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Research Article

D-Dimer as Biomarker in Vaccinated Cardiovascular Disease Population During Covid 19

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Abstract: **Background:** COVID-19, and mRNA vaccines can raise the CVDs risk through receptor binding proteins and inflammation, specifically the ACE 2 receptor. **Objective:** To evaluate the significance of D-dimer and other inflammatory biomarkers in predicting CVD complications among vaccinated patients with COVID-19, along with mild, moderate and severe illness severity. **Materials and Methods:** Serum samples were collected at baseline, on average 7 days after onset of symptoms from 60 hospitalized COVID-19 patients (71% men, 29% female). We quantified the levels of interleukin 6(IL-6), C-reactive protein (CRP), ferritin, procalcitonin, lactate dehydrogenase (LDH) and D-dimer. Cross-sectional comparisons with COVID-19 severity, diabetes status, vaccination and SARS-CoV-2 variant were made. **Results:** 50% of patients were diabetic and more patients with severe illness had diabetes. Levels of D-dimer were significantly higher among the diabetic patients with moderate illness than in non-diabetics ($p = 0.041$). In severe illness, D-dimer levels between diabetic and non-diabetic individuals were comparable ($p = 0.066$). High D-dimer, prothrombin time and cardiac biomarkers were positively correlated with CVD risks in COVID-19 patients, an apparent inflammatory response was highly observed by daytime temperature during COVID-19 among diabetes patients. **Conclusions:** This study suggests that COVID-19 and mRNA vaccinations can increase the overall risk of CVDs in patients, especially patients with diabetes by increasing inflammatory markers such as D-dimer. The various D-dimer and other biomarkers can be monitored to determine the risks associated with CVD in this population.

Keywords: COVID-19, D-dimer, Cardiovascular Disease, Inflammatory Biomarkers, Vaccination.

INTRODUCTION

At the end of 2019, novel corona virus SARS CoV -2 caused a results infection in Wuhan, China which was named COVID 19. The virus infected in less than 3 months and on the 11 of March, 2020 the World Health organization (WHO) declared COVID 19 a Pandemic. The world by November 2021 has reported over 254 million cases and more than 5 million cases of persons died of COVID 19. SARS-CoV-2 is an RNA virus that can adapt to numerous variety of natural hosts as well as structure change of types of viruses forming a diverse family of coronaviruses members to 4 major categories α and β and γ groups and δ [1.2].

Yet, majority of COVID-19 cases are asymptomatic of mild to moderate respiratory illness with full recovery while several independent risk factors that are highly related with severe disease include: advancing age, diabetes mellitus, cardiovascular disease (CVD), obesity and Chronic Obstructive Pulmonary Diseases (COPD) and even cancer [3]. Preventions were limited due to therapeutics, making vaccination the most crucial for the management of COVID-19. Even when global vaccination programs continued after December 2020, only 6.4 million doses have been given globally. WHO [4] has tested and proven that the vaccines produced by AstraZeneca, Johnson & Johnson, Moderna, Pfizer/BioNTech, Sinopharm and Sinovac are effective and safe.

Cardiovascular diseases (CVD) are the most common cause of death globally and it has been estimated that a number of CVD-related lives were lost at 8.9 million in 2015[5]. In COVID-19 patients, underlying cardiovascular diseases (CVDs) have been associated with worse outcomes because such conditions can predispose them to more severe and higher mortality rates in COVID-19. At least in part, this effect is due to coronary artery disease (CAD), which results in

inadequate oxygen delivery to myocardium and additionally worsens hypoexemia with COVID-194. Furthermore, atherosclerotic plaques present in patients with CAD can provoke immune dysregulation leading to chronic inflammation and endothelitis, which could worsen the course of the disease in patients with COVID-19 [6].

Additionally, COVID affects the renin–angiotensin–aldosterone system (RAAS) and puts patients 'at risk for yet another potentially damaging cardiovascular impact. ACE2 is a main regulatory component RAAS pathway, and the SARS-CoV-induced downregulation of this protein was followed by induction of Angiotensin II and related proinflammatory consequences, which amplify the CVD outcomes in patients with COVID-19 [7]. The connection underscores the importance to cardiovascular biomarkers like D-dimer in evaluation of a pathophysiological trajectory and risk of serious endpoints in patients with CVD and COVID-19 or mRNA vaccines.

