

The correlation between C-reactive protein, D-dimer and Glomerular Filtration Rate and the clinical outcomes of COVID-19 patients with Diabetes Mellitus: A Literature Review

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World Journal of Advanced Research and Reviews, 2023, 20(02), 1114–1119

Publication history: Received on 09 October 2023; revised on 18 November 2023; accepted on 20 November 2023

Article DOI: <https://doi.org/10.30574/wjarr.2023.20.2.2359>

Abstract

Coronavirus disease 2019 (COVID-19) is an infectious disease that has caused millions of deaths. COVID-19 patients with diabetes mellitus have increased mortality rates in comparison to COVID-19 patients without diabetes mellitus. Laboratory findings such as C-reactive protein, D-dimer, and glomerular filtration rates may potentially provide predictive value on mortality in COVID-19 patients with diabetes mellitus. The purpose of this literature review is to summarize previous findings on the association of C-reactive protein, D-dimer, and Glomerular Filtration Rate with clinical outcomes of COVID-19 patients with Diabetes Mellitus.

Keywords: Diabetes; COVID-19; GFR; D-Dimer; CRP

1. Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by a variant of the SARS Coronaviruses-2 (SARS-COV-2) virus. Coronavirus Disease 2019 (COVID-19) is a disease with variable clinical signs, ranging from asymptomatic to fatal, particularly in people with comorbidities such as diabetes mellitus and in the elderly [1]. According to World Health Organization (WHO) data as of May 16, 2022, COVID-19 caused 6.27 million fatalities globally [1].

Diabetes mellitus is a chronic metabolic disorder characterized by elevated blood sugar levels. According to WHO data, the number of diabetic patients worldwide will reach 422 million in 2022, with the number of fatalities increasing by 1.5 million each year [1]. According to one study, COVID-19 patients with diabetes have a greater mortality rate in comparison to COVID-19 patients without diabetes [2].

Laboratory tests for C-reactive protein [3], D-dimer [4], and Glomerular Filtration Rate (GFR) [5] in COVID-19 patients are helpful in identifying individuals whose conditions are at risk of deteriorating. Diabetes can impair the activation of adaptive immune response by lowering Th1 cell-mediated immunity stimulation, resulting in a delayed hyperinflammatory response in diabetic patients [6]. Thus, the purpose of this study is to investigate the association between GFR, CRP, and D-dimer levels and the clinical outcomes of COVID-19 patients with diabetes mellitus. It is intended that these findings will serve as a reference for the care of COVID-19 patients with diabetes mellitus, as well as a retrospective study to better prepare for similar incidents in the future.

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2. Materials and Method

PubMed, GoogleScholar and ScienceDirect and other search engines were used to explore articles regarding this topic. For the search strategy, we used keywords “Diabetes”; “C- Reactive Protein”, “D-Dimer”, “Glomerular Filtration Rate” “COVID-19”, and its synonyms to find all relevant related articles. Boolean operators (“OR,” “AND”) were used to get more specific results. The search was limited to articles in the English language only. We also use the information of COVID-19 from the World Health Organization website.

3. Results and Discussion

3.1. COVID-19 in Patients with Diabetes Mellitus

Comorbidities, complications, and demographic variables can contribute to the severity of COVID-19 disease in diabetic patients. COVID-19 disease can cause inflammation, which can lead to insulin resistance and interfere insulin release of pancreatic beta cells. Hyperglycemia can lead to glucose toxicity, which exacerbates the already-existing symptoms of insulin resistance and decreased insulin secretion [7].

The study discovered that COVID-19 patients with diabetes mellitus required higher insulin dosages to manage their blood sugar than they did before getting COVID-19. This demonstrates that the SARS CoV-2 virus has an adverse effect on glucose metabolism. Impaired glucose metabolism can raise the risk of problems induced by high blood sugar levels, such as diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS). The following complications were discovered to be linked with the severity of diabetes and higher patient mortality [8].

Immunostaining of SARS CoV-2 and the ACE-2 receptor suggests that SARS CoV-2 can cause beta cell injury in the islets of Langerhans. A study involving over 2000 COVID-19 patients discovered that the prevalence of diabetes was up to two times greater in COVID-19 patients who died compared to COVID-19 patients who survived. In conclusion, diabetes enhances the severity of COVID-19, resulting in higher mortality of COVID-19 patients with diabetes mellitus [9].

