SMD = 0.31, CI 0.09–0.52, p = 0.005) than the non-diabetic COVID-19 cases.
- These results indicate that diabetic COVID-19 patients are more susceptibility to coagulation dysfunction and inlammatory storm.

Introduction

The world is struggling in lockdown for months since December of 2019 due to novel coronavirus disease (COVID-19) outbreak, a pandemic declared by the World Health Organization [1]. Research evidence is growing on the role of several symptoms, comorbidities, inflammation and hypercoagulability markers in relation to disease progression and deaths in COVID-19 patients. The incidence of diabetes, one of the leading causes of morbidity has been shown to be high and is associated with disease progression in COVID-19 [2, 3].

Diabetic patients due to low pulmonary function have been reported to be more susceptible to intensive care admissions, mechanical ventilation and deaths due to COVID-19 than those without diabetes [4, 5]. Though several studies have reported various inflammatory and coagulability markers such as serum ferritin, C-reactive protein (CRP), interleukin-6 (IL-6), fibrinogen and D-dimers in relationship to disease severity and progression, much attention has to be paid to the comparisons between diabetic and non-diabetic COVID-19 cases [6–8].

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Methods

In this pooled analysis, we aim to compare inflammatory storm and hypercoagulability status between diabetic and non-diabetic COVID-19 patients comprising a PROSPERO registered protocol (CRD42020186661). A total of 413 records were primarily identified. Of which, 39 relevant articles dealing with the inflammatory and hypercoagulation markers in COVID-19 patients were considered for full text evaluation. Out of these, 20 articles were excluded for not having relevant data, and 16 studies excluded for not comparing between diabetic and non-diabetic groups resulting in an inclusion of six observations from three studies for each of the variable between diabetic (n = 252) and non-diabetic (n = 497) COVID-19 cases [3–5]. These observations included for meta-analysis compared several markers between 252 diabetic and 497 non-diabetic cases. The study characteristics were presented in Table 1.

The standardized mean difference (SMD) with 95% confidence intervals (CI) were obtained for the difference of inflammatory and hypercoagulability markers between diabetic and non-diabetic COVID-19 cases. The between study heterogeneity was examined by the Cochrane's Q statistic and expressed as the percentages of I^2. A *p* value of < .05 was considered statistically significant. A one-study leave-out sensitivity analysis was performed to validate the results. All analyses were conducted using Review Manager Version 5.3.

Results

The forest plots of this meta-analysis were shown in Fig. 1. With a significant between-study heterogeneity ($I^2 = 64\%$, $p < 0.0001$), the random-effects model showed significantly higher levels of inflammatory and hypercoagulability markers in diabetic COVID-19 group when compared to that of non-diabetic COVID-19 group (Fig. 1). The pooled SMD and 95% CI were 0.43 (0.30; 0.55). The overall effect size for SMD calculated as Z was 6.67 ($p < 0.0001$). The sub-group analysis showed that serum ferritin (SMD: 0.47 95% CI 0.17–0.77, p = 0.002), CRP (SMD: 0.53 95% CI 0.20–0.86, p = 0.002), IL-6 (SMD: 0.31 95% CI 0.09–0.52, p = 0.005), fibrinogen (SMD: 0.31 95% CI 0.09–0.54, p = 0.007), and D-dimer (SMD: 0.54 95% CI 0.16–0.91, p = 0.005) levels are significantly elevated in diabetic patients as compared to non-diabetic counterparts with COVID-19. The sensitivity analysis showed that no single study had significantly influenced the overall result, which remained to be stable and significant after leaving-out any particular study/observation.

Discussion

These results show that the inflammatory and hypercoagulability markers significantly increase in diabetic group of COVID-19 patients when compared to their non-diabetic counterparts. Various reports suggest that diabetes activate several pathways leading to T-cell differentiation, immune system imbalance, pro- and anti-inflammation imbalance [4, 9]. Diabetes has been reported to be associated with infection and disease progression [3, 10]. According to recent research, virus invasion results in induction of coagulation activation, inflammatory responses, hypercoagulability induction and cytokine storms which may eventually cause disease progression in COVID-19 patients [2, 3].