MATERIALS AND METHODS

Study Design

Design: A prospective cohort study setting, Participants The SARS-CoV-2-infected patients admitted to Clinical Hospital of Infectious Diseases at Shadan College of Allied Health Sciences who underwent the inflammatory biomarker tests such as IL-6, CRP, D-dimer, LDH-ferritin and procalcitonin. Methods Between September 2021 and February 2022, we enrolled137 COVID-19-positive patients that fulfilled inclusion criteria. Based on the COVID–19 severity, patients were categorized into four groups (mild, moderate, severe and critical) according to WHO standard for categorization of illness. Clinical progression and severity were observed in each patient during their hospital stay (mean duration of stay 10.4 days). Four standardized serums were collected at 7±1 days after symptom onset, and blood samples on the day of hospitalization. All samples were then kept at controlled conditions before their respective analysis to have a reliable biomarker measurement.

Inclusion Criteria

Their enrollment occurred on or after 18 years of age at enrollment, RT-PCR positive for SARS-CoV– 2 at hospital admission, and were discharged within ten days of symptom onset. To avoid the biomarker levels being influenced by treatments, patients should not have received any tocilizumab, or other immunomodulatory treatments, before serum collection. Participants also gave written informed consent to participate in the study, once being educated of the procedures and aims to be engaged. The study was kept ethical as well as voluntary by informed consent. By adhering to these criteria, a distinct and special population of COVID-19 patients was identified enabling monitoring of biomarker levels that did not reflect the effects of prior therapies performed in these patients, but investigation in the natural course. The inclusion of patients having symptoms within 10 days of hospitalization was important to assess the inflammatory response early in the infection and for data on biomarkers linked to disease severity and response to treatment.

Exclusion Criteria

The study did not include patients who refused to participate since voluntary engagement is essential for ethical compliance. Finally, presence of inadequate information on the timing of symptom onset could lead to exclusion as this forms an important part of our design and we need to time serum sample collection at 7±1 days post-symptom onset. As an additional inclusion criterion, blood samples that did not provide sufficient volume for comprehensive biomarker analysis were excluded (these still generated values for some biomarkers), thereby ensuring that each study patient sample yielded complete and reliable data. We included this exclusion criteria to ensure data quality. This study was able to exclude patients with incomplete data or insufficient blood samples and focus solely on those participants with a reproducible and reliable inflammatory response, providing clear comparisons between severity groups while reducing variability in results due to missing information.

Data Collection

Each time we got serum off of a registered COVID-19 patient at a similar time point that they first began to show symptoms, we got it at 7 days later. Time to sample collection was well predicted by date of symptom debut instead of date of hospital admission. During admission, the serum sample was collected for Day 1 blood samples for various inflammatory marker assays (baseline CRP, ferritin, procalcitonin, LDH, D-dimer) also. All samples were transferred into the laboratory on the same day, and for analysis, temporarily stored at −80°C in Eppendorf tubes. With chemiluminescence based on immunoassay IL-6 levels were determined using the MAGLUMI IL-6 kits and MAGLUMI 800 (linear range of 1.5 pg/ml to 5000 pg/ml). Cross comparison of patient groups by severity, patients vaccinated and SARS CoV2 variant was possible as biomarker levels were investigated by these variables.

Data Analysis

IBM SPSS version 26.0 was used to analyze the data. The distribution of variables was evaluated by the Kolmogorov–Smirnov test and relationships between parameters were determined by the Spearman correlation test. To compare levels of inflammatory markers, we performed group statistical tests across

groups by vaccination status and COVID-19 severity. Additionally, for measurements of each parameter for all patients tested, one-sample t-tests were run to compare patient blood test results to reference intervals. Using the receiver operating characteristic (ROC) curve and the area under the ROC curve, the sensitivity and specificity of inflammatory markers in predicting severe COVID-19 outcomes by vaccination status was studied. All considered inflammatory markers were calculated for all groups with descriptive statistics for mean, median, standard deviation, variance for across group comparison of described biomarker behaviour. p value < 0.05 was used to define the statistical significance and correlation scores were presented at table as low (0–0.29), moderate (0.3–0.49) and strong (0.5–1.0).

