Immune-inflammatory biomarkers and the risk of cardiac injury in COVID-19 patients with diabetes: a retrospective cohort study

Yi Bo, Cai Yuli, Wang Ye, Li Junfeng, Chen Xiaolin, Bao Yan* and Wen Zhongyuan*

Abstract

Background: To determine the risk-assessment role of the immune-inflammatory biomarkers on myocardial damage in COVID-19 patients with diabetes mellitus (DM).

Methods: This retrospective study was conducted on 822 COVID-19 inpatients from 1 January to 10 March 2020 at Renmin Hospital of Wuhan University. The demographic data, clinical data, and immune-inflammatory parameters of participants were collected. The predictors of cardiac injury were assessed by Logistics regression analysis.

Results: A total of 246 COVID-19 inpatients were diagnosed with DM (29.9%). The incidence of cardiac injury was higher in patients with DM than in non-DM cases (28.9% vs 9.0%, p < 0.001), even grouped by age, gender, and the level of fasting plasma glucose (FPG). The mortality in diabetic COVID-19 patients with cardiac injury and without cardiac injury was 42.9% and 3.4%, respectively (p < 0.001). COVID-19 patients with DM and cardiac injury presented a decreased number of immunocyte subsets, lower C3 concentration, and a higher level of interleukin-6 (IL-6) and immunoglobulin A (IgA). The independent risk factors for cardiac injury in COVID-19 patients with DM were CD3+CD4+ T cells counts ≤ 288 cells/μl (adjusted Odds ratio (OR), 2.501; 95% confidence interval (CI) 1.282–4.877; p = 0.007) and IL-6 > 25.68mpg/ml (adjusted OR, 4.345; 95% CI 2.192–10.374; p < 0.001) (all Pinteraction < 0.05).

Conclusions: For diabetic patients with COVID-19, cardiac injury not only induce severer immune-inflammatory responses, but also increase in-hospital mortality. The decreased number of CD3+CD4+ T cells and increased IL-6 are recommended to distinguish the people who refer to high risk of cardiac injury and mortality from those persons. However, it remains a testable theory whether decision-making strategies based on the risk status of cardiac injury in COVID-19 patients, especially with DM, would be expected to get better outcomes.

Keywords: Cardiac injury, COVID-19, Diabetes mellitus, Immune-inflammatory biomarkers, Mortality

Background

The Coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a persistent serious challenge for global public health, even the use of coronavirus vaccines [1]. Our previous study found that diabetes mellitus (DM) confer approximately 20% of in-hospital mortality of COVID-19 patients [2]. Similar findings were also reported in England, Italy, France, and America [3–6]. Notably, among COVID-19 patients, the prevalence of cardiac injury in DM is nearly twice as high as people in non-DM [7, 8]. Importantly, higher cardiac
troponin T (cTnT) levels, the biomarker of cardiac injury, were robustly associated with the severity and mortality of COVID-19 patients[5, 9–11] and adults with DM [12]. Thus, for guiding the effective clinical management of COVID-19 with DM, it is an urgent need to identify high-risk subgroups with elevated cardiac injury risk.

Dysregulation of the immune-inflammatory responses was the prominent characteristic of both COVID-19 patients with DM and with cardiac injury [2, 13–15]. These persons all present lymphopenia, T cell exhaustion, and elevated level of inflammatory factors, such as interleukin-6 (IL-6) [7, 14]. These changes have a dramatic relevance to the severity and mortality of COVID-19 [7, 14]. Inflammatory markers and lymphocytic infiltrates are also markedly elevated in the heart of deceased patients from cardiac pathological data [16, 17]. Notably, diabetes facilitates SARS-CoV-2 viral entry into the heart via the overexpression of cellular angiotensin-converting enzyme 2 (ACE2) and Transmembrane serine protease 2 (TMPRSS2) [18, 19]. Thus, immune-inflammatory responses may be a “bridge” between DM and myocardial injury in COVID-19. However, only one study of 124 COVID-19 patients reported that minimal lymphocyte percentage <7.8% was an independent risk factor for cardiac injury [15]. Moreover, this study based on small sample sizes was not specifically designed for diabetic COVID-19 patients.

Herein, this retrospective study of 822 COVID-19 patients was conducted to comprehensively clarify the potential risk-assessment role of the immune-inflammatory reaction on cardiac injury in DM during hospitalization.

**Methods**

**Study design**

This retrospective study was conducted at Renmin Hospital of Wuhan University. All consecutive patients reviewed from 1 January to 10 March 2020 were regularly followed up to 26 April 2020, the day of the discharge of the last cases in Wuhan. Only confirmed COVID-19 patients were enrolled in the survey. The exclusion criteria included suspected cases, neonates, pregnancy, duplicated cases, and cases lack of cardiac biomarkers.

**Definitions**

According to the 7th edition guideline published by the China National Health Commission (http://kjfy.meetngchina.org/msite/news/show/cn/3337.html), confirmed COVID-19 case was identified as positive for SARS-COV-2 after real-time reverse-transcriptase polymerase chain reaction (RT-PCR) test, high-throughput sequencing, and/or COVID-19 specific immunoglobulin M (IgM) and IgG antibodies examination. Cardiac injury was defined as the maximum level of cTnT >99th percentile upper reference limit (URL) (0.04 ng/ml) after hospitalization, regardless of the new manifestations in echocardiography or electrocardiogram, based on previous clinical studies [9, 10, 13, 20]. DM was the person with a history of DM, and/or the use of antidiabetic therapies, and/or the presence of at least two abnormal blood glucose (fasting glucose ≥7.0 mmol/l and/or random glucose ≥11.1 mmol/l and/or hemoglobin A1c ≥6.5%). Coagulopathy was described as the score for sepsis-induced coagulopathy >4.

**Data collection**

We collected age, gender, initial symptoms, laboratory findings, history of comorbidities, treatments, records of chest computed tomographic (CT) scans, and clinical outcomes from the electronic medical records system by two independent investigators (Cai Yuli and Wang Ye).

The detection procedure of COVID-19 by PCR depended on sputum and throat swab samples was described in our previous study [2]. cTnT was evaluated by kit from Siemens based on the chemiluminescence immunonotechnolgy. BD FACSCanto II Flow Cytometer was used to assess the proportions and numbers of total CD3+ T cells, CD3+CD4+ T cells, CD3+CD8+ T cells, CD16+CD56+ Natural Killer cells (NK cells), and CD19+ B cells subsets (BD Multitest). Serum levels of IgG, IgM, IgA, IgE, and complements component (C3, C4) were detected by rate nephelometry immunoassay (N Antiserum to Human Ig Kit series, Siemens, Germany). Cytometric Bead Array with the human helper T cells 1/2 cytokine kit II (BD Ltd., USA) was used to test the plasma levels of cytokines, including interleukin-2 (IL-2), IL-4, IL-5, IL-6, IL-10, tumor necrosis factor-α (TNF-α), and y-interferon. All tests were conducted according to the manufacturer’s instructions in routine clinical practices during the COVID-19 pandemic in our hospital.

**Statistical analyses**

Categorical data and continuous data were presented as proportions (%) and median (interquartile range [IQR]) values, respectively. For continuous variables, we used the t-test or Mann–Whitney U test to compare the differences between COVID-19 patients with and without DM; otherwise, the one-way ANOVA or Kruskal–Wallis H-test was used depending on parametric or nonparametric data. Categorical variables were compared by the χ² test or Fisher’s exact test. Survival curves were plotted using the Kaplan–Meier method, while the linear correlation was calculated by spearman’s correlation test. The cutoff value of immune-related biomarkers to differentiate between survivors and deceased were performed by the receiver operating characteristic curve (ROC).
also used Logistics regression analysis to determine the risk factors of cardiac injury and the interaction between DM and immune-related indicators.