The significant rise in ferritin, CRP and IL-6 levels reflect monocyte-macrophage activation resulting in inflammatory storm and cytokine storm. With its expression time longer than others, the cytokine IL-6 levels have been reported to be better predictors of disease progression [11]. It is known that during inflammatory storm, as a result of plasmin activation, the significant rise in D-dimer level indicates hypercoagulability [5, 7]. The significant rise in fibrinogen and D-dimer indicate diabetic COVID-19 patients are more susceptible to hypercoagulable state/intravascular coagulation. It is noteworthy that the association of diabetes and hyperglycemia with disease progression has been linked to increased inflammation, hypercoagulability and lung dysfunction in COVID-19 [3, 12].

It is well documented in several studies [6, 13, 14] that inflammatory and hypercoagulation status increase in COVID-19 cases as compared to non-COVID-19 respiratory illness. And, the presence of diabetes could further influence the magnitude of inflammatory and coagulation dysfunction in COVID-19. Strikingly, a recent study showed a significant increase in these markers in diabetic group as compared to non-diabetic group of COVID-19 patients without other comorbidities, indicating the independent impact of diabetes [3]. Moreover, the presence of diabetes has been associated with the poorer survival of COVID-19 cases with a hazard ratio (HR) of 3.17 (95% CI 1.93–5.20). And, this association remained to be significant even after adjusting for age and other comorbidities like hypertension, cardiovascular and cerebrovascular diseases (HR = 1.53, 95% CI 1.02–2.30). In a study by Zhang et al. [5], after adjusting for

Table 1 The characteristics of included studies

Characteristic	Study								
	Guo et al. [3]			Yan et al. [4]		Zhang et al. [5]			
Country	China			China		China			
Study type	Retrospective observational study			Retrospective observational study		Retrospective observational study			
Criteria	WHO interim guidance			WHO interim guidance		Chinese National Health Committee (version 7)			
RT-PCR	Yes			Yes		Yes			
Outcomes	Comparisons between diabetic and non-diabetic cases			Comparisons between diabetic and non-diabetic cases		Comparisons between diabetic and non-diabetic cases			
Overall and between group comparisons	Study								
	Guo et al. [3]			Yan et al. [4]		Zhang et al. [5]			
	Overall COVID-19	Diabetic vs. non-Diabetic	Diabetic vs. non-diabetic (No-CUD)	Overall COVID-19	Diabetic vs. non-diabetic	Overall COVID-19	Diabetic vs. non-diabetic	Diabetic vs. hyperglycemia with other comorbidities	Hyperglycemia vs. non-diabetic
Total (n)	174	37 vs. 137	24 vs. 26	193 with severe COVID	48 vs. 145	166	61 vs. 84	61 vs. 21	21 vs 84
Age	59	61 vs. 58	61 vs. 32	64	70 vs. 60	62.7	65.6 vs. 59.4	65.6 vs. 67.6	67.6 vs. 59.4
Male (n)	76	20 vs. 56	12 vs. 9	114	33 vs. 81	85	33 vs. 41	33 vs. 11	11 vs. 41
Female (n)	98	17 vs. 81	12 vs. 17	79	15 vs. 64	81	28 vs. 43	28 vs. 10	10 vs. 43
Signs and symptoms (n)									
Fever/ fatigue/ headache	136/47/12	22 vs. 114/11 vs. 36/2 vs. 10	18 vs. 22/5 vs. 9/1 vs. 3	173/101/21	43 vs. 130/28 vs. 73/5 vs. 16	139/99/53	53 vs. 70/35 vs. 49/17 vs. 27	53 vs. 46/35 vs. 15/17 vs. 9	16 vs. 70/15 vs. 49/9 vs. 27
Chill/ cough/ dizziness	119/56/23	21 vs. 98/8 vs. 48/6 vs. 17	19 vs. 20/11vs. 15/4 vs. 2	NA/135/NA	NA/37 vs. 98/NA	NA/136/NA	NA/50 vs. 71/NA	NA/50 vs. 15/NA	NA/15 vs. 71/NA
Chest pain/ chest tightness/ shortness of breath	15/45/42	1 vs. 14/5 vs. 40/5 vs. 37	0 vs. 1/2 vs. 4/5 vs. 4	10/NA/115	1 vs. 9/ NA/33 vs. 82	25/NA/115	11 vs. 10/ NA/44 vs. 55	11 vs. 4/ NA/44 vs. 16	4 vs. 10/ NA/16 vs. 55
Myalgia/ pharyngalgia/ nausea-vomiting	36/9/17	6 vs. 30/1 vs. 8/5 vs. 12	3 vs. 4/0 vs. 4/4 vs. 0	NA/NA/19	NA/NA/4 vs. 15	NA/NA/73	NA/NA/29 vs. 34	NA/NA/29 vs. 11	NA/NA/11 vs. 34
Anorexia/ diarrhoea	NA/21	NA/3 vs. 18	NA/3 vs. 4	68/51	21 vs. 47/10 vs. 41	75/77	27 vs. 38/30 vs. 37	27 vs. 10/30 vs. 10	10 vs. 38/10 vs. 37
Comorbidities (n)	NA	NA	NA	94	29 vs. 65	NA	NA	NA	NA
Hypertension/ cardiovascular disease/ malignancy	43/32/17	10 vs. 33/12 vs. 20/1 vs. 16	None	73/31/NA	24 vs. 49/13 vs. 18/NA	76/30/3	35 vs. 30/16 vs. 10/3 vs. 0	35 vs. 11/16 vs. 4/3 vs. 0	11 vs. 30/4 vs. 10/0 vs. 0

