The Association of COVID-19 with Coagulopathy and Cardiac Injury

COVID-19 and Coagulopathy

Nour R. Ali 1, Haneen A. Dwesh 2, Iman H. Shewael 3

1 Department of Medical Laboratory Technologies, College of Health and Medical Technologies, National University of Science and Technology, Thi-Qar, Iraq.
2 Department of Anesthesiology, College of Health and Medical Technologies, Al-ayen University, Thi Qar, Iraq.
3 Department of Optometry, College of Health and Medical Technologies, Al ayen university, Thi-Qar, Iraq.

Email: 1: noor.rali@nust.edu.iq, Email 2: Haneen.wahid@alayen.edu.iq, Email 3: Iman.shewael@alayen.edu.iq

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ABSTRACT

Cardiac injury is a common side effect of the coronavirus disease 2019 (COVID-19) and has been linked to poor clinical outcomes. In this study, we assessed the complex interaction between TNHS and D-dimer in defining the risk of an adverse outcome in the patients with a diagnosis of mild and severe acute respiratory syndrome due to coronavirus 2. In retrospective study, from 1st of August till 15th of August 2021 all the patient diagnosed with COVID-19 and admitted on Respiratory Care Unit (RCU) in Nasiriya Heart Center, Dhi Qar, Iraq due to acute respiratory syndrome were enrolled in this study. About 40 COVID-19 patients were divided into two groups according to the severity of disease (mild and severe). Blood sample was collected to determine the concentration of TNHS high sensitivity troponin I and D-Dimer concentrations via VIDAS® machine and compared between groups.

Of the 40 patients with COVID-19 who admitted in RCU, there were 20 (50%) participants in each group (20 patients with mild disease and 20 patients' severe disease). In comparison between the groups, there was no statistically significant difference among the groups in terms of age, gender, underlying disease. However, significant increase in the concentration level of TNHS and D-dimer in group with severe symptoms was observed (p = 0.001 and < 0.001), respectively. Cardiac injury is a common complication of COVID-19. High levels of D-dimer and TNHS are significantly associated with cardiac injury in the patients with severe acute respiratory syndrome. Therefore, the pathogenesis of cardiac injury in COVID-19 may be primarily due to coagulation dysfunction along with microvascular injury.

Keywords: COVID-19; TNHS; Troponin I; D-Dimer.

Introduction

Although the coronavirus disease 2019 (COVID-19) is a viral illness in which lungs are the primary and severely affected target as the name suggests but in fact, it is a system illness in which most of the organ systems are affected with varying degree. The severity of the disease depends on factors such as the age of the patient, immune status, and preexisting comorbidities. The disease gradually progresses and evolves, and the signs and symptoms depend on the viral infiltration and replication and host immune response (1). The disease progression over time can be divided into 3 stages, early infection stage, a pulmonary stage, and a severe hyper inflammation stage in which systemic complications. In the first stage, viral infiltrate and replicate, and lymphopenia is observed. Later as the disease progresses, lung involvement increases, resulting in various respiratory signs and symptoms. As the disease progresses, the body’s immune system tries to control and limit the viral damage, but unfortunately, this results in an exaggerated hyper-inflammatory response, causing extensive collateral tissue damage and severely affecting many organs. In this stage, cardiac and vascular systems are no exception, and cardiovascular injury can be severe and fatal (1). There are various patterns of cardiovascular involvement in COVID-19. First of all, cardiovascular disease presents as preexisting comorbidity which becomes apparent or becomes more complicated and decompensated during COVID 19 (2). Second cardiovascular system involvement results due to systemic inflammatory response during the course COVID 19. The third cardiovascular system can be affected during treatment due to the side effects of some medication or secondary hospital-acquired infections and complication (3). There is ample evidence of COVID-19-related rise in cardiac troponin T and cardiac troponin I. The severe
cardiac injury is defined as when the TNHS serum concentration exceeds the upper reference point three times (4). Studies have shown that COVID-19 patients with raised TNHS levels had poor prognosis. The risk of ventilation support and intensive care unit need rises by up to five times (5). It established a relationship between TNHS levels and disease severity and outcome and validated findings of earlier studies. It will set a path for other researchers to follow suit to understand better the predictive value of cardiac biomarkers and myocardial damage in COVID-19 (6).

