Journal of Al Azhar University-Gaza (Medical and Health Sciences), Vol. 3 No.1, June 2023, p: 1-19

ICU-hospitalized COVID-19 Patients with Pre-existing Cardiovascular Diseases Showed Increased Cardiac Injury and Mortality

Mohammed Taha[1*], Ismail Mansour[2]

[1]Department of Pharmacology and Medical Sciences, Faculty of Pharmacy, Al-Azhar University of Gaza, Gaza, Palestine.
[2]Palestinien Ministry of Health, Gaza, Palestine

(Received 18/12/2022, Accepted 28/06/2023)

مرضى كوفيد-19 في وحدة العناية المركزة المصابين بأمراض القلب والأوعية الدموية أظهروا زيادة في إصابات عضلة القلب ومعدل الوفيات

محمد محمود طه[1*]، اسماعيل أحمد منصور[2]

[1*] قسم علم الادوية والعلوم الطبية، جامعة الأزهر-غزة ، فلسطين.
[2] وزارة الصحة، غزة ، فلسطين.

(تاريخ الاستلام 2022/12/18، تاريخ القبول 2023/06/28)

[*]المؤلف المراسل: محمد محمود طه ، قسم علم الادوية والعلوم الطبية ، جامعة الأزهر-غزة ، فلسطين.

[*]**Contact**:
Mohammed TAHA Department of Pharmacology and Medical Sciences, Al-Azhar University, Gaza Strip, Palestine.
Email: m.taha@alazhar.edu.ps

Abstract

Despite the fact that COVID-19 is a respiratory disease, clinical data has shown that COVID-19 is associated with cardiovascular complications. This study aimed to evaluate the effect of SARS-CoV-2 infection on cardiac biomarkers in cardiovascular patients during ICU hospitalization. The study population (n = 60) was divided into three groups: group A (n=20, COVID-19 patients with cardiovascular diseases); group B (n=20, patients with cardiovascular diseases who didn't have COVID-19); and group C (n=20, COVID-19 patients who didn't have cardiovascular diseases). The levels of cardiac biomarkers were estimated in the blood samples of each participant. Our findings showed a significant increase in the serum levels of cTnI (pg/dL), CK-MB (mg/dL) and LDH (IU/L) among ICU-hospitalized COVID-19 patients with pre-existing cardiovascular diseases compared with the ICU-hospitalized COVID-19 patients and the ICU-hospitalized patients with cardiovascular diseases (p values: 0.006, 0.004, and 0.0001, respectively). Additionally, we found that group A and group C COVID-19 patients had significantly higher D-dimer levels than group B patients; however, the increase was more evident in COVID-19 patients with pre-existing cardiovascular disorders (p value=0.04). Moreover, the results revealed that SARS-CoV-2 infection significantly increased both PT and PPT values during ICU-hospitalization, and the increase was more marked in patients with pre-existing cardiovascular diseases. Finally, we found that the mortality rate was higher in the patients with severe myocardial injury which was more noticeable in group A, where 13 (65%) of the patients had severe myocardial injury, of whom 9 patients died. In conclusion, these findings suggest that SARS-CoV-2 infection may increase the severity of myocardial injury and the likelihood of death in ICU patients, particularly those with cardiovascular diseases.

Keywords: Myocardial injury, COVID-19, SARS-CoV-2, Cardiac biomarkers

الملخص:

على الرغم من أن مرض كوفيد-19 يعتبر مرضاً يصيب الجهاز التنفسي, إلا أن البيانات الاكلينيكية تشير إلى أنه مرتبط بمضاعفات القلب والأوعية الدموية. لذلك فإن هذا الدراسة تهدف إلى تقييم أثر الإصابة بمرض مرض كوفيد-19 على الدلائل الحيوية للقلب لدى مرضى القلب والأوعية الدموية المتواجدين في وحدة العناية المركزة. تم تقسيم المشاركين (ن = 60) إلى 3 مجموعات: مجموعة أ : (ن = 20) المرضي المصابين بمرض كوفيد-19 وأمراض القلب والأوعية الدموية, مجموعة ب : (ن = 20) المرضي المصابين بأمراض القلب والأوعية الدموية الذين لم يسبق لهم الإصابة بمرض كوفيد-19, مجموعة ج : (ن = 20) المرضي المصابين بمرض كوفيد-19 وغير مصابين بأمراض القلب والأوعية الدموية. تم قياس مستويات الدلائل الحيوية للقلب في عينات الدم لكل مشارك.

أظهرت النتائج زيادة ملحوظة في مستويات الدم لكل من cTnI (pg/dL) و CK-MB (mg/dL), LDH (IU/L) بين مرضى كوفيد-19 المصابين بأمراض القلب والمتواجدين في العناية المركزة بالمقارنة مع مرضى كوفيد-19 المتواجدين في العناية المركزة ومرضى العناية المركزة المصابين بأمراض القلب ((p values: 0.006, 0.004, and 0.0001، على التوالي. بالإضافة إلى ذلك، وجدنا أن مرضى كوفيد-19 في المجموعة أ والمجموعة ج لديهم مستويات D-Dimer أعلى بكثير من مرضى المجموعة ب ؛ ومع ذلك، كانت الزيادة أكثر وضوحًا في مرضى COVID-19 الذين يعانون من اضطرابات القلب (p=0.04) . بجانب ذلك, كشفت النتائج أن الإصابة بفيروس كورونا 2 أدى الى زيادة واضحة في قيم PT و PTT أثناء التواجد في العناية المركزة وأن الزيادة كانت أكثر وضوحاً لدى المرضي المصاحبين لأمراض القلب. أخيرًا، وجدنا أن معدل الوفيات كان أعلى في المرضى الذين يعانون من إصابات شديدة في عضلة القلب والتي كانت أكثر وضوحًا في المجموعة أ، حيث تعرض 13 (65٪) من المرضى لإصابة شديدة في عضلة القلب، والتي أدت الى وفاة 9 مرضى منهم. الخاتمة: تفترض هذه النتائج إلى أن الاصابة بفيروس كورونا 2 ربما تزيد من شدة إصابة عضلة القلب واحتمالية الوفاة لدى مرضى وحدة العناية المركزة، وخاصة المصابين بأمراض القلب

كلمات مفتاحية: إصابة عضلة القلب؛ كوفيد - 19؛ وفيروس كورونا 2؛ أمراض القلب والأوعية الدموية؛ الدلائل الحيوية للقلب.

Introduction

Coronavirus disease 2019 (COVID-19), formerly known as 2019 novel coronavirus, is caused by an infection with severe acute respiratory syndrome coronavirus 2 (SARS CoV-2), which was discovered for the first time in December 2019 in China (Guzik et al., 2020; Lee et al., 2021; Zhang & Holmes, 2020). SARS CoV-2 is a member of the coronavirus group, which has a crown-like morphology and consists of four structural proteins known as spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins (Taha & Haboub, 2020). The SARS CoV-2 infection occurs through the coupling of the S-protein located on the surface of the virus with angiotensin-converting enzyme 2 (ACE2), which acts as a receptor for the virus. Moreover, it is reported that the binding affinity of the SARS CoV-2 S protein to ACE2 receptors is nearly 10 to 20-fold higher than that of SARS-CoV-1, making it easier to spread from human to human. ACE2 receptors are highly expressed in the cells of lungs and seem to be the main gateway for the virus (Hoffmann et al., 2020; Lu et al., 2020; Zou et al., 2020). They are also present in significant levels in the heart and blood vessels, which suggests that SARS CoV-2 can infect the cardiovascular system via binding to these receptors, causing cardiovascular complications (Hoffmann et al., 2020; Zou et al., 2020). Several reports showed that COVID-19 patients had symptoms of cardiovascular system abnormality, which influences the prognosis and deterioration of COVID-19 disease as well as worsened clinical outcomes among COVID-19 patients with preexisting cardiovascular diseases and increased mortality rates (Deng & Peng, 2020; Grasselli et al., 2020; Guo et al., 2020; Luo et al., 2021; Nishiga et al., 2020; Ruan et al., 2020; S. Shi et al., 2020; Yang et al., 2020; Zhou et al., 2020) .

