A Case-Control Study of the Role of Haematological Biomarkers in the Disease Monitoring of Diabetic COVID-19 Infected Patients.

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ABSTRACT

COVID-19 is an infectious disease caused by the SARSCoV-2 virus, triggering a worldwide sanitary emergency. COVID-19 has many clinical manifestations, ranging from asymptomatic infection to mild to severe pneumonia. The current study conducted blood parameters change in diabetic COVID-19-infected patients with treatment and without treatment. Biomarkers make them useful as important biomarkers to assess disease progression and categorise patients who may present with severe and fatal clinical conditions. The study was conducted on 1000 patients in a multi-facility hospital in Hyderabad to examine the biochemical parameters (CRP, NT-Pro-BNP, D-Dimer, Ferritin, Interleukin-6 (IL-6), Lactate dehydrogenase (LDH), Procalcitonin (PCT) and Troponin I) markers levels in diabetic COVID-19 patients with medication and without medication. The study investigated

various biochemical markers variables in diabetic COVID-19 patients with treatment and without treatment. In Diabetic COVID-19 patients without treatment/medication, biochemical markers CRP, NT-Pro-BNP, D-Dimer, Ferritin, Interleukin-6 (IL-6), Lactate dehydrogenase (LDH), Procalcitonin (PCT) and Troponin I levels are remarkably increased, which indicate severely suffering patient with diabetic and COVID-19 infection. In Diabetic COVID-19 patients with treatment/medication, biochemical markers CRP, Ferritin, NT-Pro-BNP, D-Dimer, Interleukin-6 (IL-6), Lactate dehydrogenase (LDH), Procalcitonin(PCT) and Troponin I levels are remarkably reduced as compared with the untreated diabetic COVID-19 patients. From the experimental results, we can conclude that CRP, Ferritin, NT-Pro-BNP, D-Dimer, Interleukin-6 (IL-6), Lactate dehydrogenase (LDH), Procalcitonin (PCT) and Troponin I are used as the markers for the detection and identification of the patient's condition those suffer with diabetic COVID-19. The experimental findings will be presented as mean SEM. ANOVA is used to evaluate the data. Control and infected variation values; 0.05 was considered statistically significant.

KEYWORDS: Covid-19, Diabetic disease, CRP, Ferritin, NT-Pro-BNP, D-Dimer,Interleukin-6 (IL-6), Lactate Dehydrogenase (LDH), Procalcitonin(PCT) and Troponin I Biomarkers

INTRODUCTION

COVID-19, which was first reported from Wuhan, China, on December 31, 2019, [1] affected over seven hundred sixty-one million seventy-one thousand eight hundred twenty-six million people worldwide until March 21, 2023, and over six million eight hundred seventy-nine thousand six hundred seventy-seven people died as a result by March 2023 [2]. India reported its first incidence on January 30, 2020, and there have been over forty-four million seven hundred five thousand nine hundred fifty-two confirmed illnesses and five hundred thirty thousand eight hundred thirty-seven fatalities as of March 16, 2023 [3]. Urban areas are significant hubs for uncontained epidemics worldwide, making it challenging to control illness spread and mitigate its harmful consequences on the economy and society. Early in the pandemic, metropolitan areas had the highest frequency of COVID-19 infections. Almost 95% of COVID-19 cases reported worldwide in six months after the epidemic began from cities. Until February 2020, five Indian cities, led by Hyderabad, accounted for over half of the COVID-19 cases identified. The frequency of multigenerational households, the frequent socialisation of extended family and friends in society, and increasingly densely populated areas impeded public health policies aimed at limiting transmission [4, 5].

Based on the clinical reports, the COVID-19 virus mostly affects the respiratory system; nevertheless, it has recently been discovered to infect various organs, including the cardiovascular and blood coagulation systems. Additional target organs include the kidney, the gastrointestinal system, and other tissues representing endothelial cells with the ACE2 surface characteristic [6]. A virus must attach to the host cell receptor, and the distribution of host receptors in cells and tissues is an important component in defining viral tropism and clinical symptoms. ACE2 is found in various tissues, including the heart, lungs, intestines, kidneys, testis, nose, and mouth. Various factors, including age groups, gender disparities, and co-morbid illnesses such as diabetes, hypertension, cardiovascular disease, immune system suppression, etc., determine the severity of these viral infections.

Diabetes may increase the pathogenicity of SARS-CoV-2 because some of the pathological pathways of diabetes coincide with COVID-19, increasing susceptibility and severity of COVID-19 in diabetic individuals.