More recently, activation of coagulation pathways has been described in a substantial proportion of patients with severe COVID-19 and their presence has been related to the development of multi-organ dysfunction, resulting in an increased risk of death. An hyperactivation of the coagulation system, marked by an elevation of the D-dimer, has been associated to an increased risk of mortality in COVID-19 (7). Post-mortem studies have confirmed the presence of a COVID-19-related coagulopathy characterized by the development of thrombotic microangiopathy in multiple organs, including the heart vessels. Such anatomical alterations can contribute to the elevation of TNHS independently from the severity of the inflammatory response, as they can further aggravate the delivery of an adequate oxygen supply to the myocardium (8).

In this study, we assessed the complex interaction between TNHS and D-dimer in defining the risk of an adverse outcome in the patients with a diagnosis of mild and severe acute respiratory syndrome due to coronavirus 2.

Material and Methods:

COVID-19 Patients:
This study was performed at the laboratory of (National University of Science and Technology, Dhi Qar, Iraq). This study was conducted according to the guidelines approved by the Faculty of Medicine and the Medical Ethics. Informed consent was obtained from all patients. The collection of samples was conducted during the period 1st of August 2021 till 15th of August 2021. All patients of were hospitalized in RCU unit in Nasiriya Heart Center (NHC) and diagnosed by physicians, the cases were confirmed by polymerase chain reaction (PCR) and Computed tomography (CT) of the chest. Blood samples were collected from each patient. The COVID-19 group who subjected to this study were (40) of COVID-19 patients ages of them were range between (40 -60) years., which were divided into two groups according to the severity of disease:
- 20 patients with mild cases of COVID-19.
- 20 patients with severe cases of COVID-19.

Ethical consideration:
The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with patients’ verbal and analytical approval before the sample was taken. The study protocol and the subject information and consent form were reviewed and approved by a local ethics committee (National University of Science and Technology).

Collection of the blood samples:
Five ml of venous blood were withdrawn from patients and control by venipuncture pushed slowly into gel tubes. Blood was allowed to clot at room temperature for 30 min and at 2000 xg for 5 min, then the serum was divided into small Eppendorf tube and kept at (−20°C) to be used later for biochemical estimation of TNHS high sensitivity troponin I and D-Dimer concentrations (4).

Determination the Concentrations of TNHS and D-Dimer:
The concentrations of TNHS high sensitivity troponin I and D-Dimer concentrations were estimated by using VIDAS® an automated machine using the ELFA (Enzyme Linked Fluorescent Assay) technique based on an antigen-antibody reaction where the antibodies are tagged (labelled) with a fluorescent dye and the antigen-antibody complex is visualized using ultra-violet (fluorescent) microscope. Therefore, it allows the visualization of the distribution of the target molecule through the sample. The intensity of the Fluorescence is inversely proportional to the concentration of antigen present in the sample (4).

Statistical Analysis:
The mean ± SD described the quantitative variables, and frequency (percent) was used for qualitative variables. We assessed the normality as the assumption of the variables in the study by the Kolmogorov-Smirnov test. When data were non-normally distributed, the non-parametric test was used. The student's test was used to assess a probable statistically significant difference between qualitative variables for limitations on the observed frequency of Fisher's exact test. The collected data were analyzed by SPSS version 20. A P-value less than 0.05
was considered statistically significant.

**Results:**
The patient's characteristics were summarized in (Table 1). The duration from the beginning of symptoms to hospital admission was similar in both groups. The majority of patients in both groups were treated with anti-viral medications (91.0%), antibiotics (97.1%) and oxygen inhalation (64.5%). In comparison between the groups, there was no statistically significant difference among the groups in terms of age, gender, underlying disease. However, significant increase in the concentration level of TNHS and D-Dimer in group with severe symptoms was observed (p = 0.001 and < 0.001), respectively (Table 2).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mild group</th>
<th>Sever group</th>
<th>P-value</th>
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<tr>
<td>Age, years</td>
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<td>Gender</td>
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<td>Comorbidities, n (%)</td>
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<td>Complications, n (%)</td>
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<td>Duration of hospital admission, n (%)</td>
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<td>Outcomes, n (%)</td>
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Note: * P-values of < 0.05 were considered significant.