The mechanisms of cardiovascular injury caused by SARS CoV-2 infection have not been fully clarified, but it is supposed that SARS CoV-2 affects the cardiovascular system through multiple mechanisms, including direct injury, immune injury, hypoxia injury, and psychological injury. Despite the fact that SARS CoV-2 mostly affects the respiratory system, it can directly infect cardiomyocytes through blood circulation, triggering inflammation, apoptosis, and necrosis of cardiomyocytes, thereby resulting in acute myocardial injury and myocarditis (W. Chen et al., 2020). Accordingly, upon entry into cardiomyocytes, SARS CoV-2 rapidly replicates and triggers a strong immune response, which results in cytokine storm syndromes and heart tissue damage (Channappanavar & Perlman, 2017; Cirillo et al., 2014; S. S. Li et al., 2003; Liu et al., 2016). Hypoxia associated with severe SARS CoV-2 infection could induce myocardial injury, leading to cardiac insufficiency and heart failure (Guan et al., 2020; MacLaren et al., 2020; Yang et al., 2020). In addition, it has been reported that patients with COVID-19 have different degrees of psychological stress, which may increase catecholamine release and stimulate sympathetic nerve activity, leading to a number of cardiovascular dysfunctions (Ueyama et al., 2008). In general, detection and diagnosis of cardiovascular complications are performed by evaluating specific cardiac biomarkers, including cardiac troponin I (cTn), creatine kinase MB (CK-MB), D-dimer, lactate

dehydrogenase (LDH), prothrombin time (PT), and activated partial thromboplastin time (PTT). Numerous studies showed a significantly increased level of cTnI, CK-MB, LDH, and D-dimer among COVID-19 patients, and the mortality rate was much higher in those patients than in patients with normal levels (Gohar et al., 2017; S. Shi et al., 2020; Wan et al., 2020; D. Wang et al., 2020).

According to the health annual report 2021 in Palestine, the total number of reported deaths in Palestine was 17273, of which 7140 (41.3%) were in Gaza Strip, and the leading cause of death in Gaza Strip was cardiovascular diseases (29.3%), while COVID-19 was the second cause of death (24%), (moh.ps, 2022). Regarding COVID-19, as of February 2022, there had been 647,203 confirmed cases of COVID-19 in Palestine, of which 245,917 were in Gaza Strip (WHO, 2022). Despite the rapid spread of COVID-19 disease, accompanied by an increase in the number of deaths in the Gaza Strip, there has been no study so far to explain the effect of COVID-19 on patients with cardiovascular diseases, as well as the correlation between COVID-19 and the risk of cardiovascular complications. So, we seek to study the impact of SARS CoV-2 on COVID-19 patients with pre-existing cardiovascular diseases who were admitted to the intensive care unit (ICU) in Gaza Strip and to assess the association between COVID-19 mortality and the pre-existing cardiovascular diseases among patients.

Methods and Patients

Study design and settings

This study was a prospective cross-sectional study that assessed the effect of COVID-19 on cardiac biomarkers in cardiovascular disease patients who were infected by COVID-19 and entered the ICU. The study was carried out from December 2021 to March 2022 on cardiovascular disease patients who were infected by COVID-19 and admitted to the ICUs at the European Gaza Hospital, Nasser Hospital. An informed consent was obtained from each subject or subject's guardian, after the approval of the experimental protocol by the responsible committee on human experimentation at Al-Azhar University of Gaza and from the research and ethics committee in Palestine (Helsinki). The ethical approval number is PHRC/HC/1033/22.

Study population

Patients were included in the study if they were admitted with SARS-CoV-2 infection confirmed by the real-time polymerase chain reaction (RT-PCR) of nasal swab samples. In this study, 60 adult participants of both genders were admitted to the ICU at the European Gaza Hospital and Nasser Hospital in the Gaza Strip. The participants were divided into three groups: group A (20 COVID-19 patients with cardiovascular diseases); group B (control group, 20 patients with cardiovascular diseases who didn’t have COVID-19); group C (20 COVID-19 patients who didn’t have cardiovascular diseases). Patients who have not been admitted to the ICU, whether they have cardiovascular diseases and/or COVID-19, kidney diseases, cancer, or any other life-threatening disease, were excluded from the study.

Data collection

During participants admission to the ICU at the European Gaza Hospital and Nasser Hospital, peripheral blood samples were collected from all participants on day 1 of ICU admission. Serum levels of cardiac biomarkers including cTnI, CK-MB, D-dimer, and LDH were measured as well as

determination of PT and PT. PT and PTT were also evaluated on day 10 of the ICU admission. During the study period, clinical records and laboratory results for each participant were obtained from the participant's file. Abnormal cardiac biomarkers were defined as: cTnI > 40 pg/ml, CK-MB > 25 IU/L, D-Dimer > 0.50 mg/L, LDH > 350 IU/L, PT (11-15 sec), and PTT (25-35 sec).

Statistical analysis

Graphics and statistical analyses were carried out using GraphPad Prism software (San Diego, CA, USA). Data were presented as mean ± SD. Comparisons between two different groups were performed using unpaired Student's t test, comparisons between the parameters in the same group were performed using paired Student's t test, and multiple comparisons among the different groups were performed using ANOVA test. For all tests, P values ≤ 0.05 were considered significant (* $p \leq 0.05$, ** $p < 0.01$, *** $p < 0.001$).

Results

Demographic characteristics of the study population

Table 1 shows the characteristics of the 60 participants included in this study according to the inclusion criteria. The mean age was 62 ± 1.2 years with a range of 53-77 years in group A, 60 ± 1.5 years with a range of 41-83 years in group B, while in group C the mean age was 57 ± 1.7 years with a range of 40-78 years. The study included both genders, as among group A, 9 patients were male (45%) and 11 (55%) patients were female; 12 of the patients in group B were male (60%) and 8 (40%) patients were female; and the ratio of male to female was 1:1 in group C. In addition, 15 (75%) patients in group A were from European Gaza Hospital, and 5 (25%) patients were from Nasser Hospital. In group B, the proportion of patients from both hospitals was equal (50%), while 13 (65%) patients in group C were from European Gaza Hospital, and 7 (35%) were from Nasser Hospital. Hypertension (HTN) was the most common cardiovascular comorbidity in groups A and B patients (95% and 100%, respectively). Among patients of group A, 10% (n= 2) were diagnosed with ischemic heart disease (IHD), 15% (n= 3) with congestive heart failure (CHF), 5% (n= 1) with atrial fibrillation (AF), and 25% (n= 5) with diabetes mellitus (DM). In group B, the number of patients diagnosed with IDH and DM was equal (3 for each), and the number of patients with CHF and AF was also equal (2 for each). Finally, our findings showed that having SARS-CoV-2 infection was associated with a significantly worse progression, where there was a 5-fold and 3-fold increase in the need for invasive mechanical ventilation among COVID-19 patients with pre-existing cardiovascular diseases compared to patients in groups B and C, respectively.

Effect of COVID-19 on the cardiac injury biomarkers

To evaluate the effect of SARS-CoV-2 infection on myocadiac injury in patients with pre-existing cardiovascular diseases, we analyzed the blood samples of all participants to measure the serum levels of cardiac biomarkers, including cTnI, CK-MB and LDH because myocardial injury is characterized by an increase in serum levels of cardiac biomarkers. Our findings showed a significant increase in the serum levels of cTnI among ICU hospitalized COVID-19 patients with pre-existing cardiovascular diseases (72.06 ± 12.39) compared with the ICU-hospitalized COVID-19 patients (44.31 ± 5.19) and the ICU-hospitalized patients with cardiovascular diseases (31.85 ± 5.53), indicating an increase in the degree of

myocardial damage (figure 1A, table 2). Moreover, we found that the ICU-hospitalized COVID-19 patients had a pronounced increase in the levels of cTnI compared with the ICU-hospitalized patients with cardiovascular diseases. Figure 1B shows the changes in the serum levels of CK-MB among all participants. There were clear differences in the serum levels of CK-MB among patients of group A (42.56 ± 5.19) in comparison to patients of groups B and C (24.53 ± 3.73, 27.63 ± 2.58, respectively), while we did not show any significant change in CK-MB levels between the ICU-hospitalized patients with cardiovascular diseases (24.53 ± 3.73) and the ICU-hospitalized COVID-19 patients (27.63 ± 2.58). Regarding LDH, the results in figure 1C revealed a sharp increase in the concentration of LDH in ICU-hospitalized COVID-19 patients with cardiovascular diseases (1490 ± 128.2) compared with other groups. In addition, ICU-hospitalized COVID-19 patients also had an increase in the concentration of LDH (1161 ± 65.7) compared with ICU-hospitalized patients with cardiovascular diseases only. These findings suggest that SARS-CoV-2 infection in patients with pre-existing cardiovascular diseases could increase the degree of myocardial injury.