MATERIAL AND METHODS

The current research was conducted in the Department of clinical biochemistry care hospital and Virinchi Hospital Laboratory Hyderabad, Telangana, India. The research was conducted on patients suffering from covid with diabetic diseases to evaluate and diagnose these patients using RT-PCR, MRI scans and physical symptoms. The study was conducted on 1000 patients admitted to the hospital for the treatment covid-19 along with diabetic disease. The study was conducted duration from 2019 to 2022. Not affected by Covid-19, suffering patients with diabetic disease patients taken as control.

Statistical Analysis

The experimental results will be expressed as mean ± SEM. ANOVA assesses data. Value of control and infected variation; 0.05 was considered statistically significant. The statistical analysis will be performed using Graph Prism Software.

RESULTS AND DISCUSSION

C-Reactive Protein (CRP)

The worldwide diabetic disease is one of the major causes of death. The number of people with diabetes and the prevalence of diabetes-related problems have risen in India in recent years as living standards have grown. One of the leading causes of death in Indian patients with this complicated disease is diabetic disease. Diabetes is a non-communicable disease becoming more common worldwide [7,8]. CRP is one putative marker of vascular

inflammation and diabetic disease patients with covid-19 infection [9]. In the present study, we observed that diabetic COVID-19 patient with the treatment CRP levels is treated as compared with the untreated diabetic COVID-19 patient. Statistically showing the CRP significant variation between the treated and untreated covid-19 patients (Figure 1). From the below Figure 1, we say that the (p-value<0.001) is less than 0.05; we conclude that there is a statistically significant difference between age and test value of CRP.

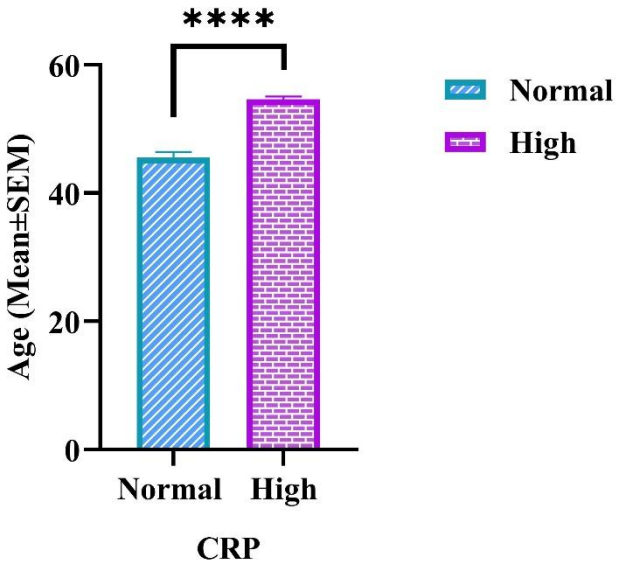

Figure 1: CRPP biomarker levels variation in treated and untreated diabetes patients with COVID-19 infection

NT-Pro-BNP

A B-type natriuretic peptide is one of the peptides from natriuretic peptides like atrial natriuretic peptide (ANP), C-type natriuretic peptide (CNP), and urodilatin. Natriuretic peptides build with 17 amino acids with a disulphide bridge between the cysteine molecules [10]. The ventricular myocardium is the primary site of BNP synthesis and secretion. Whereas ANP is stored in granules and can be released immediately after stimulation, only small amounts of BNP are stored in granules. The underlying mechanism for BNP secretion regulation is rapid gene expression with de novo peptide synthesis. Direct involvement of the myocardium tissue by inflammatory system activation, oxidative stress, demand-supply mismatch, virus-induced myocardial invasion and injury may cause NT-pro-BNP to release [11]. As a result, it will be interesting to see if a decrease in NT-pro-BNP levels indicates a better course of the disease in COVID-19 patients. Figure 2 shows the NT-Pro-BNP levels in COVID-19 diabetic patients with regular treatment and untreated diabetic COVID-19

patients. Figure 2 confirmed that the p-value is more significant than 0.05. The study observed that statistically non-significant difference between the age and test value of NT-Pro-BNP. In multiple comparison tables, there is statistically no significant difference between the age group of exclusion of diabetic COVID-19. Diabetes NT-Pro-BNP levels are increased in heart patients with COVID-19 and not effectively increased NT-Pro-BNP in diabetic patients.