3.2. C- Reactive Protein Concentration in COVID-19 Patients with Diabetes Mellitus

CRP is a measure of systemic inflammation and severe infections that is frequently used to assess disease inflammation. CRP as an acute phase reactant, binds to phosphocholine in pathogen and host cell membranes and can serve as an opsonin. Elevated CRP levels are a key component of nonspecific immune mechanisms, particularly in the early phases following inflammatory stimulation [10]. After tissue injury or during inflammation, CRP rises in response to inflammatory cytokines such as interleukin-6 (IL-6), interleukin-1 (IL-1), or tumour necrosis factor-alpha (TNF- α) [11].

High CRP levels at the time of hospitalization were also shown to be moderately associated to the severity of COVID-19 infection. High CRP values suggest chronic inflammation or bacterial co-infection [12]. As a result, CRP can be a sensitive marker in detecting tissue damage and acute inflammation, and it is frequently used to assess the severity of COVID-19 patients [12]. The findings of this study back up the findings of another study performed in Wuhan, which indicated that COVID-19 patients with more severe conditions had a higher average CRP of 57.9 mg/L compared to patients with less severe conditions with an average of 33.2 mg/L [13]. Table 1 shows more research on CRP levels in COVID-19 patients with Diabetes Mellitus.

Table 1 Studies Related to CRP Concentration in COVID-19 Patients with Diabetes Mellitus

Studies	Methods	Results
Author : Chen et al [14]. Year : 2020 Location : China	Design : Retrospective study Sample size : 563 (diabetic : 87) Characteristics : Patients diagnosed with COVID-19 according to the Diagnosis and Treatment Plan for COVID-19 by China National Health Commission.	Higher CRP concentration in diabetics patients (2.86 IQR[0.55–5.39]) compared to non-diabetic patients (0.49 IQR[0.08–2.81]) with p value <0.001.
Author : Koh et al [15]. Year : 2020	Design : Retrospective study Sample size : 809 (diabetic 140)	Higher CRP concentration in diabetic patients (10.1 IQR[2.5–34.2]) compared to non-

Location : Singapore	Characteristics : Patients were diagnosed with COVID-19 infection via reverse transcription polymerase chain reaction (RT-PCR) on throat and nasopharyngeal swab.	diabetic patients (3.3 IQR[1.1–7.7]) with p value <0.001.
Author : Zhou et al [16]. Year : 2020 Location : China	Design : Retrospective study Sample size : 44 (diabetic 14) Characteristics : Patients diagnosed with COVID-19 according to the Diagnosis and Treatment Plan for COVID-19 by China National Health Commission.	Higher CRP concentration in diabetic patients (7.5 IQR[2.67–11.94]) compared to non-diabetic patients (1 IQR[0.069–2.5]) with p value <0.001.

3.3. Serum D-Dimer Concentration in COVID-19 Patients with Diabetes Mellitus

D-dimer is a marker for fibrin formation and degradation. The formation of D-dimers is a result of plasmin-mediated fibrin breakdown [17]. D-dimer can be used as an inflammatory coagulation biomarker that plays a role in blood clotting. Since d-dimer is normally not detected in the blood or is found in low concentrations of around 0.50 g/mL, it can be used to detect inflammatory conditions if found in higher concentrations [18].

Higher levels of D-dimer at admission were found to be associated with increased need for mechanical ventilation or intubation, and higher risks of VTE as well as mortality in another study comprising 1065 COVID-19 patients [19]. Research has found that 25% of COVID-19 patients with a high degree of severity experience VTE, and 30% are diagnosed with pulmonary embolism. It was also discovered that 71% of COVID-19 patients who did not survive had DIC [20]. Since elevated D-dimer levels are linked to thrombotic disorders, it can be used to screen for venous thromboembolism (VTE) and disseminated intravascular coagulation (DIC) [17]. Table 2 lists other studies on D-Dimer levels in COVID-19 patients with Diabetes Mellitus.