Effect of SARS-CoV-2 infection on coagulation parameters

It was reported that SARS-CoV-2 infection was associated with various coagulation problems, which could lead to more vascular complications. Here, we assessed the effect of COVID-19 disease on coagulation homeostasis by evaluating the coagulation parameters, including D-dimer, PT and PTT. We were able to determine the values of PT, and PTT in all participants at the ICU admission (day 1) and at day 10 of the ICU admission, whereas for the D-dimer, we were able to measure it at the ICU admission (day 1) only (table 3). Figure 2A shows that the differences in PT values among all participants were not noticeable at the time of ICU admission (day 1). However, on day 10 of ICU admission, there was a significant increase in PT among COVID-19 patients with pre-existing cardiovascular diseases (18.9 ± 4.2 sec) compared with other patients (figure 2B). After that, we estimated the changes in PT during ICU hospitalization. Our results revealed that SARS-CoV-2 infection significantly increased PT values during ICU hospitalization, and the increase was more obvious in patients with pre-existing cardiovascular diseases (day 1: 14.1 ± 1.6 sec, day 10: 18.9 ± 4.2 sec, p value= 0.001) (figure 2 C). With respect to PPT, we found that COVID-19 patients had an increase in the mean of PPT at day 1 of ICU admission (group A: 30.2 ± 2.6 sec, group C: 31.1 ± 1.7 sec, p value= 0.01) compared with non-COVID-19 patients (group B: 27.1 ± 1.6 sec) (figure 3 A). The increase in PTT continued during ICU hospitalization, and it was more significant in both COVID-19 patients with and without pre-existing cardiovascular diseases (42.1 ± 9.2, 40.4 ± 5.8 sec, respectively) compared with non-COVID-19 patients (30.1 ± 5.2 sec) (figures 3 B, C). Then, we evaluated the changes in the serum levels of D-dimer among the patients. According to our findings, COVID-19 patients of groups A and C had significantly higher levels of D-dimer than group B patients (figure 3D). Although both patients of groups A and C showed an increase in the serum levels of D-dimer, the rise was more pronounced among COVID-19 patients with pre-existing cardiovascular diseases (5.82 ± 1.1 mg/dL, p value= 0.04). These results indicate that infection with SARS-CoV-2 may disrupt coagulation homeostasis, mainly in patients with cardiovascular diseases.

4. High mortality rate was observed among COVID-19 ICU hospitalized patients with preexisting cardiovascular diseases

Finally, we studied the relationship between mortality rate and SARS-CoV-2 infection among the ICU-hospitalized patients. In general, we found that severe cases of COVID-19 were associated with a higher death rate mainly among patients with preexisting cardiovascular diseases (n= 9, 45%) compared with patients of group B (n= 1, 5%) as well as patients of group C (n= 4, 20%) (table 1, figure 4). In addition, the results showed that the mortality rate was higher in patients with severe myocardial injury. Figure 4A displayed that 13 (65%) of the ICU-hospitalized patients with preexisting cardiovascular diseases had severe myocardial injury, of whom 9 patients died. The findings also showed that 9 (45%) of the ICU-admitted COVID-19 patients without prior cardiovascular diseases had severe myocardial injury, where 4 of them died (figure 4C). On the other hand, only 4 patients (20%) in the ICU-hospitalized due to cardiovascular diseases had severe myocardial injury, and one of them died (figure 4B). These results propose that severe SARS-CoV-2 infection could highly increase the probability of death among ICU-hospitalized patients, regardless of underlying cardiovascular status.

Discussion

This study is a prospective cross-sectional study, that assessed the effect of COVID-19 on cardiac biomarkers in patients with cardiovascular diseases who were infected by SARS-CoV2 and entered the ICU at the European Gaza Hospital and Nasser Hospital in the Gaza Strip, Palestine. Pre-existing cardiovascular diseases and/or cardiovascular risk factors make COVID-19 patients more likely to develop severe COVID-19 outcomes and mortality (Grasselli et al., 2020; Guo et al., 2020; Luo et al., 2021; Nishiga et al., 2020; S. Shi et al., 2020). Additionally, SARS-CoV2-infected patients are at a higher risk of developing cardiovascular complications, which affect the progression and outcomes of COVID-19 disease (Du et al., 2020). In this study, we evaluated changes in the levels of cTnI, CK-MB, and LDH in the peripheral blood of the study population at their ICU admission because these cardiac biomarkers are crucial for determining the extent of cardiac injury.

Molecular studies have demonstrated that SARS-CoV-2 uses the ACE2 receptor for cell entry through the activation of the viral outer membrane spike protein (Scialo et al., 2020). ACE2 is mainly expressed in the lung but can also be expressed in the circulatory system in the endothelial cells of arteries and veins as well as the myocardial pericytes (L. Chen et al., 2020). During COVID-19 infection, cardiovascular damage mediated by SARSCoV-2 may result from different mechanisms: direct myocardial damage by viral entry through ACE2, leading to myocardial cell damage and inflammation; indirect myocardial injury due to ACE2 downregulation following viral replication, with subsequent hyperactivation of the Ang II/AT1 system, responsible for proinflammatory, vasoconstrictive, and prooxidant effects; indirect myocardial injury through the activation of some immune cells, which can result in a cytokine storm with high levels of cytokines as interleukin-2 (IL-2), IL-7, IL-10, and tumor necrosis factor. In general, the cytokine storm is observed in severe cases of COVID-19 and can cause multiorgan damage such as lung injury and myocardial injury (Clerkin et al., 2020; Del Prete et al., 2022). Moreover, some inflammatory components can exert a negative inotropic effect, promote cardiomyocyte apoptosis

and fibrosis, and induce the release of procoagulant factors (Clerkin et al., 2020; Del Prete et al., 2022).

Our findings showed a significant increase in the serum levels of cTnI among ICU-hospitalized COVID-19 patients with pre-existing cardiovascular diseases compared with the ICU-hospitalized COVID-19 patients and the ICU-hospitalized non-COVID-19 patients with cardiovascular diseases. We also found that the ICU-hospitalized COVID-19 patients had a pronounced increase in the levels of cTnI compared with the ICU-hospitalized non-COVID-19 patients with cardiovascular diseases. In support of our findings, the results of a recent multi-center study performed in six hospitals in the United Kingdom, which included 434 COVID-19 patients, showed more significant increase in cTnI levels among 288 (66%) patients who had cardiovascular diseases or cardiovascular disease risk factors (Papageorgiou et al., 2022). Moreover, several studies reported a substantial elevation of cTnI levels in non-ICU hospitalized COVID-19 patients who were subsequently admitted to the ICU due to developing an acute myocardial injury (Huang et al., 2020; Lippi et al., 2020; S. Shi et al., 2020). In one of the most heterogeneous cohorts studied, which included 2163 patients admitted to a New York City hospital system, Smilowitz and colleagues found that myocardial injury developed in 665 (30.7%) cases with an increase in the level of cTnI (Smilowitz et al., 2020). They also found that critical illness (54.1% versus 28.9%) was more frequent in patients with myocardial injury. Regarding the mortality rate among the hospitalized patients, their results were also well-matched with our findings, where they revealed that in-hospital death was higher in COVID-19 patients with myocardial injury compared with those without myocardial injury (37.0% vs. 15.4%). On the other hand, some investigations indicated that an abnormal rise in cTnI levels may not be a clinically sufficient indicator of myocardial damage and increased mortality. For example, Giustino and co-authors performed a retrospective, multi-center international study to evaluate the clinical outcomes of hospitalized COVID-19 patients. They found that the risk of in-hospital mortality was more pronounced in COVID-19 patients with echocardiographic abnormalities as well as elevated cTnI levels compared to COVID-19 patients with cTnI elevation alone (Giustino et al., 2020).

Regarding CK-MB, which is predominant in the myocardium and is considered as the secondary substitute for troponins as a marker to diagnose acute myocardial injury, we found that there were clear differences in the serum levels of CK-MB among ICU-hospitalized COVID-19 patients with cardiovascular diseases in comparison to other study participants. Similar to our findings, the data collected from a meta-analysis that included 55 studies (11,791 COVID-19 patients were involved) showed that patients with severe COVID-19 or non-survivor status had significantly greater CK-MB levels than those with mild cases or survival status (Zinellu et al., 2021). Another study done by Wang et al., revealed that 36 out of 138 (26.1%) COVID-19 patients were admitted to the ICU with severe symptoms, and all of them had a significant increase in serum cTnI and CK-MB levels compared to non-ICU patients (D. Wang et al., 2020). In addition, two meta-analysis studies observed that elevated levels of CK-MB were associated with increased COVID-19 severity and mortality (J.-W. Li et al., 2020; L. Shi et al., 2020). Despite children having a lesser prevalence of COVID-19 than adults, and children with COVID-19 have also rarely reported developing heart muscle injury,

interesting results of one study showed that of 243 pediatric patients with COVID-19, 103 (42.4%) cases had an abnormal increase in serum CK-MB levels (J.-J. Wang et al., 2021). As a result, a rise in serum CK-MB may be a potential risk factor for myocardial injury following SARS-CoV2 infection.