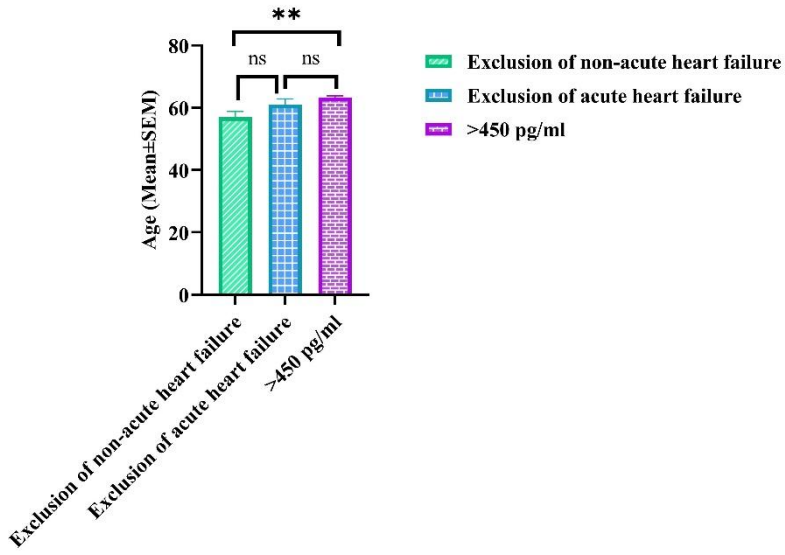

Figure 2: NT-Pro-BNP biomarker levels variation in treated and untreated diabetes patients with covid-19 infection

D-Dimer

D-Dimer is a fibrinogen derivative with a high molecular weight produced by the cleavage of cross-linked fibrin. The concentration of D-Dimer might vary greatly among healthy people, even if they are all considered to be within the normal range. D-Dimer levels are higher than normal in various disorders, including acute venous thromboembolism, ischemic cardiovascular disease, viral infections, and cancer. The D-Dimer levels depended on multiple diseases and infections, particularly a 1.7-fold increased risk of coronary heart disease in conjunction with viral infections (COVID-19) [12]. The slight increases in blood coagulation, thrombin production, and turnover of cross-linked intravascular fibrin reflected by moderately elevated D-Dimer levels may be associated with diabetic disease [13, 14]. In the present study, we observed that diabetic COVID-19 patient with the treatment D-Dimer levels is normally compared to the untreated diabetic COVID-19 patient. Statistically showing the D-Dimer significant variation between the treated and untreated covid-19 patients (Figure 3). From Figure 3, we say that the (p-value<0.001) is less than 0.05; we

conclude that there is a statistically significant difference between the age and test value of D-Dimer

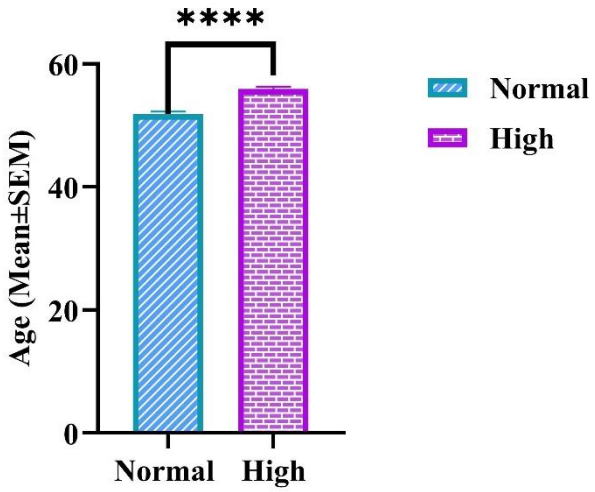

Figure 3: D-Dimer biomarker levels variation in treated and untreated diabetes patients with covid-19 infection

Ferritin

Ferritin is a crucial component of iron metabolism because it is the principal iron-storing protein found within cells. It has been connected to the host's defence against illnesses caused by pathogens. Ferritin levels can become abnormally high for several reasons, including viral infections, chronic transfusions, and hemochromatosis. The increased production and release of intracellular ferritin, the liver's and spleen's diminished capacity to transport ferritin, and the release of iron from the reticuloendothelial system have all been linked to elevated ferritin levels during infection [15, 16]. Even though viral infections are more likely to generate raised ferritin levels, elevated ferritin levels could indicate a dangerous infection in the case of COVID-19. From Figure 4, statistical observation (p-value<0.001) p-value is less than 0.05. From the overall experimental results, we conclude a statistically significant ferritin difference between treated and untreated patients and diabetic COVID-19 patients. Diabetic COVID-19 patients' ferritin values can be used as biomarkers.