All data were analyzed by SPSS Software V19.0 (IBM Corp.). Statistical charts were constructed using Prism 5 (GraphPad), Minitab Statistical Software V19 (Minitab LLC.), and MedCalc statistical software version 20.011 (MedCalc Software Ltd). A two-tailed \( p \)-value \(< 0.05\) was considered statistically significant.

**Results**

A total of 1341 cases were screened initially from 1 January to 10 March 2020 in the study (Fig. 1). After excluding 310 suspected patients with COVID-19, 52 duplicated cases, 16 neonates, 29 women with pregnancy, and 112 persons without available core medical information, there are 822 cases with confirmed COVID-19 were enrolled in the final analysis. Of these, 246 patients (29.93%) were diagnosed with DM. The characteristics of 112 patients without core medical information were shown in Additional file 1: Table S1.

**Baseline features of COVID-19 patients with and without DM**

As shown in Table 1, when compared to patients without DM, diabetic cases were older (median age was 67 years vs 60.5 years, \( p < 0.001\)), more underlying coexisting comorbidities, especially hypertension (34.2% vs 13.9%, \( p < 0.001\)) and coronary heart disease (CHD) (11.8% vs 7.5%, \( p = 0.045\)), and the less manifestation of ground-glass opacity (67.7% vs 76.5%, \( p = 0.016\)). The initial symptoms were similar between the two groups except for sore throat or throat discomfort (6.1% in no-DM patients and 2.0% in DM, \( p = 0.014\)). The mean days from illness onset to hospitalization were both 10 days in DM and non-DM patients (\( p = 0.505\)).

Regarding the laboratory findings, DM patients had a relatively higher median level of creatinine, fasting plasma glucose (FPG), and D-dimer, but less \( SPO_2 \) and albumin (all \( p < 0.05\) (Table 1). For blood lipids profile, compared with non-DM individuals, patients with DM shown the higher median (IQR) value of triglyceride (1.3 (1.0–1.7) mmol/l vs 1.2 (0.9–1.6) mmol/l, \( p = 0.001\)) and lower high-density lipoprotein (HDL-c) (0.9 (0.7–1.0) mmol/l vs 0.9 (0.8–1.1) mmol/l, \( p < 0.001\)), but with similar concentration of low-density lipoprotein (LDL-c) (Table 1). The incidence of severe complications in COVID-19 patients with and without DM was also shown in Additional file 1: Fig. S1.

