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 inflammatory 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].
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 infection 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**                     |                                     | No             | 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**        |       | 37 vs. 137     | 24 vs. 26     | 193 with severe COVID |
| **Diabetic vs. non-diabetic (No-CUD)**|       |                |               |                 |
| **Overall COVID-19**                |       |                |               |                 |
| **Diabetic vs. non-diabetic**        |       | 48 vs. 145     |               |                 |
| **Overall COVID-19**                |       |                | 61 vs. 84     | 61 vs. 21       |
| **Diabetic vs. non-diabetic**        |       |                | 21 vs 84      |                 |
| **Hyperglycaemia vs. non-diabetic**  |       |                |               |                 |

| **Total (n)**                      |       | 174            | 37 vs. 137     | 24 vs. 26       |
| **Male (n)**                       |       | 76             | 20 vs. 56      | 12 vs. 9        |
| **Female (n)**                     |       | 98             | 17 vs. 81      | 12 vs. 17       |
| **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 |
| **Chill/cough/dizziness**          |       | 119/56/23      | 21 vs. 98/8 vs. 48/6 vs. 17 | 19 vs. NA/135/NA vs. 98/NA |
| **Chest pain/cough/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 |
| **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 |
| **Anorexia/diarrhoea**             |       | NA/21          | NA/3 vs. 18    | NA/3 vs. 4      |
| **Comorbidities (n)**              |       | NA             | NA            | 94              |
| **Hypertension/cardiovascular disease/malignancy** | | 43/32/17 | 10 vs. 33/12 vs. 20/1 vs. 16 | None |

| **Fever/fatigue/headache**         |       | 173/101/21     | 43 vs. 130/28 vs. 73/5 vs. 16 | 139/99/53 |
| **Chill/cough/dizziness**          |       | NA/135/NA      | NA/37 vs. 98/NA | NA/136/NA |
| **Chest pain/cough/tightness/shortness of breath** | | 10/NA/115 | 1 vs. 9/NA/33 vs. 82 | 10/NA/115 |
| **Myalgia/pharyngalgia/nausea-vomiting** | | NA/NA/19 | NA/NA/4 vs. 15 | NA/NA/73 |
| **Anorexia/diarrhoea**             |       | 68/51          | 21 vs. 47/10 vs. 41 | 75/77 |
| **Comorbidities (n)**              |       | 94             | 29 vs. 65      | NA              |
| **Hypertension/cardiovascular disease/malignancy** | | 73/31/NA | 24 vs. 49/13 vs. 18/NA | 76/30/3 |
| **Anorexia/diarrhoea**             |       | NA/29 vs. 34   | NA/11 vs. 17   | NA/NA/94       |
| **Comorbidities (n)**              |       | NA             | NA            | NA              |
| **Hypertension/cardiovascular disease/malignancy** | | 35 vs. 30/16 vs. 10/3 vs. 0 | 35 vs. 11/16 vs. 4/3 vs. 0 | 35 vs. 10/3 vs. 0 |
| **Total (n)**                      |       | 166            | 61 vs. 84      | 61 vs. 21       |
| **Male (n)**                       |       | 73             | 24 vs. 47      | 11 vs. 11       |
| **Female (n)**                     |       | 93             | 12 vs. 32      | 11 vs. 10       |
| **Signs and symptoms (n)**         |       | 10/NA/115      | 1 vs. 9/NA/33 vs. 82 | 10/NA/16 vs. 55 |
| **Fever/fatigue/headache**         |       | 173/101/21     | 43 vs. 130/28 vs. 73/5 vs. 16 | 139/99/53 |
| **Chill/cough/dizziness**          |       | NA/135/NA      | NA/37 vs. 98/NA | NA/136/NA |
| **Chest pain/cough/tightness/shortness of breath** | | 10/NA/115 | 1 vs. 9/NA/33 vs. 82 | 10/NA/16 vs. 55 |
| **Myalgia/pharyngalgia/nausea-vomiting** | | NA/NA/19 | NA/NA/4 vs. 15 | NA/NA/73 |
| **Anorexia/diarrhoea**             |       | 68/51          | 21 vs. 47/10 vs. 41 | 75/77 |
| **Comorbidities (n)**              |       | 94             | 29 vs. 65      | NA              |
| **Hypertension/cardiovascular disease/malignancy** | | 73/31/NA | 24 vs. 49/13 vs. 18/NA | 76/30/3 |
| **Anorexia/diarrhoea**             |       | NA/29 vs. 34   | NA/11 vs. 17   | NA/NA/94       |
| **Comorbidities (n)**              |       | NA             | NA            | NA              |
| **Hypertension/cardiovascular disease/malignancy** | | 35 vs. 30/16 vs. 10/3 vs. 0 | 35 vs. 11/16 vs. 4/3 vs. 0 | 35 vs. 10/3 vs. 0 |
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.

Table 1 (continued)

| Overall and between group comparisons | Study 1 | Study 2 | Study 3 | Study 4 |
|--------------------------------------|---------|---------|---------|---------|
| Overall COVID-19                     | Diabetic vs. non-Diabetic | Diabetic vs. non-diabetic (No-CUD) | Diabetic vs. non-diabetic | Diabetic vs. non-diabetic |
| Pulmonary disease/ kidney disease/ liver disease | Guo et al. [3] | 14/13/8 2 vs. 12/1 vs. 8 | 14/4/1 4 vs. 10/0 vs. 4/0 vs. 1 | 19/9/NA 9 vs. 9/3 vs. 6/NA |
| Immune deficiency/ Hepatitis B/ cerebrovascular disease | Yan et al. [4] | 4/2/13 0 vs. 4/0 vs. 2/1 vs. 12 | NA/NA/8 NA/NA/5 vs. 3 | NA/NA/12 NA/NA/6 vs. 3 |
| Thyroid disease/ digestive system disorders/ others | Zhang et al. [5] | 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 | NA/NA/NA 1 vs. 2/2 vs. 1/37 vs. 11 |
| Mortalities (n)                      | NA/NA/NA NA/NA/NA NA/NA/NA NA/NA/NA | 108 39 vs. 69 | 24 13 vs. 8 | 13 vs. 3 3 vs. 8 |

NA not available, No-CUD no other comorbidities
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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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