For LDH, our results revealed a sharp increase in the concentration of LDH in ICU-hospitalized COVID-19 patients with cardiovascular diseases compared with other groups. In agreement with our study, a meta-analysis of 102 studies found that patients with severe COVID-19 illnesses had higher levels of LDH than those with milder cases and that patients who did not need critical care therapy had considerably lower levels of LDH than those who did (Fialek et al., 2022). According to an additional meta-analysis of 3117 hospitalized COVID-19 patients, the levels of LDH were 1.5 times higher in severe COVID-19 cases than in non-severe COVID-19 cases (Bao et al., 2020). The results of Tao and his colleagues also agree with our findings in terms of the mortality rate among COVID-19 patients. They have reported the results of 799 COVID-19 patients, of whom 62% had cardiovascular complications, and 77% died as a result of cardiac injury. They found that levels of cTnT and LDH were markedly higher in the deceased patients.

Then we evaluated the effect of SARS-CoV2 infection on vascular damage by assessing the changes in the levels of D-dimer as well as PT and PTT among the participants. D-dimer is the product resulting from the fibrinolytic solubilization of fibrin, so the increase in its level indicates that there is hypercoagulation and secondary fibrinolysis in the body (Giannitsis et al., 2017). According to our findings, we found that infection with SARS-CoV2 may disrupt coagulation homeostasis mainly in patients with cardiovascular diseases, where ICU-hospitalized COVID-19 patients with cardiovascular diseases showed a significant increase in the levels of D-dimer than ICU-hospitalized COVID-19 patients without cardiovascular diseases and ICU hospitalized non-COVID-19 patients with cardiovascular diseases. Consistent with our findings, two different retrospective studies (a single-center study including 138 COVID-19 patients and a multi-center study including 191 COVID-19 patients) revealed a significant increase in D-dimer levels among COVID-19 patients on ICU admission compared with non-ICU patients, and the increased D-dimer levels on ICU admission were highly associated with more in-hospital deaths (Huang et al., 2020; D. Wang et al., 2020). Moreover, an early report from China including 1099 patients with COVID-19 revealed that 46% of COVID-19 patients had elevated D-dimer levels, and 60% of them had severe complications (Guan et al., 2020). These findings may suggest that the patients were possibly in hyperfibrinolytic state.

Regarding the differences in PT and PPT values among all participants, there was no noticeable change at the time of ICU admission (day 1). However, on day 10 of ICU admission, there was a significant increase in PT and PPT values during ICU hospitalization, and the increase was more obvious in COVID-19 patients with pre-existing cardiovascular diseases compared with other patients. A preliminary report from Tongji Hospital in China was similar to our study, in which 183 patients with COVID-19 showed that the mortality rate was 11.5% and that non-survivors had significantly higher D-dimer levels, a longer PT, and PPT than survivors at the time of admission (Tang et al., 2020). So, prolongation of both PT and PTT may indicate the patients were in the transition from a high coagulating state into a fibrinolytic state due to the excessive

consumption of coagulating factors. Based on the study results, the levels of D-dimer, PT, and PTT were significantly higher among patients with COVID-19, suggesting that hypercoagulation was likely present in patients with COVID-19 at the early stage, and hypercoagulation is closely related to disease progression. This was followed by the activation of fibrinolysis.

Overall, we assume that the lack of diversity in results between studies can be regarded as an inability to perform extensive studies. This is due to several reasons, such as fear and caution in dealing with serious COVID-19 cases, the focus on saving the lives of critically ill patients, which lessens the chance of following patients to understand the mechanism of action of the virus, the rapid deterioration of the patient's status and the inability to predict the complications associated with critical cases of COVID-19, and the restrictions imposed due to the spread of the COVID-19 epidemic, which reduces the ability to follow patients properly and reduces the diversity in selecting the study sample.

Besides the results obtained, we believe that there are some limitations to our study. The first of these limitations is the small size of the study population, which was related to the difficulty of covering more hospitals in Gaza Strip due to the imposed restrictions of the COVID-19 pandemic. The second limitation is that we did not evaluate the levels of cardiac biomarkers during the patient's follow-up due to the imposed restrictions of the COVID-19 pandemic and financial constraints. The third limitation is the inability to assess other cardiac biomarkers such as ischemia-modified albumin, heart-type fatty acid-binding protein, atrial natriuretic peptide, brain natriuretic peptide, and glycogen phosphorylase isoenzyme BB, which are critical in the diagnosis of cardiac injury and cardiovascular complications. The fourth limitation is that we were unable to follow up the COVID-19 patients due to the imposed restrictions, and we think that the longitudinal follow-up of the COVID-19 patients might provide a more accurate picture about the effect of SARS-CoV2 infections on clinical outcomes, mainly in the presence of cardiovascular diseases.

In conclusion, our findings provided to the growing body of literature showing that SARS-CoV-2 infection is linked to the development of cardiovascular complications because it raises the risk of myocardial injury and alters the coagulation system, which are primarily exacerbated during COVID-19 severity, leading to an increased risk of COVID-19 mortality. As the pathogenesis of myocardial injury caused by SARS-CoV2 infection is not fully known, further prospective studies involving multiple centers with a larger sample size are required to explain the exact mechanism by which SARS-CoV2 infection can affect the cardiovascular system.

Tables

Table 1: Demographic characteristics of the study population

Characteristic	Group A (n=20)	Group B (n=20)	Group C (n=20)
Age (mean, range year)	62 ± 1.2 (53-77)	60 ± 1.5 (41-83)	57 ± 1.7 (40-78)
Gender (n, %) • Male • Female	 9 (45%) 11 (55%)	 12 (60%) 8 (40%)	 10 (50%) 10 (50%)
Comorbidities (n, %) • HTN • IHD • CHF • AF • DM	 19 (95%) 2 (10%) 3 (15%) 1 (5%) 5 (25%)	 20 (100%) 3 (15%) 2 (10%) 2 (10%) 3 (15%)	 -
Hospital (n, %) • Nasser Hospital • European Gaza Hospital	 5 (15%) 15 (75%)	 10 (50%) 10 (50%)	 7 (35%) 13 (65%)
Type of respiratory support • Oxygen • Non-invasive mechanical ventilation • Invasive mechanical ventilation	 3 (15%) 8 (40%) 9 (45%)	 7 (35%) 13 (65%) 0	 5 (25%) 12 (60%) 3 (15%)
Death (n, %)	9 (45%)	1 (5%)	4 (20%)
HTN: Hypertension; IHD: Ischemic Heart Disease; CHF: Congestive Heart Failure; AF: Atrial Fibrillation; DM: Diabetes Mellites			

Table 2: Effect of COVID-19 on the cardiac injury biomarkers

Parameters	Group A (n=20)	Group B (n=20)	Group C (n=20)	P value
Cardiac troponin I (cTnI) (pg/dL)	72.06 ± 12.39	31.85 ± 5.53	44.31 ± 5.19	0.006
Creatine kinase MB (CK-MB) (mg/dL)	42.56 ± 5.19	24.53 ± 3.73	27.63 ± 2.58	0.004
Lactate dehydrogenase (LDH) (IU/L)	1490 ± 128.2	562 ± 40.5	1161 ± 65.7	0.0001
P-values were calculated by one way ANOVA test for the measured parameters in the three groups				

Table 3: Serum levels of coagulation markers during ICU hospitalization

Parameters	Admission Time	Group A (n=20)	P value	Group B (n=20)	P value	Group C (n=20)	P value
Prothrombin time (PT) (Seconds)	Day 1	14.1 ± 1.6	0.01	13.1 ± 0.8	0.03	13.7 ± 1.1	0.02
	Day 10	18.9 ± 4.2		15.1 ± 2.2		17.8 ± 1.4	
Activated partial thromboplastin time (PTT) (Seconds)	Day 1	30.2 ± 2.6	0.001	27.1 ± 1.6	0.06	31.1 ± 1.7	0.001
	Day 10	42.1 ± 9.2		30.1 ± 5.2		40.4 ± 5.8	
D-Dimer (mg/dL)	Day 1	5.82 ± 1.1		1.53 ± 0.2		4.03 ± 0.6	
	Day 10	-----		-----		----	

P-values were calculated by comparing between the mean ± SD of PT and PTT at the ICU admission (day 1) and on the 10th day of ICU admission (day 10) in each group using paired Student t-test (*p ≤ 0.05, ** p < 0.01, *** p < 0.001).