Among diabetic patients, people with cardiac injury were older (median age, 74 years vs 64 years, \( p < 0.001\)) than individuals without cardiac injury. These people also required more treatment with antibiotic agents, glucocorticoids, and invasive mechanical ventilation (all
| Characteristics                  | Without DM |                                      |                                      | With DM |                                      |                                      | p value | A vs. B |
|---------------------------------|------------|---------------------------------------|---------------------------------------|---------|---------------------------------------|---------------------------------------|---------|---------|
|                                 | All (A)    | non–cardiac injury                    | cardiac injury                        | All (B) | non–cardiac injury                    | cardiac injury                        |         |         |
|                                 | n (%)      |                                       |                                       |         |                                       |                                       |         |         |
| Gender, n (%)                   |            |                                       |                                       |         |                                       |                                       |         |         |
| Female                          | 288 (50.0) | 271 (51.7)                            | 17 (32.7)                             | 115 (46.8) | 86 (49.1)                            | 29 (40.9)                            | 0.237   | 0.393   |
| Male                            | 288 (50.0) | 253 (48.3)                            | 35 (67.3)                             | 131 (53.3) | 89 (50.9)                            | 42 (59.2)                            | –       | –       |
| Age (IQR)                       | 60.5 (49.0–69.0) | 59.0 (47.3–67.0) | 76.5 (68.0–83.0) | <0.001 | 67.0 (57.0–74.0) | 64.0 (57.0–71.0) | <0.001 | <0.001 |
| Time from onset to hospital admission (IQR), days | 10.0 (7.0–14.0) | 10.0 (7.0–14.0) | 10.0 (6.3–14.0) | 0.117 | 10.0 (7.0–15.0) | 10.0 (7.0–15.0) | 10.0 (7.0–15.0) | 0.797   | 0.505   |
| SPO2 (%)                        | 97.0 (93.0–99.0) | 97.0 (94.0–99.0) | 93.5 (81.8–98.0) | 0.008 | 96.0 (91.0–98.0) | 97.0 (93.0–99.0) | 93.0 (85.0–97.0) | <0.001 | 0.022   |
| RR (beats per minute)           | 20.0 (18.0–21.0) | 20.0 (18.0–21.0) | 20.0 (19.0–24.6) | 0.068 | 20.0 (19.0–23.0) | 20.1 (19.0–21.0) | 21.0 (18.0–26.0) | 0.485   | 0.027   |
| Pulse rate (beats per minute)   | 85 (78–97) | 85 (78–97)                            | 88 (78–102)                           | 0.875 | 87 (79–101)                           | 86 (79–100)                           | 89 (78–102.5) | 0.054   | 0.326   |
| SBP (mmHg)                      | 125 (115–136) | 125 (115–135) | 130.5 (112.5–150) | 0.137 | 130 (118.25–143) | 129 (119–141) | 129 (116–150) | 0.858   | 0.001   |
| DBP (mmHg)                      | 76 (68–82.5) | 76 (68–82)                            | 75 (66–87.8)                          | 0.293 | 77 (70–84)                            | 77 (70–84)                            | 76 (68–87) | 0.839   | 0.047   |
| Symptoms, n (%)                 |            |                                       |                                       |         |                                       |                                       |         |         |
| Asymptomatic                    | 14 (2.4)   | 11 (2.0)                              | 3 (5.8)                               | 0.06   | 10 (4.1)                              | 6 (3.4)                               | 4 (5.6) | 0.48    | 0.202   |
| Fever                           | 460 (79.9) | 425 (81.1)                            | 35 (67.3)                             | 0.018  | 207 (84.2)                            | 149 (85.1)                            | 58 (81.7) | 0.502   | 0.15    |
| Dry cough                       | 361 (62.7) | 331 (63.2)                            | 30 (57.7)                             | 0.436  | 139 (56.5)                            | 103 (58.9)                            | 36 (50.7) | 0.178   | 0.097   |
| Sputum production               | 137 (23.8) | 122 (23.3)                            | 15 (28.9)                             | 0.369  | 45 (18.3)                             | 29 (16.6)                             | 16 (22.5) | 0.273   | 0.082   |
| Fatigue                         | 196 (34.4) | 179 (34.2)                            | 17 (32.7)                             | 0.832  | 77 (31.3)                             | 57 (32.6)                             | 20 (28.2) | 0.5     | 0.447   |
| Myalgia                         | 50 (8.7)   | 47 (9.0)                              | 3 (5.8)                               | 0.434  | 16 (6.5)                              | 12 (6.9)                              | 4 (5.6)  | 1       | 0.293   |
| Dyspnoea/pant                   | 212 (36.8) | 191 (36.5)                            | 21 (40.4)                             | 0.575  | 80 (32.5)                             | 60 (34.3)                             | 20 (28.2) | 0.353   | 0.24    |
| Vomiting/diarrhea/nausea        | 25 (4.3)   | 23 (4.4)                              | 2 (3.9)                               | 1      | 18 (7.3)                              | 16 (9.1)                              | 2 (2.8)  | 0.084   | 0.079   |
| Abdominal pains/diarrhea        | 80 (13.9)  | 73 (13.9)                             | 7 (13.5)                              | 0.926  | 36 (10.4)                             | 29 (16.6)                             | 7 (9.9)  | 0.177   | 0.779   |
| Sore throat/throat discomfort    | 35 (6.1)   | 31 (5.9)                              | 4 (7.7)                               | 0.609  | 5 (2.0)                               | 5 (2.9)                               | 0 (0.0)  | 0.325   | 0.014   |
| Headache/dizziness              | 33 (5.7)   | 32 (6.1)                              | 1 (1.9)                               | 0.347  | 14 (5.7)                              | 11 (6.3)                              | 3 (4.2)  | 0.763   | 0.983   |
| Chest distress                  | 138 (24.0) | 131 (25.0)                            | 7 (13.5)                              | 0.063  | 58 (23.6)                             | 44 (25.1)                             | 14 (19.7) | 0.364   | 0.907   |
| Characteristics | Without DM | | | | With DM | | | | p value | A vs. B |
|-----------------|------------|---|---|---|------------|---|---|---|---|---|
| | All (A) | non–cardiac injury | cardiac injury | p value | All (B) | non–cardiac injury | cardiac injury | p value | A vs. B |
| Coexisting comorbidities, n (%) | | | | | | | | | |
| Any | 226 (39.2) | 187 (35.7) | 39 (75.0) | < 0.001 | 160 (65.0) | 109 (62.3) | 51 (71.8) | 0.155 | < 0.001 |
| Hypertension | 80 (13.9) | 61 (11.6) | 19 (36.5) | < 0.001 | 84 (34.2) | 61 (34.9) | 23 (32.4) | 0.712 | < 0.001 |
| Coronary heart diseases | 43 (7.5) | 35 (6.7) | 8 (15.4) | 0.045 | 29 (11.8) | 17 (9.7) | 11 (15.5) | 0.196 | 0.045 |
| Cancer | 17 (3.0) | 14 (2.7) | 3 (5.8) | 0.192 | 8 (3.3) | 6 (3.4) | 2 (2.8) | 1 | 0.818 |
| Pulmonary diseases | 31 (5.4) | 24 (4.6) | 7 (13.5) | 0.016 | 17 (7.0) | 8 (4.6) | 9 (12.7) | 0.048 | 0.392 |
| Cerebrovascular diseases | 14 (2.4) | 8 (1.5) | 6 (11.5) | 0.001 | 12 (4.9) | 4 (2.3) | 8 (11.3) | 0.006 | 0.066 |
| Laboratory findings | | | | | | | | | |
| FPG (mmol/l) | 5.2 (4.7–6.0) | 5.2 (4.7–6.0) | 5.4 (4.5–6.4) | 0.956 | 7.5 (5.8–10.1) | 7.4 (5.7–10.0) | 7.8 (5.8–10.2) | 0.748 | < 0.001 |
| ALT (U/l) | 38.0 (21.0–65.0) | 38.0 (21.0–66.0) | 35.0 (21.0–56.0) | 0.378 | 39.0 (21.8–73.3) | 38.0 (22.0–74.0) | 38.0 (21.0–73.0) | 0.748 | 0.637 |
| AST (U/l) | 34.0 (24.0–51.0) | 34.0 (23.0–49.0) | 48.0 (34.0–57.0) | 0.172 | 32.1 (28.8–34.9) | 33.4 (30.4–35.8) | 28.4 (25.0–31.9) | < 0.001 | < 0.001 |
| Albumin (g/l) | 34.8 (31.6–37.6) | 35.1 (32.3–37.7) | 31.0 (27.9–32.7) | < 0.001 | 32.1 (28.8–34.9) | 33.4 (30.4–35.8) | 28.4 (25.0–31.9) | < 0.001 | < 0.001 |
| Urea (mmol/l) | 5.3 (4.3–6.8) | 5.2 (4.2–6.6) | 7.6 (6.5–9.7) | 0.021 | 7.0 (5.4–9.2) | 6.2 (5.2–7.8) | 9.4 (7.6–18.8) | < 0.001 | < 0.001 |
| Creatinine (µmol/l) | 64.0 (53.0–76.0) | 63.0 (53.0–75.0) | 73.0 (61.0–99.0) | 0.179 | 67.5 (56.8–85.3) | 65.0 (55.0–78.0) | 78.0 (65.0–98.0) | 0.07 | 0.002 |
| Platelet (× 10^9/l) | 214.0 (164.0–272.3) | 217.0 (166.0–276.0) | 180.5 (145.5–229.8) | 0.001 | 209.0 (150.5–275.5) | 220.0 (165.0–289.0) | 177.0 (119.0–200.0) | < 0.001 | 0.174 |
| APTT (sec) | 25.9 (24.2–28.1) | 25.9 (24.2–27.9) | 26.8 (24.7–28.1) | 0.374 | 25.7 (24.0–27.4) | 25.5 (24.0–27.1) | 26.4 (24.1–28.7) | 0.466 | 0.129 |
| PT (sec) | 12.0 (11.5–12.7) | 12.0 (11.4–12.7) | 12.7 (12.0–14.2) | < 0.001 | 12.4 (11.8–13.4) | 12.1 (11.6–12.8) | 13.4 (12.6–16.4) | 0.015 | < 0.001 |
| TT (sec) | 17.1 (16.4–17.8) | 17.1 (16.4–17.8) | 16.9 (16.0–18.0) | 0.92 | 16.8 (15.9–17.7) | 16.9 (16.1–17.7) | 16.4 (15.5–17.6) | 0.828 | 0.002 |
| INR | 1.0 (1.0–1.1) | 1.0 (1.0–1.1) | 1.1 (1.0–1.2) | < 0.001 | 1.1 (1.0–1.2) | 1.1 (1.0–1.1) | 1.2 (1.1–1.4) | 0.019 | < 0.001 |
| D–dimer (mg/l) | 4.6 (3.6–5.7) | 4.6 (3.5–5.7) | 4.6 (3.8–5.6) | 0.997 | 16.8 (15.9–17.7) | 5.0 (4.2–6.4) | 5.4 (4.0–6.8) | 0.987 | < 0.001 |
| Fibrinogen (g/l) | 3.8 (3.3–4.4) | 3.8 (3.3–4.4) | 3.8 (3.3–4.2) | 0.249 | 3.7 (1.5–4.3) | 3.8 (3.2–4.3) | 3.6 (3.0–4.0) | 0.127 | 0.189 |
| TC (mmol/l) | 1.2 (0.9–1.6) | 1.2 (0.9–1.6) | 1.3 (0.9–1.5) | 0.926 | 1.3 (1.0–1.7) | 1.3 (1.0–1.7) | 1.3 (1.1–1.7) | 0.992 | 0.001 |
| Triglyceride (mmol/l) | 0.9 (0.8–1.1) | 0.9 (0.8–1.1) | 0.9 (0.7–1.1) | 0.559 | 0.9 (0.7–1.0) | 0.8 (0.7–1.0) | 0.8 (0.7–1.0) | 0.334 | < 0.001 |
| HDL–c (mmol/l) | 0.003 (0.003–0.012) | 0.003 (0.003–0.007) | 0.014 (0.009–0.027) | < 0.001 | 0.011 (0.003–0.057) | 0.003 (0.003–0.012) | 0.159 (0.070–0.757) | < 0.001 | < 0.001 |
| LDL–c (mmol/l) | 2.3 (1.9–2.9) | 2.4 (1.9–2.9) | 2.2 (1.9–2.6) | 0.097 | 2.3 (1.7–2.8) | 2.4 (1.8–2.9) | 2.1 (1.7–2.6) | 0.032 | 0.18 |
On the hypoglycemic strategies, the use of insulin was more frequent in DM patients with cardiac injury ($p < 0.001$) (Table 1).