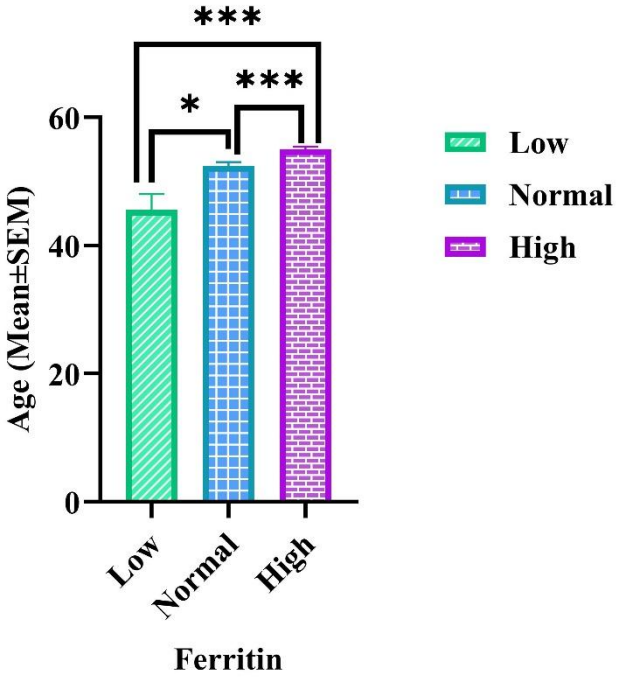

Figure 4: Ferritin biomarker levels variation in treated and untreated diabetes patients with covid-19 infection

Interleukin-6 (IL-6)

The pathophysiology of diabetes is thought to be influenced by chronic systemic inflammation. Interleukin-6 (IL)-6, tumour necrosis factor (TNF), and IL-1 are pro-inflammatory cytokines that play important roles in synovial inflammation and have systemic effects on extra-articular tissues [17]. IL-6 has pleiotropic effects on the immune and other cell types, including pancreatic cells, skeletal muscle, adipose tissue, and liver. IL-6 can signal through both membrane-bound and soluble IL-6 receptors. Chronically high levels of systemic IL-6 have been linked to impaired glucose homeostasis and metabolism and the development of insulin resistance in adipose and hepatic tissue. Increased levels of IL-6 alone or in conjunction with IL-1 impair cell function and represent a different risk factor for T2D.

Similarly, increases in TNF and IL-1 are linked to effects on glucose metabolism, insulin resistance, pancreatic cell function, and diabetes risk. At the same time, IL-1 antagonistic therapy lowers hyperglycemia and enhances pancreatic cell function in T2D patients. Patients with RA and concurrent T2D have much more significant metabolic effects of IL-1 antagonism, suggesting that the inflammatory burden and the effectiveness of anti-cytokine biologics are correlated. In COVID-19 patients with inflammation, higher levels of IL-6 were found in those admitted to ICU and those who died. Similarly, other researchers

found that hyperglycemic patients had higher levels of IL-6 during COVID-19 hospitalisation.

Furthermore, intensive insulin therapy has been shown to reduce hospital mortality by 34% and bloodstream infections by 46%. Those with hyperglycemia who received insulin infusion had a lower risk of severe disease than those who did not [18]. We conclude from the experimental results that an IL-6 statistically significant difference exists between treated and untreated diabetic COVID-19 patients. For Diabetic COVID-19 patients, IL-6 levels can be used as the biomarkers.

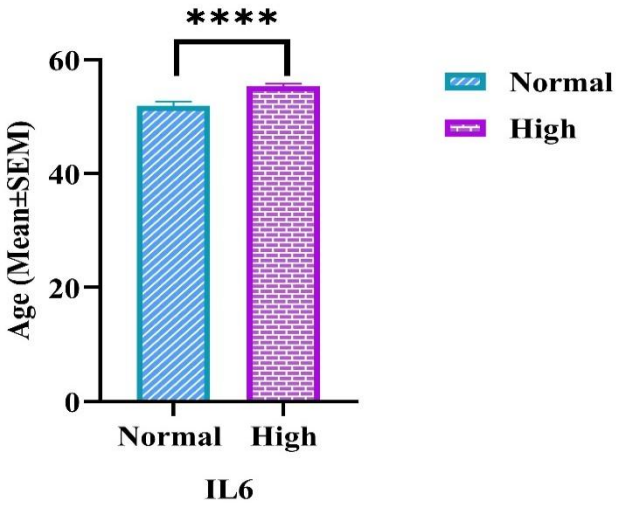

Figure 5: IL-6 biomarker levels variation in treated and untreated diabetes patients with covid-19 infection