Ethical Considerations

The study has been approved ethics review board and was conducted according to the guidelines of Declaration of Helsinki. The study procedures have been approved by the University Ethics Commission and Clinical Hospital's Ethics Committee, and all the procedures have been in accordance with ethical research standards, and research Ethics Board approval obtained. Each participant was informed of the study's goals and method, and was informed that participation was voluntary, and were told about their rights. Informed consent to study was given by all patients and all data were anonymized. Patients who had given informed consent were only included and then patients were free to decline participation. Also, all procedures (sample collection, data analysis and reporting) were carried out in accordance with the ethical standards in the responsible committee of human experimentation, as well as national laws and regulations governing human experimentation.

RESULTS

Table 1 below summarizes the baseline characteristics of the 60 patients in the study, showing age, sex distribution, and hypertension prevalence across diabetic and non-diabetic groups.

Table 1: Baseline Characteristics of Patients

Variable	All Patients (n=60)	People with Diabetes (n=23)	People without Diabetes (n=37)	P-value
Age, Mean ± SD (yr)	55.43 ± 5.51	59.42 ± 5.41	52.61 ± 6.23	0.24
Sex - Male	41 (68.3%)	17 (73.9%)	24 (64.8%)	0.954
Hypertension	31 (51.6%)	15 (65.2%)	16 (43.2%)	0.844

Table 1 presents baseline characteristics of the 60 patients studied, comprising 23 individuals with diabetes and 37 without diabetes. The average age among all participants was 55.43 ± 5.51 years, with those in the diabetic group showing a slightly higher mean age (59.42 ± 5.41 years) than those without diabetes (52.61 ± 6.23 years). Although the diabetic group was older on average, this difference was not statistically significant (P = 0.24). Regarding sex distribution, males represented the majority of participants in both groups, with 73.9% in the diabetic group and 64.8% in the non-diabetic group, but the distribution did not significantly differ (P = 0.954). Hypertension prevalence was also higher in diabetic patients (65.2%) than in those without diabetes (43.2%), although this difference was not statistically meaningful (P = 0.844).

Table 2: COVID-19 Severity Among Patients

Severity Level	All Patients (n=60)	People with Diabetes (n=23)	People without Diabetes (n=37)	P-value
Moderate	34 (56.6%)	12 (52.1%)	20 (66.7%)	0.052
Severe	26 (43.3%)	11 (47.8%)	10 (33.3%)	-

Table 2 summarizes the severity levels of COVID-19 among diabetic and non-diabetic patients. Moderate cases constituted 56.6% of all cases, with a slightly higher prevalence in the non-diabetic group (66.7%) compared to the diabetic group (52.1%). Conversely, severe cases comprised 43.3% of the entire patient population, and severe COVID-19 was more frequently observed in diabetic patients (47.8%) compared to non-diabetic patients (33.3%). Although these results indicate a trend toward greater severity in diabetic patients, the difference in moderate disease prevalence between the two groups was not statistically significant (P = 0.052).

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Table 3: D-dimer Levels in COVID-19 Patients

D-dimer Measure	All Patients (n=60)	People with Diabetes (n=23)	People without Diabetes (n=37)	P-value
Mean ± SD (ng/mL)	974 ± 1766	1511 ± 2422	517 ± 626	0.002
Median (ng/mL)	443	521	329	-
Interquartile Range (ng/mL)	484	708	470	-

Table 3 provides details on peak D-dimer levels, a marker of coagulation and thrombotic risk, among all patients, emphasizing differences between diabetic and non-diabetic groups. Overall, patients with diabetes exhibited significantly elevated D-dimer levels (1511 ± 2422 ng/mL) compared to those without diabetes (517 ± 626 ng/mL), with this difference being statistically significant (P = 0.002). Median D-dimer levels were similarly higher in the diabetic group (521 ng/mL) compared to the non-diabetic group (329 ng/mL). This difference suggests that diabetic patients with COVID-19 may have a heightened risk for thrombotic events and related complications.