Figures

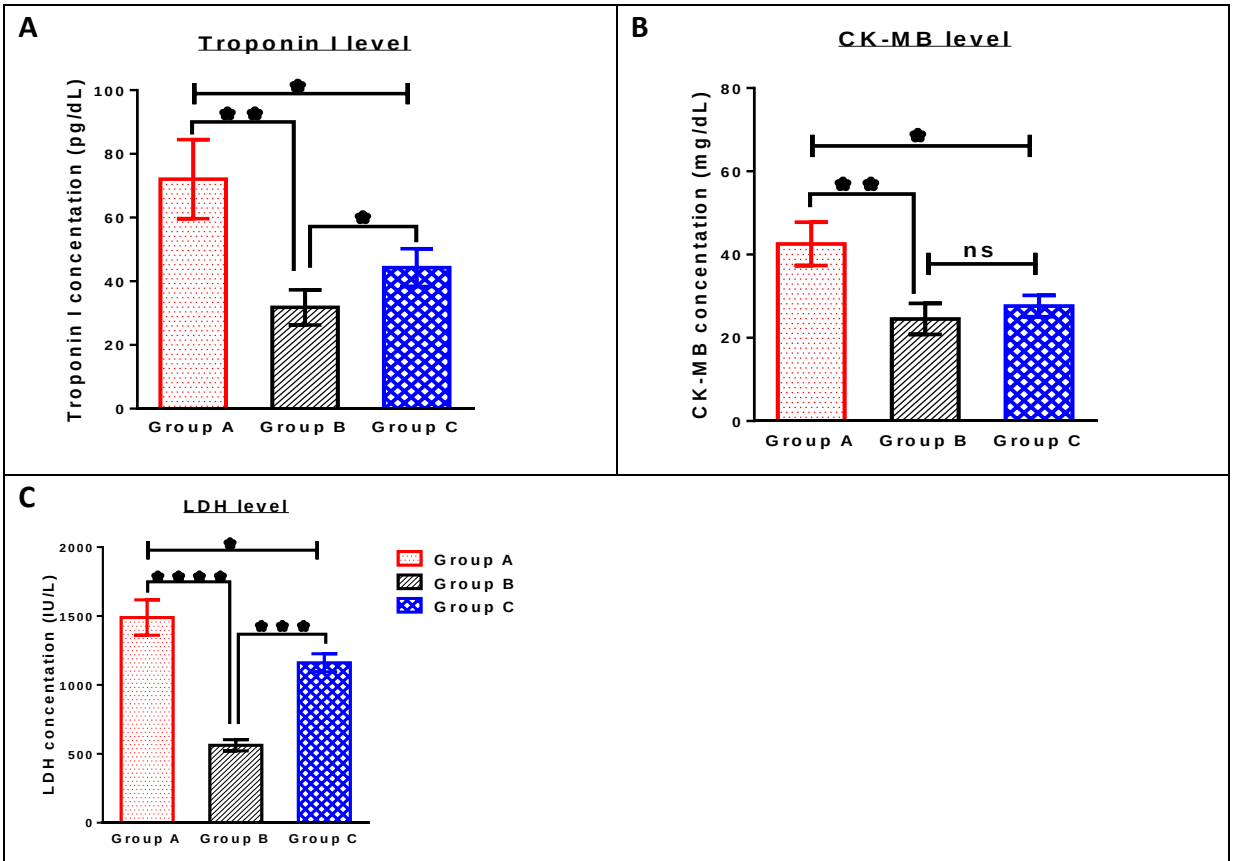

Figure 1: COVID-19 patients with pre-existing cardiovascular diseases showed high degree of cardiac injury. Peripheral blood samples were obtained from all participants to measure the concentrations of troponin I (pg/dL), CK-MB (mg/dL) and LDH (IU/L). (A-C) Bar graphs displaying the mean ± SD of troponin I (pg/dL), CK-MB (mg/dL) and LDH (IU/L) levels in the peripheral blood of COVID-19 patients with pre-existing cardiovascular diseases (Group A, n=20, red columns), patients with pre-existing cardiovascular diseases only (Group B, n=20, black columns), and COVID-19 patients without pre-existing cardiovascular diseases (Group C, n=20, blue columns). Comparisons between each two groups were performed using unpaired Student t-test (*p ≤ 0.05, ** p < 0.01, *** p < 0.001). Multiple comparisons were performed using one way ANOVA test.

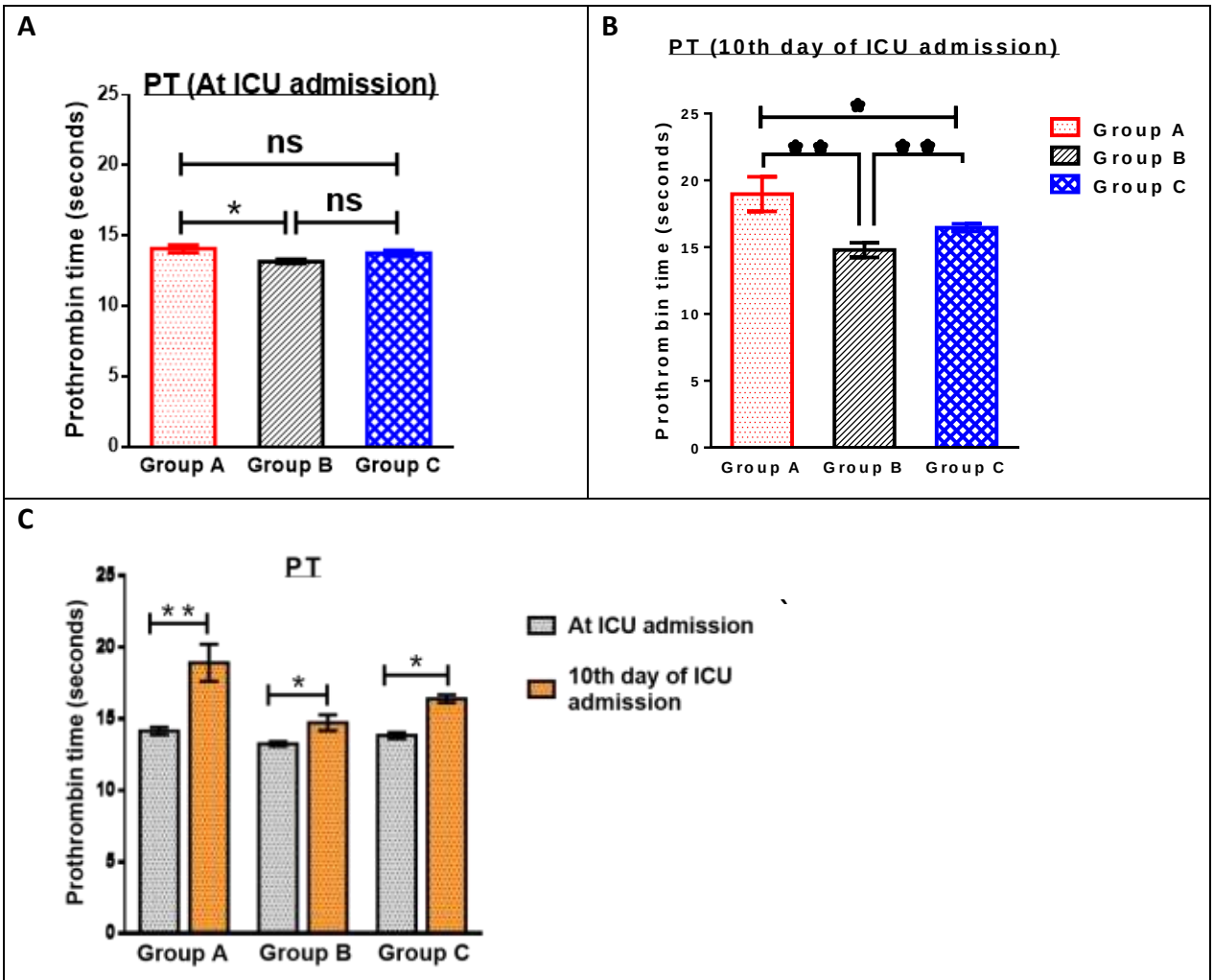

Figure 2: COVID-19 patients with pre-existing cardiovascular diseases showed higher prothrombin time. Prothrombin time, PT (seconds) was calculated for all participants before the ICU admission and on the 10th day of ICU admission. (A, B) Bar graphs presenting the mean ± SD of PT (seconds) before the ICU admission (A) and on the 10th day of ICU admission (B) for COVID-19 patients with pre-existing cardiovascular diseases (Group A, n=20, red columns), patients with pre-existing cardiovascular diseases only (Group B, n=20, black columns), and COVID-19 patients without pre-existing cardiovascular diseases (Group C, n=20, blue columns). (C) Bar graphs comparing between the mean ± SD of PT (seconds) before the ICU admission (Black columns) and on the 10th day of ICU admission (Orange columns) for the patients in each group. Comparisons between each two groups and parameters were performed using paired and unpaired Student t-test (*$p \leq 0.05$, ** $p < 0.01$, *** $p < 0.001$). Multiple comparisons were performed using one way ANOVA test.