Table 1 (continued)

Overall and between group comparisons	Study								
	Guo et al. [3]			Yan et al. [4]		Zhang et al. [5]			
	Overall COVID-19	Diabetic vs. non-Diabetic	Diabetic vs. non-diabetic (No-CUD)	Overall COVID-19	Diabetic vs. non-diabetic	Overall COVID-19	Diabetic vs. non-diabetic	Diabetic vs. hyperglycemia with other comorbidities	Hyperglycemia vs. non-diabetic
Pulmonary disease/ kidney disease/ liver disease	14/13/8	2 vs. 12/1 vs. 12/0 vs. 8	None	14/4/1	4 vs. 10/0 vs. 4/0 vs. 1	19/9/NA	9 vs. 9/3 vs. 6/NA	9 vs. 1/3 vs. 0/NA	1 vs. 9/0 vs. 6/NA
Immune deficiency/ Hepatitis B/ cerebrovascular disease	4/2/13	0 vs. 4/0 vs. 2/1 vs. 12	None	NA/NA/8	NA/NA/5 vs. 3	NA/NA/12	NA/NA/6 vs. 3	NA/NA/6 vs. 3	NA/NA/3 vs. 3
Thyroid disease/ digestive system disorders/ others	NA/NA/NA	NA/NA/NA	NA/NA/NA	NA/NA/NA	NA/NA/NA	3/5/91	1 vs. 2/2 vs. 2/37 vs. 43	1 vs. 0/2 vs. 1/37 vs. 11	0 vs. 2/1 vs. 2/11 vs. 43
Mortalities (n)	9	4 vs. 5	4 vs. 0	108	39 vs. 69	24	13 vs. 8	13 vs. 3	3 vs. 8

NA not available, *No-CUD* no other comorbidities

confounders like; age, sex, BMI and other comorbidities, a significantly higher rate of composite outcomes (ICU admission/mechanical ventilation/deaths) in both hyperglycemia (odds ratio-OR = 5.47, 95% CI 1.51–19.82) and diabetic groups (OR = 2.61, 95% CI 0.86–7.88) than the non-diabetic COVID-19 group were reported.

Our pooled analysis shows that diabetic COVID-19 patients are more susceptible to coagulation dysfunction and inflammation than the non-diabetic COVID-19 cases. The sensitivity analysis indicated the robustness of overall result. Though, the included studies matched the diabetic and non-diabetic groups for overall comorbidities [4] and all comorbidities except for CVD [3] and hypertension [5], the results should be interpreted with a caution that diabetes may coexist with other conditions in COVID-19 patients. Therefore, further well controlled studies are needed in future to establish an independent role of diabetes in COVID-19.