### Higher incidence of cardiac injury in COVID-19 patients with DM

Overall, the incidence of cardiac injury was higher in patients with DM than in non-DM cases (28.9% vs 9.0%, $p < 0.001$), even grouped by age, gender, and the level of FPG (Fig. 2). During hospitalization, the mean peak concentration of cTnl, creatine kinase MB (CK-MB), myoglobin (Myo), and B-type natriuretic peptide (BNP) was higher in COVID-19 patients with DM (Table 1). The distribution of cTnl showed that DM patients had a great proportion of cTnl > 0.04 ng/ml and cTnl > 0.78 ng/ml, which indicated acute myocardial infarction possible (all $p < 0.01$ with $\chi^2$ test) (Fig. 2).

Of patients with COVID-19, 500 cases (60.8%) underwent an examination of 12-lead electrocardiogram after admission. The features of electrocardiogram were similar in COVID-19 patients with or without DM, except the incidence of atrial arrhythmia (Fig. 2). However, in these

### Table 1 (continued)

| Characteristics | Without DM | With DM | $p$ value | $p$ value A vs. B |
|-----------------|-----------|---------|-----------|------------------|
|                 | All (A)   | non–cardiac injury | cardiac injury | non–cardiac injury | cardiac injury |
| CK–MB (ng/ml)   | 0.9 (0.6–1.4) | 0.8 (0.6–1.3) | 2.1 (1.3–3.3) | <0.001 | 1.3 (0.8–2.4) | 0.99 (0.73–14.14) | 2.96 (1.69–4.26) | <0.001 | <0.001 |
| Myoglobin (µg/l) | 36.9 (25.5–59.9) | 35.3 (25.0–54.3) | 111.3 (46.4–255.5) | <0.001 | 543 (33.8–98.6) | 45.0 (30.8–82.6) | 89.9 (61.2–165.4) | <0.001 | <0.001 |
| BNP (pg/ml)     | 89.9 (42.4–300.9) | 79.5 (38.0–196.1) | 626.0 (324.0–1467.0) | <0.001 | 250.0 (79.0–779.0) | 131.7 (68.0–452.4) | 877.0 (454.0–5528.0) | <0.001 | <0.001 |
| Findings on chest CT, n/N (%) | | | | | | | | |
| Unilateral      | 17/467 (3.6) | 14/432 (3.2) | 3/35 (8.6) | 0.111 | 2/190 (1.1) | 1/146 (0.7) | 1/44 (2.3) | 0.41 | 0.069 |
| Bilateral       | 444/467 (95.1) | 412/432 (95.4) | 32/35 (91.4) | – | 188/190 (99.0) | 145/146 (99.3) | 43/44 (97.7) | – | – |
| Ground–glass opacity | 357/467 (76.5) | 333/432 (77.1) | 24/35 (68.6) | 0.254 | 128/190 (67.4) | 109/146 (74.7) | 19/44 (43.2) | <0.001 | 0.016 |
| Treatment, n (%) | | | | | | | | |
| Antiviral therapy | 521 (90.5) | 477 (91.0) | 44 (84.6) | 0.138 | 229 (93.1) | 164 (93.7) | 65 (91.6) | 0.582 | 0.221 |
| Antibiotic therapy | 418 (72.6) | 376 (71.8) | 42 (80.8) | 0.165 | 203 (62.5) | 135 (77.1) | 68 (95.8) | <0.001 | 0.002 |
| Invasive mechanical ventilation | 31 (5.4) | 24 (4.6) | 7 (13.5) | 0.016 | 54 (22.0) | 24 (13.7) | 30 (42.3) | <0.001 | <0.001 |
| Glucocorticoid therapy | 249 (43.2) | 221 (42.2) | 28 (53.9) | 0.105 | 145 (58.9) | 93 (53.1) | 52 (73.2) | 0.004 | <0.001 |
| Only insulin therapy | – | – | – | – | 73/168 (43.5) | 39/120 (32.5) | 34/48 (70.8) | <0.001 | – |
| Insulin and OAH therapy | – | – | – | – | 63/168 (37.5) | 51/120 (42.5) | 12/48 (25.0) | <0.001 | – |
| Only OAH therapy | – | – | – | – | 32/168 (19.1) | 30/120 (25.0) | 2/48 (14.3) | <0.001 | – |
| Coagulopathy, n (%) | 21 (3.7) | 11 (2.1) | 10 (19.2) | <0.001 | 47 (19.1) | 22 (12.6) | 25 (35.2) | <0.001 | <0.001 |
| Death, n (%) | 36 (6.3) | 20 (3.8) | 16 (30.8) | <0.001 | 37 (15.0) | 6 (3.4) | 31 (42.9) | <0.001 | <0.001 |

$ALT$ alanine transaminase, $APTT$ activated partial thromboplastin time, $AST$ aspartate transaminase, $BNP$ brain natriuretic peptide, $CK$-MB creatine phosphokinase-MB, COVID-19 the Coronavirus disease 2019, $cTn I$ cardiac troponin I, $DBP$ diastolic pressure, $DM$ diabetes mellitus, $FPG$ fasting plasma glucose, $HDL$-c high-density lipoprotein cholesterol, INR international normalized ratio, $LDL$-c low-density lipoprotein cholesterol, $OAH$ oral anti-hyperglycemia, $PT$ prothrombin time, $RR$ respiratory rate, $SBP$ systolic pressure, $TC$ total cholesterol, $TG$ triglycerides, $TT$ thrombin time

$p < 0.05$. On the hypoglycemic strategies, the use of insulin was more frequent in DM patients with cardiac injury ($p < 0.001$) (Table 1).
Fig. 2 The distribution of cTnI and the electrocardiographic features of COVID-19 patients with and without diabetes. The peak levels of cTnI (A) are higher in patients with DM during hospitalization. The incidence of cardiac injury in COVID-19 patients is higher in DM groups according to the level of cTnI (B) and FPG (C) and age and gender (D). E Present the electrocardiographic characteristics of COVID-19 patients. *Present p < 0.05, **present p < 0.01. §Defined as the composite of ST-segment elevations, depressions, or T-wave inversions.

cTnI cardiac troponin I, DM diabetes mellitus, FPG fasting plasma glucose

Fig. 3 The effect of cardiac injury on mortality of COVID-19 with and without DM. Kaplan–Meier survival curves showed higher mortality in patients with DM and cardiac injury by the days after hospitalization (A) and illness onset (B). The contour plot revealed the mortality was higher in patients of senior age and elevated cTnI level in all COVID-19 patients (C), DM patients (D), and non-DM patients (E). cTnI cardiac troponin I, DM diabetes mellitus
## Table 2: The immunological features of COVID-19 patients with and without cardiac injury grouped by DM