<table>
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<th>Table 2: Mean and standard deviation of TNHS and D-dimer Concentration Between sever and mild cases of COVID-19.</th>
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<td>Groups</td>
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<td>TNHS (pg/mL)</td>
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<td>Mild</td>
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<tr>
<td>Sever</td>
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<tr>
<td>D-Dimer (μg/mL)</td>
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<td>Sever</td>
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**Discussion:**
Elevated D-dimer is common in COVID-19 patients and may be attributed to sepsis-induced coagulopathy and reflect the higher thromboembolic risk in severe COVID-19 cases (9). D-dimer levels were significantly higher in severe than in mild COVID-19 patients(10). Lala A. et.al in their A meta-analysis study including (5872) COVID-19 patients found higher D-dimer concentrations were associated with severity and mortality in these patients (11). Dynamic changes of serum D-dimer may be more closely associated with disease severity and outcome of COVID-19. A reduction in D-dimer levels was observed in recovered patients, independent of anticoagulating therapy, whereas a continuous increase in the levels of D-dimer was predictive of a higher risk of thromboembolism and adverse outcomes (12). Ye W et. al. reported that monitoring the dynamic variations of D-dimer is a useful diagnostic tool in predicting the prognosis of COVID-19 patients, and peak D-dimer levels were strongly associated with mortality in COVID-19 patients (13). Cardiac injury is manifested in patients with COVID-19. Cardiac troponin I TNHS has been identified as a biomarker of cardiac injury. Chen et al reported that elevated TNHS was an independent risk factor of critical disease(14). Lala et al showed that the degree of cardiac injury was significantly associated with COVID-19 fatality (11). Our study findings suggest that increased TNHS levels are associated with COVID-19 severity and mortality.

In this prospective single-center study, we reported that TNHS level at admission was the best biomarker to predict ICU transfer and respiratory severity in COVID-19 patients. Moreover, we evidenced the D-dimer involvement in the pathophysiology of COVID-19, which allows us to confirm pulmonary vascular obstruction as a site of coagulopathy and a source of circulating D-dimer. D-dimer increase has been widely reported during SARS-CoV-2 infection (15). D-dimer may reflect the consequences of the COVID-19-associated coagulopathy (16) ,as it probably participates in the respiratory disease through the development of capillary microthrombosis as observed in postmortem studies (17), and attributed to a vascular thickening or vascular congestion(18). Moreover, another pulmonary vascular issue in COVID-19 is related to a high incidence of pulmonary embolism PE ,whose exact association still needs to be determined (19). However, our results observed that the of D-dimer level providing an interface for efficient gas exchange between the alveolar space and blood cells within lung capillaries. We previously described an early endothelial lesion that drives prognosis and ICU transfer of patients. This thromboinflammatory process in pulmonary vessels is probably the main actor of microthrombosis in lung
capillaries (reflected by increased D-dimer) driving consequences in right ventricle. Thus, troponin increase is mainly reflecting RV afterload increase.

Conclusion:
Cardiac injury is a common complication of COVID-19. High levels of D-dimer and TNHS are significantly associated with cardiac injury in the patients with severe acute respiratory syndrome. Therefore, the pathogenesis of cardiac injury in COVID-19 may be primarily due to coagulation dysfunction along with microvascular injury. Financial support and sponsorship: Nil.

Conflicts of interest: There are no conflicts of interest.

Authors’ contributions:
All authors contributed to the conception and design of the study, and drafting the article, and gave final approval of the version to be submitted.

Ethic Statement:
The studies involving human participants were reviewed and approved by the ethics committees of National University of Science and Technology. Written informed consent to participate in this study was provided by the participants.

References:

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