Table 2 Studies Related to D-Dimer Concentration in COVID-19 Patients with Diabetes Mellitus

Studies	Methods	Results
Author : Zhang et al [21]. Year : 2021 Location : China	Design : Case-control study Sample size : 81 (diabetic: 50) Characteristics : Participants were diagnosed with COVID-19 based on chest computed tomography (CT) manifestations and/or reverse transcription-polymerase chain reaction (RT-PCR) following the criteria of the New Coronavirus Pneumonia Prevention and Control Program.	Higher D-Dimer concentration in diabetic patients (2.57 IQR [0.83–3.88]) compared to non-diabetic patients (0.85 IQR[0.43– 2.57]) with p value =0.001.
Author : Yan et al [22]. Year : 2020 Location : China	Design : Single-center, retrospective, observational study Sample size : 145 (diabetic: 48) Characteristics : Participants were diagnosed with COVID-19 according to WHO interim guidance.	Higher D-Dimer concentration in diabetics patients (2.6 IQR[1–21]) compared to non-diabetic patients (1.2 IQR[0.4–10.7])with p value =0.012.
Author : Chen et al [14]. Year : 2020 Location : China	Design : Retrospective study Sample size : 563 (diabetic: 87) Characteristics : Patients diagnosed with COVID-19 according to the Diagnosis and Treatment Plan for COVID-19 by China National Health Commission.	Higher D-Dimer concentration in diabetics patients (0.98 IQR[0.42–2.39]) compared to non-diabetic patients (0.50 IQR[0.23–1.22]) with p value <0.001.

3.4. Glomerular Filtration Rate in COVID-19 Patients with Diabetes Mellitus

The SARS-CoV-2 virus can cause a cytopathic effect on kidney tissue. The SARS-CoV-2 virus can infect kidney cells more easily than lung cells because ACE2 expression is higher in kidney cells than in lung cells [5]. Rapid viral multiplication, cellular damage, virus-mediated downregulation and shedding of ACE2, and antibody-dependent enhancement all contribute to the severe inflammation generated by SARS-CoV-2. The first phase of rapid viral multiplication may cause massive epithelial and endothelial cell death as well as vascular leakage [23].

COVID-19 disease progresses to Acute respiratory distress syndrome (ARDS) which can cause various systemic conditions such as decreased cardiac output due to damage to the right heart, venous congestion, hypoxia, tissue edema, etc. which can contribute to kidney damage or Acute Kidney Injury (AKI) [24]. An eGFR of less than 45 was discovered to be an additional risk factor for developing AKI in COVID-19 patients. The data demonstrated that renal function was as an accurate predictor of mortality like other key risk factors including age and frailty [25]. Table 3 lists more research on GFR in COVID-19 patients with Diabetes Mellitus.

Table 3 Studies Related to GFR in COVID-19 Patients with Diabetes Mellitus

Studies	Methods	Results
Author : Alshukry et al [26]. Year : 2021 Location : Kuwait	Design : Single center, retrospective study Sample size : 417 (diabetic: 122) Characteristics : Patients were diagnosed through a positive RT-PCR assay of nasal and/or pharyngeal swabs.	Higher GFR in non-diabetic patients (109.64 ± 19.27) compared to diabetic patients (95.10 ± 17.2) with p-value <0.001 in asymptomatic patients. Higher GFR in non-diabetic patients (104.97 ± 18.61) compared to diabetic patients (91.71 ± 23.59) with p-value = 0.002 in patients with mild-moderate symptoms. Higher GFR in non-diabetic patients (76.46 ± 34.14) compared to diabetic patients (57.50 ± 33.81) with p-value = 0.035 in patients with severe symptoms.
Author : Al-Salameh et al [27]. Year : 2021 Location : France	Design : Observational cohort study Sample size : 433 (diabetic: 115) Characteristics : Patients diagnosed through a nasopharyngeal swab specimen that tested positive in a reverse-transcriptase polymerase-chain-reaction assay.	Higher GFR in non-diabetic patients (85 IQR[60-111]) compared to diabetic patients (71.5 IQR[40.5-88.5]) with p-value <0.001 .
Author : Ramesh et al [28]. Year : 2021 Location : India	Design : Retrospective study Sample size : 175 (diabetic: 102) Characteristics : Patients were diagnosed with COVID-19 infection via a positive reverse transcription polymerase chain reaction (RT-PCR) assay.	Higher GFR (48.01) in non-diabetic patients compared diabetic patients (43.6) with p-value <0.001 .

4. Conclusion

According to the findings, higher CRP and D-Dimer levels were associated with poor outcomes due to inflammation. Lower GFR were associated with poor outcomes as a result of renal injury. The results of this study revealed the significance of CRP, D-dimer as well as GFR testing in determining the prognosis of COVID-19 patients with Diabetes Mellitus.

Compliance with ethical standards

Acknowledgments

The authors acknowledge all the studies involved in writing this manuscript.

Disclosure of conflict of interest

No conflict of interest.

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