| Characteristic                      | Without DM | With DM | p value | p value A vs. B |
|-------------------------------------|------------|---------|---------|-----------------|
|                                     | All (A)    | non-cardiac injury | cardiac injury |    |                |
| C3 (g/l)                            | 1.0 (0.9–1.2) | 1.0 (0.9–1.2) | 1.0 (0.9–1.1) | 0.287 |      |
| C4 (g/l)                            | 0.3 (0.2–0.3) | 0.3 (0.2–0.3) | 0.3 (0.2–0.3) | 0.015 | 0.001 |
| IgA (g/l)                           | 2.3 (1.7–2.9) | 2.3 (1.7–2.9) | 2.4 (2.0–3.0) | 0.082 | 0.237 |
| IgE (IU/ml)                         | 42.0 (9.2–106.3) | 42.0 (9.2–107.8) | 40.5 (9.2–90.5) | 0.928 |      |
| IgG (g/l)                           | 11.7 (10.0–13.9) | 11.7 (10.0–13.9) | 11.8 (9.6–13.9) | 0.835 | 0.009 |
| IgM (g/l)                           | 0.9 (0.7–1.2) | 0.9 (0.7–1.2) | 0.9 (0.6–1.2) | 0.249 | 0.695 |
| WBC (× 10³/µl)                      | 5.2 (3.9–7.0) | 5.1 (3.9–6.8) | 6.2 (4.4–10.0) | 0.001 |      |
| LYM (× 10³/µl)                      | 1.1 (0.8–1.5) | 1.1 (0.8–1.5) | 0.8 (0.6–1.3) | < 0.001 |      |
| NEU (× 10³/µl)                      | 3.3 (2.4–5.1) | 3.2 (2.3–4.8) | 4.7 (3.0–7.8) | < 0.001 |      |
| Baso (× 10³/µl)                     | 0.01 (0.00–0.02) | 0.01 (0.00–0.02) | 0.01 (0.00–0.02) | 0.332 |      |
| EOS (× 10³/µl)                      | 0.02 (0.00–0.00) | 0.02 (0.00–0.00) | 0.01 (0.00–0.00) | 0.226 |      |
| CD3+ T cells (cells/µl)             | 657.5 (442.5–940.5) | 677.0 (457.5–962.5) | 452.0 (240.0–619.0) | < 0.001 |      |
| CD3+ CD4+ T cells (cells/µl)        | 392.5 (246.5–576.0) | 407.0 (260.5–596.5) | 265.0 (158.0–414.0) | < 0.001 |      |
| CD3+ CD8+ T cells (cells/µl)        | 223.0 (138.0–334.8) | 228.0 (147.0–338.0) | 165.0 (74.0–232.0) | < 0.001 |      |
| CD4/CD8 ratio                       | 1.8 (1.2–2.6) | 1.8 (1.3–2.5) | 1.8 (1.1–2.7) | 0.942 |      |
| CD19+ B cells (cells/µl)            | 135.0 (90.0–205.0) | 138.0 (92.0–206.0) | 112.0 (64.0–158.0) | 0.004 | 0.033 |
| CD16+ CD56+ NK cells (cells/µl)     | 118.0 (77.0–185.0) | 117.0 (77.0–183.0) | 145.0 (59.0–252.0) | 0.438 | 0.044 |
| IL2 (pg/ml)                         | 3.8 (3.4–4.1) | 4.0 (3.4–4.0) | 4.0 (3.4–4.0) | 0.542 | 0.156 |
| IL4 (pg/ml)                         | 3.4 (3.0–3.9) | 4.0 (3.4–4.0) | 4.0 (3.4–4.0) | 0.663 | 0.604 |
| IL5 (pg/ml)                         | 2.2 (2.1–2.3) | 2.2 (2.1–2.3) | 2.3 (2.1–2.3) | 0.992 | 0.578 |
| IL6 (pg/ml)                         | 6.0 (3.1–11.7) | 6.0 (3.0–11.0) | 9.5 (5.0–22.3) | 0.007 | 0.641 |
| IL10 (pg/ml)                        | 5.5 (4.7–6.7) | 6.0 (5.0–7.0) | 6.0 (5.0–8.5) | 0.022 | 0.583 |
| TNF-α (pg/ml)                       | 3.4 (2.9–4.7) | 3.0 (3.0–5.0) | 3.0 (3.0–4.0) | 0.35 | 0.115 |
| γ-interferon (pg/ml)                | 3.5 (3.0–4.3) | 3.0 (3.0–4.0) | 3.0 (3.0–4.0) | 0.001 | 0.008 |
| CRP (mg/l)                          | 4.8 (2.2–28.4) | 4.0 (2.0–21.0) | 36.0 (7.0–65.0) | 0.009 | 0.032 |
| PCT (mg/ml)                         | 0.1 (0.0–0.1) | 0.0 (0.0–0.0) | 0.0 (0.0–0.0) | < 0.001 | 0.137 |
| NLR                                 | 3.0 (1.9–5.0) | 2.8 (1.8–5.1) | 5.1 (3.5–12.5) | < 0.001 | 0.001 |

*Baso = basophils, C3 = complement 3, C4 = complement 4, CRP = C-reactive protein, DM = diabetes mellitus, EOS = eosinophils, IgA = immunoglobulin A, IgE = immunoglobulin E, IgG = immunoglobulin G, IgM = immunoglobulin M, IL-2 = interleukin-2, IL-4 = interleukin-4, IL-5 = interleukin-5, IL-6 = interleukin-6, IL-10 = interleukin-10, LYM = lymphocytes, NLR = neutrophils to lymphocytes ratio, PCT = procalcitonin, TNF-α = tumor necrosis factor-α, WBC = white blood cells*
two groups, patients with cardiac injury more frequently had ischemic changes, especially ST-segment shifts (elevation or depression), compared with those without myocardial infarction (all \( p < 0.05 \)).

Increased in-hospital mortality in DM patients with cardiac injury

The overall in-hospital mortality in patients with and without DM was 37/246 (15.0%) and 36/576 (6.3%), respectively (\( p < 0.001 \)). It was also higher in people with cardiac injury, both in DM patients (42.9% vs 3.4%, \( p < 0.001 \)) and in non-DM patients (32.1% vs 3.8%, \( p < 0.001 \)) (Figs. 1 and 3A, B). The contour plot shows the elevated fatality rate was closely related to the elderly and higher levels of cTnI (Fig. 3C–E).

Severer immune-inflammatory responses in DM patients with cardiac injury

As compared to non-DM cases, COVID-19 with DM patients showed relatively higher median counts of white blood cells (WBC) and Neutrophils (NEU), but a lower number of lymphocytes (LYM), which led to a higher level of neutrophil to lymphocyte ratio (NLR) (5.9 (3.0–10.5) vs 3.0 (1.9–5.4), \( p < 0.001 \)). These subjects also present higher levels of IL-6 (10.7 (5.5–25.1) vs 6.0 (3.1–11.7) pg/mL, \( p < 0.001 \)) and IL-10 (6.3 (5.1–8.0) vs 5.5 (4.7–6.7) pg/mL, \( p < 0.001 \)). Moreover, the absolute counts of all immunocytes were decreased in DM patients compared to non-DM cases, including CD3\(^+\) T cells, CD3\(^+\)CD4\(^+\) T cells counts, CD3\(^+\)CD8\(^+\) T cells, CD19\(^+\) B cells, and CD16\(^+\)CD56\(^+\) NK cells (all \( p < 0.05 \)). The concentrations of immunoglobulin A (IgA) and IgG were also risen in DM patients (all \( p < 0.01 \)) (Table 2).

COVID-19 patients with DM and cardiac injury had a further decreased count of LYM and increased number of Neutrophils and relatively higher NLR than those without cardiac injury. The inflammation-related biomarkers were also augmented in COVID-19 patients with cardiac injury more than those without cardiac injury. In addition, the decreased level of C3 was a specific character present in DM with cardiac injury, while the increased value of C4 was more distinctive in non-DM patients with cardiac injury (Table 2). Regarding the immunocyte subset, we also found the descending absolute counts of immune cells in cardiac injury groups (all \( p < 0.01 \)) (Table 2). However, when compared with cases with cardiac injury but without DM, diabetic people with cardiac injury had a relatively higher frequency of CD3\(^+\) T cells, CD3\(^+\)CD4\(^+\) T cells, and CD19\(^+\) B cells (Additional file 1: Fig. S2).

Correlation between immune-inflammatory indicators and cTnI in DM patients

In DM patients, spearman’s correlation analysis found negative connection between cardiac injury with
C3 concentration ($r = -0.237$), CD3+ T cells counts ($r = -0.288$), CD3+CD4+ T cells counts ($r = -0.287$), CD3+CD8+ T cells counts ($r = -0.286$), CD19+ B cells counts ($r = -0.178$), CD16+CD56+ NK cells counts ($r = -0.135$), and positive association with IgA concentration ($r = 0.179$), the proportion of CD19+B cells ($r = 0.072$), CD16+CD56+ NK cells ($r = 0.079$), the level of IL-10 and IL-6 ($r = 0.359$ and 0.396, respectively), and the value of CRP, PCT and NLR ($r = 0.48$, 0.459 and 0.3375, respectively) (all $p < 0.05$) (Fig. 4).