Lactate Dehydrogenase (LDH)

In humans, almost all organ systems cells have the intracellular enzyme LDH, which catalyses the conversion of pyruvate and lactate and the simultaneous conversion of NADH and NAD+ [19]. Two main subunits make up the enzyme. Multiple organ injuries, decreased oxygenation, and glycolytic pathway activation can cause abnormal LDH levels. The acidic extracellular pH caused by increased lactate caused by infection and tissue injury activates metalloproteases and promotes macrophage-mediated angiogenesis. [19] Severe infections may result in cytokine-mediated tissue damage and the release of LDH. Because LDH is present in lung tissue, patients with severe diabetic COVID-19 infections can be expected to have higher levels of LDH in their blood [20]. Figure 6 shows the higher amount of LDH in diabetic COVID-19 patients than in untreated diabetic COVID-19 patients. The study was confirmed by the increased LDH levels in the aged people with diabetic COVID-19 patients

compared to the less-aged diabetic COVID-19 patients. Conclusion of the report LDH can be used as the biomarker of diabetic COVID-19 patients.

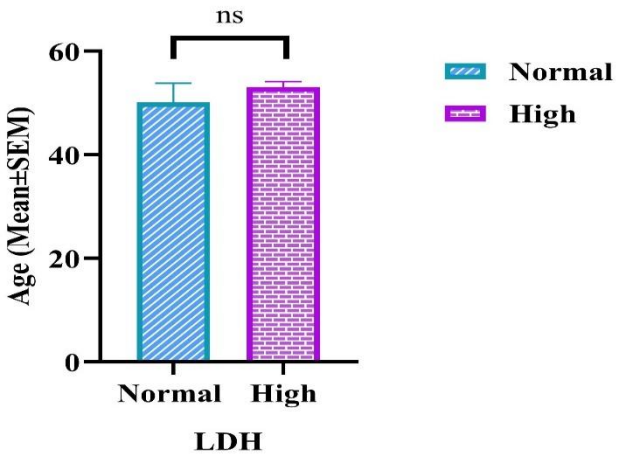

Figure 6: LDH biomarker levels variation in treated and untreated diabetes patients with covid-19 infection

Procalcitonin (PCT)

The 116-amino acid precursor to the hormone calcitonin is called Procalcitonin (PCT). Several investigations have found a favourable correlation between increased PCT levels and COVID-19 severity. A meta-analysis also showed a 5-fold higher risk of severe SARS-CoV-2 infection is associated with higher PCT readings [21]. To differentiate between individuals with COVID-19 who are critically ill and those who are only moderately sick and to determine their prognosis more accurately. When using routine assays, it might be challenging to identify healthy individuals because their serum procalcitonin levels often need to be improved [22]. According to Figure 5, which supports our assertion that the (p-value0.001) is less than 0.05, there is a statistically significant difference between age and the procalcitonin test value. This study shows that PCT may be a marker of disease severity and may help to assess the severity of COVID-19 patients. Serial PCT readings may also aid in determining the prognosis.