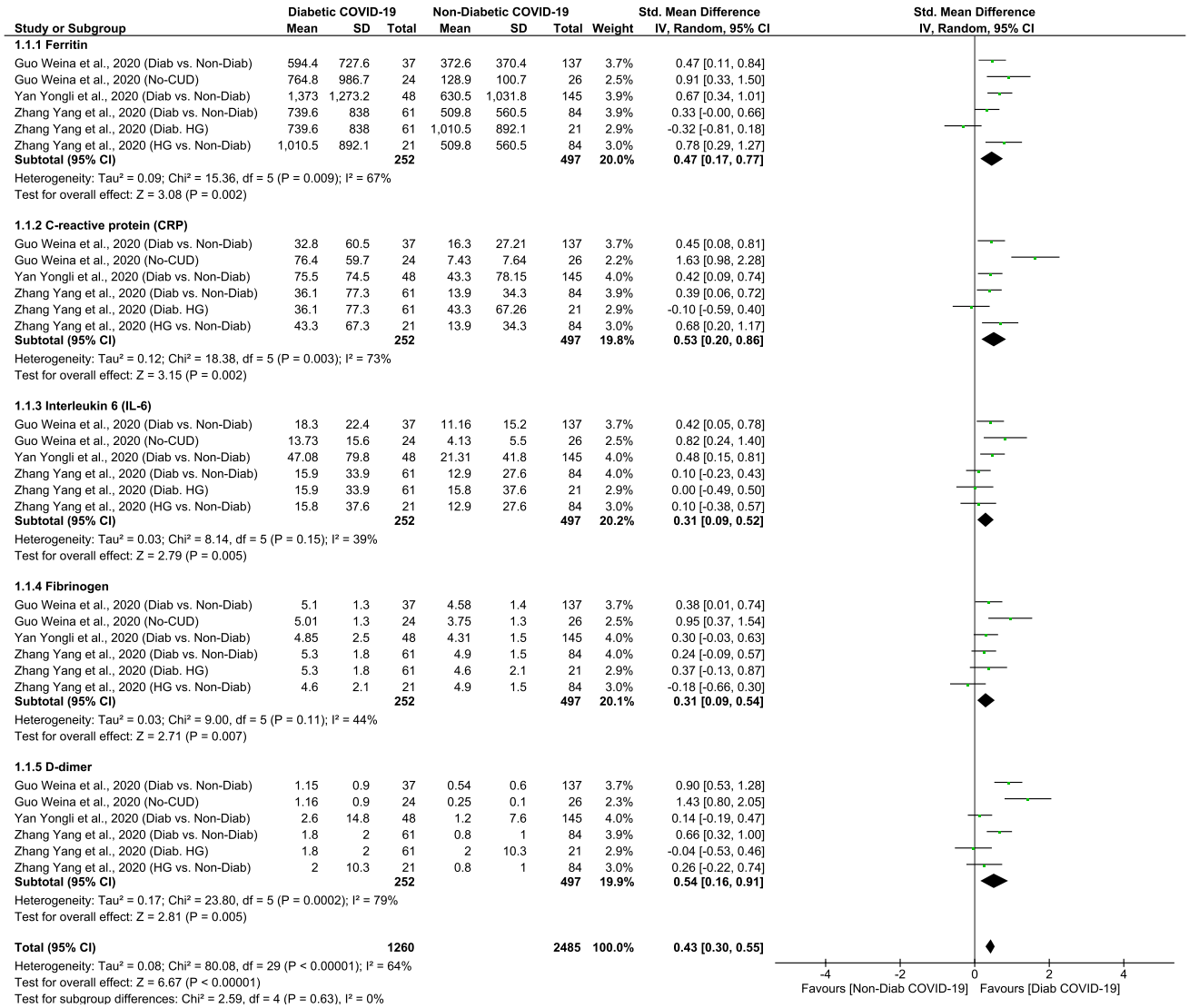

Fig. 1 The forest plots comparing hypercoagulability and inflammatory status between diabetic and non-diabetic COVID-19 cases

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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