**Immune-inflammatory biomarkers as risk factors for cardiac injury in DM patients**

Given the specific changes in DM groups, especially with cardiac injury, the ROC and Logistics regression analysis were performed on absolute counts of immunocyte subset, level of C3, IgA, IgG, IL-6, IL-10, γ-interferon, PCT, and NLR. The ROC curve disclosed significant cutoff levels for the immune-related biomarkers that were statistically related with in-hospital mortality in all participants: C3 ≤ 1.05 g/l; IgA > 3.18 g/l; IgG > 10.5 g/l; CD3+ T cells counts ≤ 333 cells/μl; CD3+CD4+ T cells counts ≤ 288 cells/μl; CD3+CD8+ T cells counts ≤ 188 cells/μl; CD19+ B cells counts ≤ 102 cells/μl; CD16+CD56+ NK cells ≤ 59 cells/μl; IL-6 > 25.68 μg/ml; IL-10 > 5.71 pg/ml; γ-interferon ≤ 3.58 ng/ml; PCT > 0.078 ng/ml; NLR > 7.525 (Additional file 1: Fig. S3).

To assess the risk factors for cardiac injury by logistics regression analysis, the value of these indicators was transformed into categorical variables according to the ROC cut-off point. In univariable analysis, all the above biomarkers were risk factors of cardiac injury in COVID-19 patients with DM with $P_{interaction} < 0.01$ (Fig. 5). After adjusting age, sex, CRP, LDL-c, the presence of comorbidities (including hypertension, coronary heart disease, coagulopathy, and glucocorticoid therapy), the independent predictors for cardiac injury in DM patients were IL-10 > 5.71 pg/ml (adjusted OR, 4.582; 95% CI 1.606–13.075; $p = 0.004$) and NLR > 7.525 (adjusted OR, 3.426; 95% CI 1.930–6.080; $p = 0.002$), with no detectable evidence of interaction with DM ($P_{interaction} > 0.05$). In turn, CD3+CD4+ T cells counts ≤ 288 cells/μl (adjusted OR, 2.501; 95% CI 1.282–4.877; $p = 0.007$), IL-6 > 25.68 μg/ml (adjusted OR, 4.345; 95% CI, 2.192–10.374; $p < 0.001$) and PCT > 0.078 ng/ml (adjusted OR, 5.917; 95% CI, 2.788–12.557; $p < 0.001$) were significantly associated with cardiac injury in diabetic patients with $P_{interaction} < 0.05$ (Fig. 5).

**Discussion**

In this retrospective study of 822 COVID-19 cases, three major observations were demonstrated: (i) cardiac injury was prevalent in diabetic patients with COVID-19, and conferred a nearly 13-fold higher risk of in-hospital...
mortality in those people; (ii) COVID-19 patients with DM and cardiac injury present much severer immune-inflammatory responses; and (iii) decreased number of CD3+CD4+ T cells and increased IL-6 value particularly refer high risk of cardiac injury in diabetic COVID-19 patients.

Consistent with previous studies [3–6], the higher overall in-hospital mortality was found in COVID-19 patients with DM (15.0% vs 6.3%, p < 0.001) (Fig. 1). However, studies from France and England did not support this hypothesis [21, 22]. Notably, the mean age of participants in these two studies (>71.2 years) was older than our study (<67 years). The older age groups always mean a higher incidence of mortality in the present study (Figs. 2 and 3) and other studies [3, 5, 6, 13]. This might prominently overestimate the mortality of COVID-19, and cover the potential effects caused by DM.

Previous reports have demonstrated that cardiac injury caused by COVID-19 can lead to poor clinical outcomes [5, 9–11]. In the present study, the risk of in-hospital death for diabetic COVID-19 patients with higher cTnI was nearly 13-fold higher than without cardiac injury (42.9% vs 3.4%, p < 0.001). When excluding patients with cardiac injury, the incidence of death was similar between DM and non-DM participants (3.4% vs 3.8%, p = 0.113). This means that cardiac injury also increases the risk of in-hospital mortality from DM in COVID-19 patients.

Despite cardiac injury is prevalent in diabetic patients with COVID-19 (Fig. 1) [7, 8], the etiology and risk factors of cardiac injury are not clear yet. It has been reported that basal cTnI levels were slightly increased in DM with coronary heart disease [23]. However, cTnI values in those patients were not up to the 99th percentile URL [23]. Among diabetic patients with a normal level of cTnI, the probability of being free of future cardiovascular diseases at follow-up was 92.2%. Once they have elevated cTnI above the cutoff, the risk of cardiovascular diseases was significantly increased [24]. In addition, the basal cTnI levels were lower in women than men in the general population [25], however, it was similar between diabetic men and diabetic women [26]. Kimenai et al. found the doubling of cardiovascular risk required similar thresholds of cTnI value in women and men (2.1 ng/l vs. 2.5 ng/l). The discrimination of cTnI for the prediction of cardiovascular events between women and men was also attenuated [25]. Therefore, the criterion of cardiac injury in this study was based on a single cTnI 99th percentile cutoff but not sex-specific cutoffs. Our results showed that the incidence of cardiac injury was significantly augmented both in male and female diabetic COVID-19 patients (Fig. 2).

Acute viral infections are associated with a higher risk of acute cardiac injury, ischemia, and infarction [27]. In keeping with this, cardiac pathological examinations have found cardiomyocyte hypertrophy, the infiltration of immunocytes, and possible myocardial localization of viral particles [16, 17, 20]. Among COVID-19 patients with cardiac injury, nearly 14.7%-25.8% had ST segment shift in 12-lead electrocardiogram (the common features of acute coronary syndrome) (Fig. 2E), while 63.2%-78.3% present echocardiographic abnormalities [9, 28]. Meanwhile, 38.7% of COVID-19 patients with poor outcomes had possible myocarditis [29]. These indicated that the above diseases accounted for the major causes of cardiac injury following COVID-19 infection. But the next important question is why.

One of the answers is the immunity function disturbance after COVID-19 infection. COVID-19 Patients with cardiac injury have increased inflammatory markers, such as IL-6, lymphopenia, and higher counts of leukocytes and neutrophils [10, 11, 13, 15, 20]. Trends of these changes were far graver in diabetic COVID-19 patients with cardiac injury (Table 2 and Additional file 1: Fig. S2.). What's more, lower C3 level and increased IgA antibodies [30]. The consequence of increased IgA is leading to IL-6 mediated inflammatory effects [31]. Meanwhile, the SARS-CoV-2 virus may directly clip C3 to make C3a, namely complement activation, and then accelerates the development of neutrophils-induced thrombosis, coagulopathy, and tissue injury [32]. Thus, complement system and IgA-mediated mucosal immunity may involve the initiation of cardiac injury in COVID-19 patients with DM.

In particular, this study demonstrated that the decreased CD3+CD4+ T cells (≤288 cells/ul) were an independent risk of cardiac injury in DM patients with COVID-19 (adjusted OR, 2.501; 95% CI, 1.282–4.877; p = 0.007; Pinteraction = 0.018), but not in patients without DM (Fig. 5). It has been reported that lower blood lymphocyte percentage was an independent risk factor of cardiac injury in COVID-19 patients [15]. However, this study based on small sample sizes was not specifically designed for diabetic COVID-19 patients [15]. Actually, the impaired immune state in diabetes is characterized by an initial interruption in the activation of Th1 CD4+ T cell-mediated immunity and late hyperimmune response, which may contribute to cytokine storm dominated by IL-6 [33]. In diabetic mice infected by Middle East respiratory syndrome coronavirus (MERS-CoV), the alterations in CD4+ T cells were associated with the
server and prolonged disease [34]. Consistent with this, the absolute count of T cell subsets was decreased in severe COVID-19 cases with DM [2, 14].