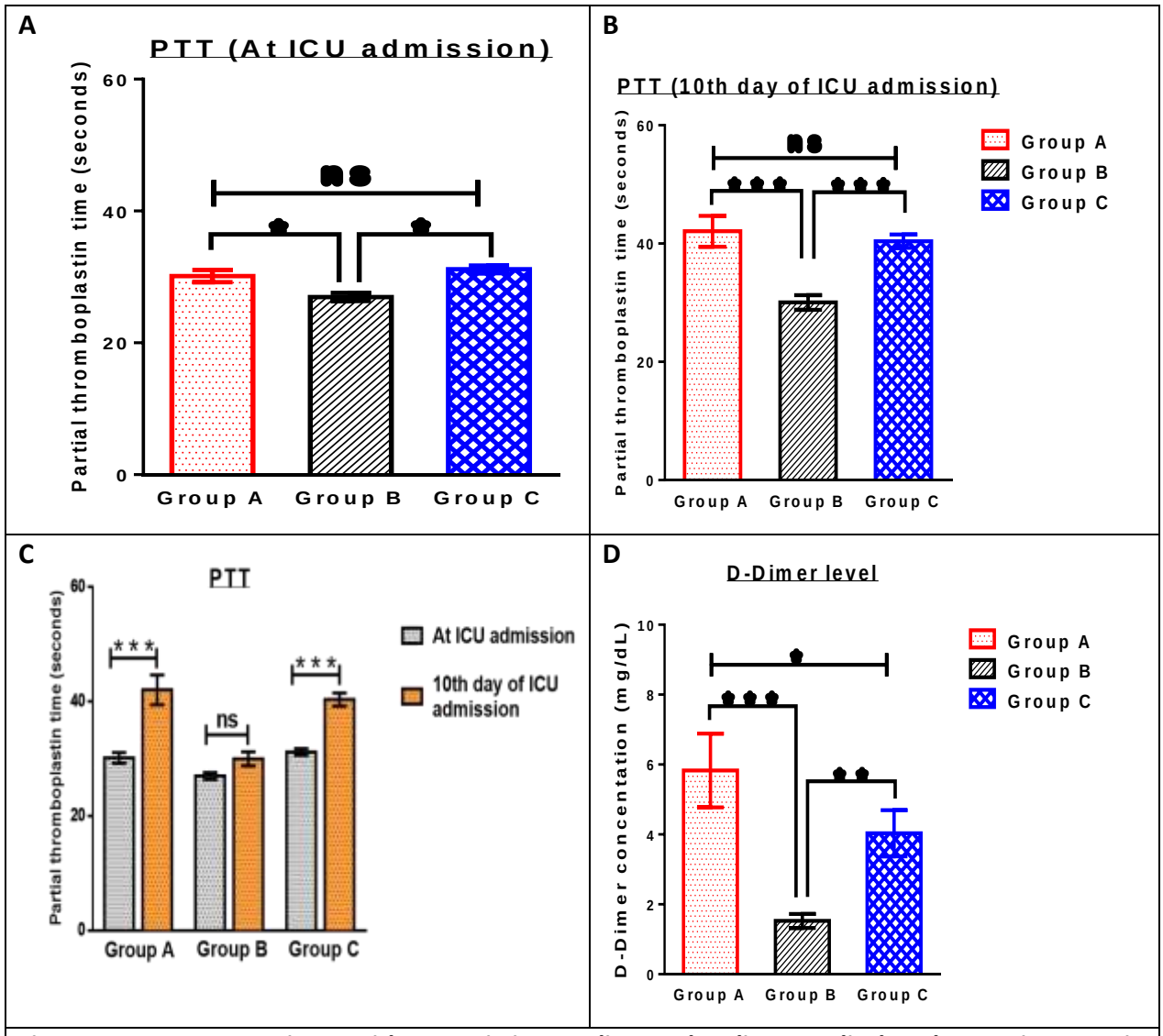

Figure 3: COVID-19 patients with pre-existing cardiovascular diseases displayed more increase in partial thromboplastin time and D-Dimer levels. Peripheral blood samples were obtained to measure the levels of D-Dimer (mg/dL) in all participants. Partial thromboplastin time, PTT (seconds) was calculated for all participants before the ICU admission and on the 10th day of ICU admission. (A, B, D) Bar graphs presenting the mean ± SD of PTT (seconds) before the ICU admission (A) and on the 10th day of ICU admission (B), and the mean ± SD of D-Dimer (mg/dL) levels in the peripheral blood of COVID-19 patients with pre-existing cardiovascular diseases (Group A, n=20, red columns), patients with pre-existing cardiovascular diseases only (Group B, n=20, black columns), and COVID-19 patients without pre-existing cardiovascular diseases (Group C, n=20, blue columns). (C) Bar graphs comparing between the mean ± SD of PTT (seconds) before the ICU admission (Black columns) and on the 10th day of ICU admission (Orange columns) for the patients in each group. Comparisons between each two groups and parameters were performed using paired and unpaired Student t-test (*$p \leq 0.05$, ** $p < 0.01$, *** $p < 0.001$). Multiple comparisons were performed using one way ANOVA test.

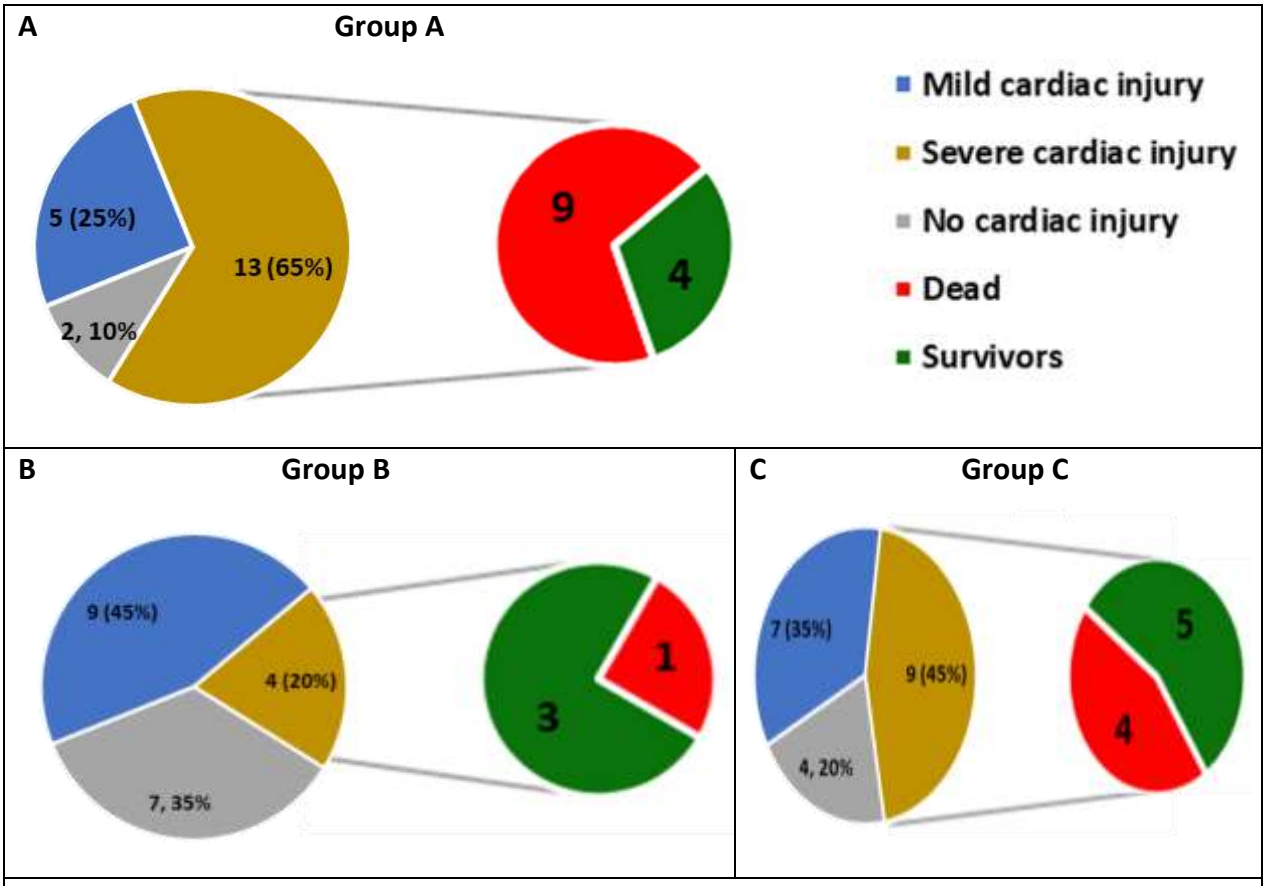

Figure 4. High mortality rate was observed among COVID-19 ICU hospitalized patients with preexisting cardiovascular diseases. Based on the obtained results of troponin I (pg/dL), CK-MB (mg/dL) and LDH (IU/L) levels, participants were classified into three classes: patients with no cardiac injury (Gray color), patients with mild cardiac injury (Blue color), patients with severe cardiac injury (Gold color). The mortality rate was calculated in each group (Red color: number and proportion of dead; green color: number and proportion of survivors). (A-C) Pie chart showing the percentages of COVID-19 patients with pre-existing cardiovascular diseases (Group A, n=20), patients with pre-existing cardiovascular diseases only (Group B, n=20), and COVID-19 patients without pre-existing cardiovascular diseases (Group C, n=20), respectively.