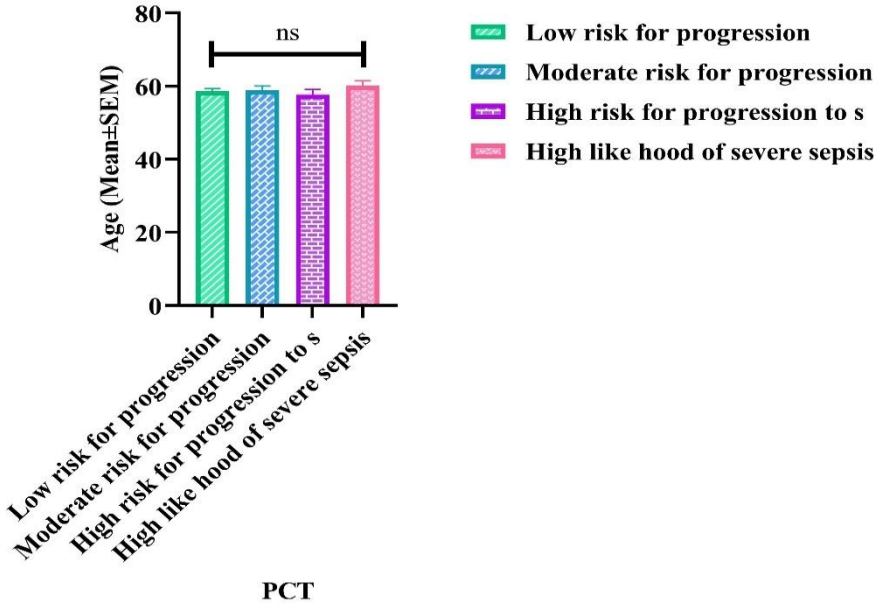

Figure 7: PCT biomarker levels variation in treated and untreated diabetes patients with covid-19 infection

Troponin I

Diabetes is a microvascular disease, and as a result, it contributes to chronic myocite injury. Several mechanisms may contribute to the increased risk of coronary artery disease developing due to diabetes, such as metabolic factors, coagulation abnormalities, endothelial dysfunction, and higher levels of oxidative stress. The prevalence of type 2 diabetes mellitus was previously a known predictor of higher cardiac Troponin I in the general population using older assays. This is consistent with the functional abnormalities that have been described. Circulating high-sensitivity Troponin I was detectable in 90% of diabetic patients who were otherwise healthy [23]. When compared with patients who do not have diabetes, these elevations are associated with cardiovascular disease as well as death from cardiovascular causes. We investigated the prevalence of troponin levels in diabetic COVID-19 patients based on their baseline characteristics. Troponin I elevation detected diabetic patients who underwent such testing during the first week of hospitalisation. In patients with diabetic disease hospital mortality rate was higher and increased with Troponin I level. Age, diabetic complications like metabolic organ function and coinfection like COVID-19 were also linked to in-hospital mortality. From Figure 8, we say that the (p-value<0.001) is less than 0.05; we conclude that there is a statistically significant difference between age and test value of Troponin I.

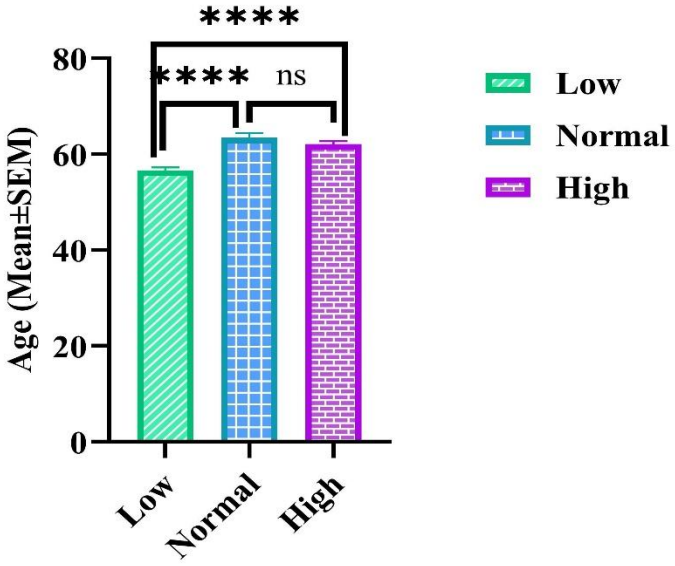

Figure 8: Troponin I biomarker levels variation in treated and untreated diabetes patients with covid-19 infection

CONCLUSION

The severity of the diabetic COVID-19 disease and mortality have been linked to higher levels of inflammatory markers like procalcitonin (PCT) CRP, IL-6, Ferritin, LDH, NT-Pro-BNP and D-Dimer. Resource allocation, especially for needs related to respiratory support, has been demonstrated to benefit greatly from using biomarkers to anticipate illness severity. In this study, we investigated the relationships between several clinical variables and diabetic COVID-19 patients with treatment and without treatment. The values that were available to the intensivist at the initial critical care consultation were the subject of this study. We did this to find variables the critical care team might use to risk stratify and prioritise diabetic COVID-19 patients more accurately.

ACKNOWLEDGEMENT: The authors would like to express their gratitude to Virinchi Hospital Banjara Hills and Annamalai University for allowing them to conduct this research study.

CONFLICT OF INTEREST: Nil

ETHICAL APPROVAL: To conduct a case-control study of biochemical alterations in Covid-19 patients with coronary heart disease was conducted with the approval of the ethics committee before starting the study. Approval number: VH/IEC/17-22/2022/ER-04.

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