The present study also revealed that elevated levels of IL-6 (>25.68 pg/ml) increase the risk of the occurrence of cardiac injury in DM persons \(P_{\text{interaction}} < 0.05\). Previous studies have investigated that higher plasma IL-6 level is an independent marker for macrovascular events and mortality in type 2 diabetic patients [35, 36]. Mostly, Zhou et al. confirmed that in COVID-19 patients, CD4+ T cells, but not CD8+ T cells, NK cells, and B cells, are the main source of IL-6 production [37]. Once IL-6 is released, it not only induces apoptosis pathway and excessive exhaustion of T cells in server COVID-19 patients, but also plays a pathological role in chronic inflammatory disease (including cardiovascular disease) after SARS-CoV-2 infection [38, 39]. Thus, IL-6 derived from SARS-CoV-2 specific CD4+ T cells is required for cardiac complications and death in COVID-19 patients with DM.

This study found higher IL-10, an anti-inflammatory cytokine, was associated with cardiac injury (Table 1 and Fig. 5). This is similar to previous studies [40–42]. Actually, IL-10 can predict disease severity and poor outcomes in CVOID-19 patients [40, 41]. There are some potential mechanisms to explain these results. Firstly, higher IL-10 concentrations may reflect an extreme attempt to counteract severe inflammation in COVID-19. This is because IL-10-producing regulatory T cells, which is significant increase in severe COVID-19 patients, might contribute to inhibiting innate inflammatory responses [41, 43]. Secondly, IL-10 concentrations are elevated earlier than IL-6 in COVID-19 patients [42]. IL-10 might stimulate the production of other mediators of the cytokine storm, such as IL-6, through a negative feedback mechanism [42]. Thirdly, IL-10 directly enlarges cytotoxic effector CD8+ T cells and hyperactivation of adaptive immunity to exacerbate COVID-19 severity and tissue injury [42]. Lastly, IL-10 decreased the expression of HLA class II molecules by antigen-presenting cells [41].

Nonetheless, despite a lot of efforts we made, our study still had some notable limitations. Firstly, the single-center retrospective nature of the study leads to a lack of some data (such as the echocardiography and continuous monitoring of blood glucose and cTnI) and the absence of a prospective validation cohort. Secondly, given the continually increasing number of COVID-19 infection cases, a relatively small sample size of the study may throw doubt on the reliability of our study. Thirdly, there is no dynamic alteration of immune-inflammatory biomarkers and cardiac injury indicators in DM patients after hospitalization. At last, we no doubt have a possible selection bias in this study. Patients with chest distress and/or high risk of cardiovascular diseases, such as hypertension, were more prone to do the cTnI test for assessment of myocardial injury during the COVID-19 pandemic in our hospital. This may overestimate the rate of cardiac injury in the study.

Conclusions

For diabetic patients with COVID-19, cardiac injury not only induced severer immune-inflammatory responses, but also increased in-hospital mortality. The decreased number of CD3+CD4+ T cells and increased level of IL-6 were independent risk factors of cardiac injury, which can be promoted by the presence of diabetes. Thus, immune-inflammatory indicators, especially CD3+CD4+ T cells and IL-6, are recommended to distinguish the people who refer to a high risk of cardiac injury and mortality from COVID-19 patients with DM. However, it remains a testable theory whether decision-making strategies based on the risk status of cardiac injury in COVID-19 patients, especially with DM, would be expected to get better outcomes.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-022-01625-2.

Additional file 1: Table S1. The comparison of COVID-19 patients with and without core examination results. Figure S1. The incidence of complications of COVID-19 patients with and without DM. Figure S2. The ROC analysis of immune-inflammatory parameters for in-hospital mortality of all COVID-19 patients.

Acknowledgements

We are grateful to all patients who participated in the study. Sincere gratitude to the whole medical staff of the world for their unyielding effort in managing COVID-19 patients.

Author contributions

YB, BY and WZY designed the study. YB, CYL, WY collected the data. YB, LIF, and CXL performed analysis and interpretation of the data. YB drafted the manuscript, and BY and WZY contributed to editing and revising the manuscript. All authors read and approved the final manuscript.

Funding

This study was funded by the National Natural Science Foundation of China (81900749), Zhejiang University special scientific research fund for COVID-19 prevent and control (2020KZGX015), and the Nature Science Foundation of Hubei province (2018CFB150).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.
Declarations

Ethics approval and consent to participate
This study was organized according to the principles of the Declaration of Helsinki and approved by the Clinical Research Ethics Commission of Renmin Hospital of Wuhan University (WDRY2020-K021). Informed consent was exempted by ethics commission because of the retrospective design of the study for emerging infectious diseases.

Consent for publication
Not applicable.

Competing interests
All authors declare that there are no relationships and activities that might influence this work.

Received: 6 May 2022 Accepted: 7 September 2022
Published online: 19 September 2022