References:

Bao, J., Li, C., Zhang, K., Kang, H., Chen, W., & Gu, B. (2020). Comparative analysis of laboratory indexes of severe and non-severe patients infected with COVID-19. Clinica Chimica Acta; International Journal of Clinical Chemistry, 509, 180–194.

Channappanavar, R., & Perlman, S. (2017). Pathogenic human coronavirus infections: Causes and consequences of cytokine storm and immunopathology. Seminars in Immunopathology, 39(5), 529–539. https://doi.org/10.1007/s00281-017-0629-

Chen, L., Li, X., Chen, M., Feng, Y., & Xiong, C. (2020). The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. Cardiovascular Research, 116(6), 1097–1100. https://doi.org/10.1093/cvr/cvaa078

Chen, W., Lan, Y., Yuan, X., Deng, X., Li, Y., Cai, X., Li, L., He, R., Tan, Y., Deng, X., Gao, M., Tang, G., Zhao, L., Wang, J., Fan, Q., Wen, C., Tong, Y., Tang, Y., Hu, F., … Tang, X. (2020). Detectable 2019-nCoV viral RNA in blood is a strong indicator for the further

clinical severity. Emerging Microbes & Infections, 9(1), 469–473. https://doi.org/10.1080/22221751.2020.1732837

Cirillo, P., Cimmino, G., D'Aiuto, E., Di Palma, V., Abbate, G., Piscione, F., Golino, P., & De Palma, R. (2014). Local cytokine production in patients with Acute Coronary Syndromes: A look into the eye of the perfect (cytokine) storm. International Journal of Cardiology, 176(1), 227–229. https://doi.org/10.1016/j.ijcard.2014.05.035

Clerkin, K. J., Fried, J. A., Raikhelkar, J., Sayer, G., Griffin, J. M., Masoumi, A., Jain, S. S., Burkhoff, D., Kumaraiah, D., Rabbani, L., Schwartz, A., & Uriel, N. (2020). COVID-19 and Cardiovascular Disease. Circulation, 141(20), 1648–1655. https://doi.org/10.1161/CIRCULATIONAHA.120.046941

Del Prete, A., Conway, F., Della Rocca, D. G., Biondi-Zoccai, G., De Felice, F., Musto, C., Picichè, M., Martuscelli, E., Natale, A., & Versaci, F. (2022). COVID-19, Acute Myocardial Injury, and Infarction. Cardiac Electrophysiology Clinics, 14(1), 29–39. https://doi.org/10.1016/j.ccep.2021.10.004

Deng, S.-Q., & Peng, H.-J. (2020). Characteristics of and Public Health Responses to the Coronavirus Disease 2019 Outbreak in China. Journal of Clinical Medicine, 9(2), 575. https://doi.org/10.3390/jcm9020575

Du, Y., Tu, L., Zhu, P., Mu, M., Wang, R., Yang, P., Wang, X., Hu, C., Ping, R., Hu, P., Li, T., Cao, F., Chang, C., Hu, Q., Jin, Y., & Xu, G. (2020). Clinical Features of 85 Fatal Cases of COVID-19 from Wuhan. A Retrospective Observational Study. American Journal of Respiratory and Critical Care Medicine, 201(11), 1372–1379. https://doi.org/10.1164/rccm.202003-0543OC

Fialek, B., Pruc, M., Smereka, J., Jas, R., Rahnama-Hezavah, M., Denegri, A., Szarpak, A., Jaguszewski, M. J., Peacock, F. W., & Szarpak, L. (2022). Diagnostic value of lactate dehydrogenase in COVID-19: A systematic review and meta-analysis. Cardiology Journal, 29(5), 751–758. https://doi.org/10.5603/CJ.a2022.0056

Giannitsis, E., Mair, J., Christersson, C., Siegbahn, A., Huber, K., Jaffe, A. S., Peacock, W. F., Plebani, M., Thygesen, K., Möckel, M., Mueller, C., Lindahl, B., & Biomarker Study Group of the European Society of Cardiology (ESC) Acute Cardiovascular Care Association (ACCA). (2017). How to use D-dimer in acute cardiovascular care. European Heart Journal. Acute Cardiovascular Care, 6(1), 69–80. https://doi.org/10.1177/2048872615610870

Giustino, G., Croft, L. B., Stefanini, G. G., Bragato, R., Silbiger, J. J., Vicenzi, M., Danilov, T., Kukar, N., Shaban, N., Kini, A., Camaj, A., Bienstock, S. W., Rashed, E. R., Rahman, K., Oates, C. P., Buckley, S., Elbaum, L. S., Arkonac, D., Fiter, R., … Goldman, M. E. (2020). Characterization of Myocardial Injury in Patients With COVID-19. Journal of the American College of Cardiology, 76(18), 2043–2055. https://doi.org/10.1016/j.jacc.2020.08.069

Gohar, A., Chong, J. P. C., Liew, O. W., den Ruijter, H., de Kleijn, D. P. V., Sim, D., Yeo, D. P. S., Ong, H. Y., Jaufeerally, F., Leong, G. K. T., Ling, L. H., Lam, C. S. P., & Richards, A. M. (2017). The prognostic value of highly sensitive cardiac troponin assays for adverse events in men and women with stable heart failure and a preserved vs. Reduced ejection fraction. European Journal of Heart Failure, 19(12), 1638–1647. https://doi.org/10.1002/ejhf.911

Grasselli, G., Zangrillo, A., Zanella, A., Antonelli, M., Cabrini, L., Castelli, A., Cereda, D., Coluccello, A., Foti, G., Fumagalli, R., Iotti, G., Latronico, N., Lorini, L., Merler, S.,

Natalini, G., Piatti, A., Ranieri, M. V., Scandroglio, A. M., Storti, E., … COVID-19 Lombardy ICU Network. (2020). Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA, 323(16), 1574–1581. https://doi.org/10.1001/jama.2020.5394

Guan, W., Ni, Z., Hu, Y., Liang, W., Ou, C., He, J., Liu, L., Shan, H., Lei, C., Hui, D. S. C., Du, B., Li, L., Zeng, G., Yuen, K.-Y., Chen, R., Tang, C., Wang, T., Chen, P., Xiang, J., … Zhong, N. (2020). Clinical Characteristics of Coronavirus Disease 2019 in China. New England Journal of Medicine, 382(18), 1708–1720. https://doi.org/10.1056/NEJMoa2002032

Guo, T., Fan, Y., Chen, M., Wu, X., Zhang, L., He, T., Wang, H., Wan, J., Wang, X., & Lu, Z. (2020). Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). JAMA Cardiology, 5(7), 811–818. https://doi.org/10.1001/jamacardio.2020.1017

Guzik, T. J., Mohiddin, S. A., Dimarco, A., Patel, V., Savvatis, K., Marelli-Berg, F. M., Madhur, M. S., Tomaszewski, M., Maffia, P., D'Acquisto, F., Nicklin, S. A., Marian, A. J., Nosalski, R., Murray, E. C., Guzik, B., Berry, C., Touyz, R. M., Kreutz, R., Wang, D. W., … McInnes, I. B. (2020). COVID-19 and the cardiovascular system: Implications for risk assessment, diagnosis, and treatment options. Cardiovascular Research, 116(10), 1666–1687. https://doi.org/10.1093/cvr/cvaa106

Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., Schiergens, T. S., Herrler, G., Wu, N.-H., Nitsche, A., Müller, M. A., Drosten, C., & Pöhlmann, S. (2020). SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell, 181(2), 271-280.e8. https://doi.org/10.1016/j.cell.2020.02.052

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., Cheng, Z., Yu, T., Xia, J., Wei, Y., Wu, W., Xie, X., Yin, W., Li, H., Liu, M., … Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet (London, England), 395(10223), 497–506. https://doi.org/10.1016/S0140-6736(20)30183-5