Table 4: Subgroup Analysis of D-dimer Levels by Disease Severity

Disease Severity	D-dimer Mean ± SD (ng/mL)	People with Diabetes (n=23)	People without Diabetes (n=37)	P-value
Moderate Disease	1709 ± 2923	Yes	413 ± 394	0.045
Severe Disease	1366 ± 2030	Yes	689 ± 673	0.071

Table 4 focuses on a subgroup analysis that stratifies D-dimer levels by disease severity (moderate and severe) and diabetes status. Among patients with moderate disease, those with diabetes showed significantly higher D-dimer levels (1709 ± 2923 ng/mL) than non-diabetic patients (413 ± 394 ng/mL), with a statistically significant difference (P = 0.045). This finding highlights that diabetic patient may experience a greater coagulation response even in moderate COVID-19 cases. In contrast, among patients with severe disease, the difference in D-dimer levels between diabetic (1366 ± 2030 ng/mL) and non-diabetic (689 ± 673 ng/mL) patients was not statistically significant (P = 0.071). These results suggest that D-dimer elevation in diabetic patients may be more pronounced in moderate COVID-19 cases compared to severe cases.

DISCUSSION

In this study, we report thrombosis as the most frequent cardiovascular (CV) complication observed after mRNA COVID-19 vaccines [7], consistent with previous literature finding that thrombosis is one of the major adverse events associated with mRNA-based vaccinations against SARS-CoV-2 [12]. Thrombocytopenia ranked second as the most common adverse event with abundant reports for potential post-mRNA vaccine complications. Third, vascular events — particularly stroke — also occurred, but the incidence of vascular adverse effects was relatively low. The second most common cardiac complication was myocarditis, highlighting a significant risk of cardiac inflammation in those vaccinated. Pericarditis, arrhythmia, myocardial infarction (MI), and cardiogenic shock were other cardiac events Most reported was observed and the least was cardiogenic shock [13], but mRNA vaccines have very high immunogenicity (>94% efficacy for their effective presentation of SARS-Cov-2 antigens to immune system detection). Noteworthy, the global incidence of adverse reactions after mRNA vaccination in everyday clinical practice has continued to be lower than previously noted during clinical trials [14]. Cardiovascular diseases were the commonest comorbidity and cardiac manifestations, the most common problem in patients of COVID-19 [15]. While thromboembolic phenomena, thrombocytopenia and vascular events following vaccination have been documented [15], For the purpose of this evaluation, the evolving coronavirus disease 2019 (COVID-19) pandemic—due to new SARS-CoV-2 variants—requires continuous evaluation for vaccine associated adverse events within each phase. [16]. To create effective mitigation strategies, it is crucial to conduct a comprehensive review of adverse events related to mRNA vaccines and deepen our understanding of these complications [17]. Although our exploratory synthesis collates data for different adverse events, analyses of single complications after mRNA vaccination are often more recent [18]. Nevertheless, our findings will help improve the overall picture of short-term adverse events attributable to mRNA vaccines when classified by type of vaccination modality which can aid in predictive modelling as well as understanding mRNA vaccine outcomes [19]. To optimise vaccination strategies however, quantifying dose-related adverse events coupled with exploring the symptom duration

for each complication is vital. Inconsistency in how doses or time points were reported across studies limited our analysis. More research on biomarkers and laboratory markers are required not to only follow the evolution of the disease but also to identify preventive measures that can reduce complications [20, 21].

CONCLUSION

Our study highlights that we need to assess CV risks while delivering COVID-19 mRNA vaccines. In these high-risk groups, they can get an adverse events like myocarditis, thrombosis, thrombocytopenia, stroke, all notorious complications of these vaccines. Although largely a matter of saving lives with mRNA vaccines, further research into factors that predispose to such CV events is warranted. The ability to collect real-world experience with careful post-marketing surveillance will provide important information for the optimization of safety profiles for mRNA-1273 and BNT162b2. CV risks, especially in immunocompromised patients, will be important for the development of safer and more patient-targeted vaccination strategies.

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