References

1. World Health Organization. Coronavirus disease 2019 (COVID-19) situ- 
ation report. 2020. https://www.who.int/emergencies/diseases/novel-
coronavirus-2019/situation-reports.
2. Cai Y, Shi S, Yang F, Yi B, Chen X, Li J, et al. Fasting blood glucose level is a predictor of mortality in patients with COVID-19 independent of diabetes history. Diabetes Res Clin Pract. 2020;169:108437.
3. Barron E, Bakhai C, Kar P, Weaver A, Bradley D, Ismail H, et al. Associa-
tions of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. Lancet Diabetes Endocrinol. 2020;8(10):813–22.
4. Grasselli G, Greco M, Zanella A, Albano G, Antonelli M, Bellani G, et al. Risk factors associated with mortality among patients with COVID-19 in intensive care units in Lombardy, Italy. JAMA Intern Med. 2020;180(10):1545–55.
5. Bonnet G, Weizman O, Trimaillé A, Pommier T, Cellier J, Geneste L, et al. Characteristics and outcomes of patients hospitalized for COVID-19 in France: the Critical COVID-19 France (CCF) study. Arch Cardiovasc Dis. 2021;11(4):352–63.
6. Kim L, Garg S, O’Halloran A, Whitaker M, Pham H, Anderson EJ, et al. Risk factors for intensive care unit admission and in-hospital mortality among hospitalized adults identified through the US Coronavirus Disease 2019 (COVID-19)-associated hospitalization surveillance network (COVID-NET). Clin Infect Dis. 2021;72(9):e206–14.
7. Shi Q, Zhang X, Jiang F, Zhang X, Hu N, Bimu C, et al. Clinical character-
istics and risk factors for mortality of COVID-19 patients with diabetes in Wuhan, China: a two-center, retrospective study. Diabetes Care. 2020;43(7):1382–91.
8. Zhu L, She ZG, Cheng X, Qin J, Zhang XJ, Cai J, et al. Association of blood glucose control and outcomes in patients with COVID-19 and pre-
existing type 2 diabetes. Cell Metab. 2020;31(6):1068–1077.e1063.
9. Giustino G, Croft LB, Stefanini GG, Bragato R, Silbiger JJ, Vicenzi M, et al. Characterization of myocardial injury in patients with COVID-19. J Am Coll Cardiol. 2020;76(18):2043–55.
10. Lala A, Johnson KW, Januzzi JL, Russak A, Paranjpe J, Richter F, et al. Prevalence and impact of myocardial injury in patients hospitalized with COVID-19 infection. J Am Coll Cardiol. 2020;76(5):533–46.
11. Shi S, Qin M, Cai Y, Liu T, Shen B, Yang F, et al. Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019. Eur Heart J. 2020;41(22):2070–9.
12. Tang Q, Matsushita K, Coresh J, Nduka J, McEvoy M, Sharrett AR, et al. High-sensitivity cardiac troponin I and T for cardiovascular risk strati-
fication in adults with diabetes. Diabetes Care. 2020;43(10):e144–6.
13. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol. 2020;5(7):802–10.
14. Zhao R, Sun Y, Zhang Y, Wang W, Wang S, Wang C, et al. Distinguishable immunologic characteristics of COVID-19 patients with comorbid type 2 diabetes compared with nondiabetic individuals. Mediators Inflamm. 2020;2020:6914878.
15. Zhou W, Song L, Wang X, Xu Z, Wang S, Wang J, et al. Cardiac injury prediction and lymphocyte immunity and inflammation analysis in hos-
pitalized patients with coronavirus disease 2019 (COVID-19). Int J Cardiol. 2021;326:237–42.
16. Hallbauer JD, Tzankov A, Mertz KD, Schwab N, Nienhold R, Twerenbold R, et al. Characterization of cardiac pathology in 23 autopsies of lethal COVID-19. J Pathol Clin Res. 2021;7(4):326–37.
17. Sang C, J 3rd, Burkett A, Heindl B, Litovsky SH, Prabhu SD, Benson PA, et al. Cardiac pathology in COVID-19: a single center autopsy experience. Cardiovasc Pathol. 2021;54:107370.
18. Beyerstedt S, Casaro EB, Rangel EB. COVID-19: angiotensin-converting enzyme 2 (ACE2) expression and tissue susceptibility to SARS-CoV-2 infection. Eur J Clin Microbiol Infect Dis. 2021;40(5):905–19.
19. Herman-Edelstein M, Guetta T, Barnea A, Waldman M, Ben-Dor N, Barac 
YD, et al. Expression of the SARS-CoV-2 receptor ACE2 in human heart is associated with uncontrolled diabetes, obesity, and activation of the renin angiotensin system. Cardiovasc Diabetol. 2021;20(1):90.
20. Sandoval-Y, Januzzi JL Jr, Jaffe AS. Cardiac troponin for assessment of myocardial injury in COVID-19: JACC review topic of the week. J Am Coll Cardiol. 2020;76(10):1244–58.
21. Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO clinical characterisation protocol: prospective observational cohort study. BMJ. 2020;369:m1865.
22. Sutter W, Duceau B, Vignac M, Bonnet G, Carlier A, Roussel R, et al. Asso-
ciation of diabetes and outcomes in patients with COVID-19: propensity score-matched analyses from a French retrospective cohort. Diabetes Metab. 2021;47(4):101222.
23. Segre CA, Hube L, Garcia RM, Rezende PC, Favaro D, Strunz CM, et al. Troponin in diabetic patients with and without chronic coronary artery disease. BMC Cardiovasc Disord. 2015;15:172.
24. Yu KH, Lau KK, Zhao CT, Chan YH, Chen Y, Zhou Z, et al. Predictive value of high-sensitivity troponin-I for future adverse cardiovascular outcome in stable patients with type 2 diabetes mellitus. Cardiovasc Diabetol. 2014;13:63.
25. Kimeris DM, Shah AV, McAllister DA, Lee KK, Tsanas A, Meek SJ, et al. Sex Differences in cardiac troponin I and T and the predic-
tion of cardiovascular events in the general population. Clin Chem. 2021;67(10):1351–60.
26. Leutner M, Tschere M, Farhan S, Taghizadeh Waeghe H, Harente J, Vogel B, et al. A sex-specific analysis of the predictive value of troponin I and T in patients with and without diabetes mellitus after successful coronary intervention. Front Endocrinol. 2019;10:105.
27. Musker DM, Abers MS, Corrales-Medina VF. Acute infection and myocar-
dial infarction. N Engl J Med. 2019;380(2):171–6.
28. Xu H, Hou K, Xu R, Li Z, Fu H, Wen L, et al. Clinical characteristics and risks factors of cardiac involvement in COVID-19. J Am Heart Assoc. 2020;9(18):e016807.
29. Deng Q, Hu B, Zhang Y, Wang H, Zhou X, Hu W, et al. Suspected myocar-
dial injury in patients with COVID-19: evidence from front-line clinical observation in Wuhan, China. Int J Cardiol. 2020;311:116–21.
30. Zhao Y, Liu Y, Yi F, Zhang J, Xu Z, Lu Y, et al. Type 2 diabetes mellitus impaired nasal immunity and increased the risk of hyposmia in COVID-19 mild pneumonia patients. Int Immunopharmacol. 2021;93:107406.
31. Yu HQ, Sun BQ, Fang Z, Zhao JC, Liu XY, Li YM, et al. Distinct features of SARS-CoV-2-specific IgA response in COVID-19 patients. Eur Respir J. 2020;56(2):2001526. https://doi.org/10.1183/13993003.01526-2020.
32. Skendros P, Mitsios A, Chrysanthropoulou A, Mastellos DC, Metallidis S, Rafaïlidi P, et al. Complement and tissue factor-enriched neutrophil extracellular traps are key drivers in COVID-19 immunothrombosis. J Clin Invest. 2020;130(11):e16517–.
33. Munipaya R, Gobbi S. COVID-19 pandemic, coronaviruses, and diabetes mellitus. Am J Physiol Endocrinol Metab. 2020;318(5):E736–41.
34. Kulcsar KA, Coleman CM, Beck SE, Fireman MB. Comorbid diabetes results in immune dysregulation and enhanced disease severity following MERS-
CoV infection. JCI Insight. 2019;4(20):e131774. https://doi.org/10.1172/jci. insight.131774.
35. Lowe G, Woodward M, Hills G, Rumley A, Li Q, Harrap S, et al. Circulat-
ing inflammatory markers and the risk of vascular complications and
mortality in people with type 2 diabetes and cardiovascular disease or risk factors: the ADVANCE study. Diabetes. 2014;63(3):1115–23.
36. Ridker PM, MacFadyen JG, Glynn RJ, Bradwin G, Hasan AA, Rifai N. Comparison of interleukin-6, C-reactive protein, and low-density lipoprotein cholesterol as biomarkers of residual risk in contemporary practice: secondary analyses from the Cardiovascular Inflammation Reduction Trial. Eur Heart J. 2020;41(31):2952–61.
37. Zhou Y, Fu B, Zheng X, Wang D, Zhao C, Qi Y, et al. Pathogenic T-cells and inflammatory monocytes incite inflammatory storms in severe COVID-19 patients. Natl Sci Rev. 2020;7(6):998–1002.
38. Copaescu A, Smibert O, Gibson A, Phillips EJ, Trubiano JA. The role of IL-6 and other mediators in the cytokine storm associated with SARS-CoV-2 infection. J Allergy Clin Immunol. 2020;146(3):S18–S34 e511.
39. Diao B, Wang C, Tan Y, Chen X, Liu Y, Ning L, et al. Reduction and functional exhaustion of T cells in patients with coronavirus disease 2019 (COVID-19). Front Immunol. 2020;11:827.
40. Han H, Ma Q, Li C, Liu R, Zhao L, Wang W, et al. Profiling serum cytokines in COVID-19 patients reveals IL-6 and IL-10 are disease severity predictors. Emerg Microbes Infect. 2020;9(1):1123–30.
41. Neumann J, Prezzemolo T, Vanderbeke L, Rocca CP, Gerbaux M, Janssens S, et al. Increased IL-10-producing regulatory T cells are characteristic of severe cases of COVID-19. Clin Transl Immunology. 2020;9(11): e1204.

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