Lee, C. C. E., Ali, K., Connell, D., Mordi, I. R., George, J., Lang, E. M., & Lang, C. C. (2021). COVID-19-Associated Cardiovascular Complications. Diseases (Basel, Switzerland), 9(3), 47. https://doi.org/10.3390/diseases9030047

Li, J.-W., Han, T.-W., Woodward, M., Anderson, C. S., Zhou, H., Chen, Y.-D., & Neal, B. (2020). The impact of 2019 novel coronavirus on heart injury: A Systematic review and Meta-analysis. Progress in Cardiovascular Diseases, 63(4), 518–524. https://doi.org/10.1016/j.pcad.2020.04.008

Li, S. S., Cheng, C., Fu, C., Chan, Y., Lee, M., Chan, J. W., & Yiu, S. (2003). Left ventricular performance in patients with severe acute respiratory syndrome: A 30-day echocardiographic follow-up study. Circulation, 108(15), 1798–1803. https://doi.org/10.1161/01.CIR.0000094737.21775.32

Lippi, G., Lavie, C. J., & Sanchis-Gomar, F. (2020). Cardiac troponin I in patients with coronavirus disease 2019 (COVID-19): Evidence from a meta-analysis. Progress in Cardiovascular Diseases, 63(3), 390–391. https://doi.org/10.1016/j.pcad.2020.03.001

Liu, Q., Zhou, Y., & Yang, Z. (2016). The cytokine storm of severe influenza and development of immunomodulatory therapy. Cellular & Molecular Immunology, 13(1), 3–10. https://doi.org/10.1038/cmi.2015.74

Lu, R., Zhao, X., Li, J., Niu, P., Yang, B., Wu, H., Wang, W., Song, H., Huang, B., Zhu, N., Bi,

Y., Ma, X., Zhan, F., Wang, L., Hu, T., Zhou, H., Hu, Z., Zhou, W., Zhao, L., … Tan, W. (2020). Genomic characterisation and epidemiology of 2019 novel coronavirus: Implications for virus origins and receptor binding. The Lancet, 395(10224), 565–574. https://doi.org/10.1016/S0140-6736(20)30251-8

Luo, J., Zhu, X., Jian, J., Chen, X., & Yin, K. (2021). Cardiovascular disease in patients with COVID-19: Evidence from cardiovascular pathology to treatment. Acta Biochimica Et Biophysica Sinica, 53(3), 273–282. https://doi.org/10.1093/abbs/gmaa176

MacLaren, G., Fisher, D., & Brodie, D. (2020). Preparing for the Most Critically Ill Patients With COVID-19: The Potential Role of Extracorporeal Membrane Oxygenation. JAMA, 323(13), 1245–1246. https://doi.org/10.1001/jama.2020.2342

Ministry of health. (2022). Retrieved May 21, 2023, from https://site.moh.ps/index/Books/BookType/2/Language/ar

Nishiga, M., Wang, D. W., Han, Y., Lewis, D. B., & Wu, J. C. (2020). COVID-19 and cardiovascular disease: From basic mechanisms to clinical perspectives. Nature Reviews. Cardiology, 17(9), 543–558. https://doi.org/10.1038/s41569-020-0413-9

Papageorgiou, N., Sohrabi, C., Prieto Merino, D., Tyrlis, A., Atieh, A. E., Saberwal, B., Lim, W.-Y., Creta, A., Khanji, M., Rusinova, R., Chooneea, B., Khiani, R., Wijesuriya, N., Chow, A., Butt, H., Browne, S., Joshi, N., Kay, J., Ahsan, S., & Providencia, R. (2022). High sensitivity troponin and COVID-19 outcomes. Acta Cardiologica, 1–8. https://doi.org/10.1080/00015385.2021.1887586

Ruan, Q., Yang, K., Wang, W., Jiang, L., & Song, J. (2020). Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Medicine, 46(5), 846–848. https://doi.org/10.1007/s00134-020-05991-x

Scialo, F., Daniele, A., Amato, F., Pastore, L., Matera, M. G., Cazzola, M., Castaldo, G., & Bianco, A. (2020). ACE2: The Major Cell Entry Receptor for SARS-CoV-2. Lung, 198(6), 867–877. https://doi.org/10.1007/s00408-020-00408-4

Shi, L., Wang, Y., Wang, Y., Duan, G., & Yang, H. (2020). Meta-Analysis of Relation of Creatine kinase-MB to Risk of Mortality in Coronavirus Disease 2019 Patients. The American Journal of Cardiology, 130, 163–165. https://doi.org/10.1016/j.amjcard.2020.06.004

Shi, S., Qin, M., Shen, B., Cai, Y., Liu, T., Yang, F., Gong, W., Liu, X., Liang, J., Zhao, Q., Huang, H., Yang, B., & Huang, C. (2020). Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. JAMA Cardiology, 5(7), 802–810. https://doi.org/10.1001/jamacardio.2020.0950

Smilowitz, N. R., Jethani, N., Chen, J., Aphinyanaphongs, Y., Zhang, R., Dogra, S., Alviar, C. L., Keller, N., Razzouk, L., Quinones-Camacho, A., Jung, A. S., Fishman, G. I., Hochman, J. S., & Berger, J. S. (2020). Myocardial Injury in Adults Hospitalized With COVID-19. Circulation, 142(24), 2393–2395. https://doi.org/10.1161/CIRCULATIONAHA.120.050434

Taha, M., & Haboub, L. (2020). Novel coronavirus disease (COVID-19): Causes, pathogenesis and efforts of treatment. Fabad Journal of Pharmaceutical Sciences, 279–296.

Ueyama, T., Kasamatsu, K., Hano, T., Tsuruo, Y., & Ishikura, F. (2008). Catecholamines and estrogen are involved in the pathogenesis

of emotional stress-induced acute heart attack. Annals of the New York Academy of Sciences, 1148, 479–485. https://doi.org/10.1196/annals.1410.079

Wan, S., Xiang, Y., Fang, W., Zheng, Y., Li, B., Hu, Y., Lang, C., Huang, D., Sun, Q., Xiong, Y., Huang, X., Lv, J., Luo, Y., Shen, L., Yang, H., Huang, G., & Yang, R. (2020). Clinical features and treatment of COVID-19 patients in northeast Chongqing. Journal of Medical Virology, 92(7), 797–806. https://doi.org/10.1002/jmv.25783

Wang, D., Hu, B., Hu, C., Zhu, F., Liu, X., Zhang, J., Wang, B., Xiang, H., Cheng, Z., Xiong, Y., Zhao, Y., Li, Y., Wang, X., & Peng, Z. (2020). Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. JAMA, 323(11), 1061–1069. https://doi.org/10.1001/jama.2020.1585

Wang, J.-J., Hu, Z., & Chen, J.-Y. (2021). Characteristics of abnormal serum creatine kinase-MB levels in children with COVID-19. World Journal of Pediatrics, 17(3), 326–328. https://doi.org/10.1007/s12519-020-00402-z

World Health Organization. (2022). Regional Office for the Eastern Mediterranean. Retrieved May 21, 2023, from http://www.emro.who.int/opt/information-resources/covid-19-situation-reports.html

Yang, X., Yu, Y., Xu, J., Shu, H., Xia, J., Liu, H., Wu, Y., Zhang, L., Yu, Z., Fang, M., Yu, T., Wang, Y., Pan, S., Zou, X., Yuan, S., & Shang, Y. (2020). Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: A single-centered, retrospective, observational study. The Lancet. Respiratory Medicine, 8(5), 475–481. https://doi.org/10.1016/S2213-2600(20)30079-5

Zhang, Y.-Z., & Holmes, E. C. (2020). A Genomic Perspective on the Origin and Emergence of SARS-CoV-2. Cell, 181(2), 223–227. https://doi.org/10.1016/j.cell.2020.03.035

Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., Xiang, J., Wang, Y., Song, B., Gu, X., Guan, L., Wei, Y., Li, H., Wu, X., Xu, J., Tu, S., Zhang, Y., Chen, H., & Cao, B. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet (London, England), 395(10229), 1054–1062. https://doi.org/10.1016/S0140-6736(20)30566-3

Zinellu, A., Sotgia, S., Fois, A. G., & Mangoni, A. A. (2021). Serum CK-MB, COVID-19 severity and mortality: An updated systematic review and meta-analysis with meta-regression. Advances in Medical Sciences, 66(2), 304–314. https://doi.org/10.1016/j.advms.2021.07.001

Zou, X., Chen, K., Zou, J., Han, P., Hao, J., & Han, Z. (2020). Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Frontiers of Medicine, 14(2), 185–192. https://doi.org/10.1007/s11684-020-0754-0.