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# Investigation of Serum N-terminal pro B Type Natriuretic Peptide as Early Predictors Marker of Severity in Iraqi Patients with COVD-19

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**ABSTRACT**— In patients with coronavirus disease 2019 (COVID-19), cardiac biomarkers have been linked to disease severity and mortality. Among COVID-19 patients in the hospital, heart damage is a common complication. We didn't know, however, whether or not NT-proBNP might predict the fate of patients with severe COVID-19. We aimed to evaluate the impact on severity of an early investigate of NT-proBNP as cardiac biomarkers in Iraqi patients with COVID-19. In a case-control study, 90 "COVID-19" patients and 90 healthy volunteers were compared. COVID-19 patients were categorized into mild/moderate, severe, and no survived patients categories based on the severity of their illness. Blood samples were taken from the sick and healthy groups, and all demographic and clinical characteristics were recorded. Enzyme-linked immunosorbent assay were used to evaluate BNP, and IL-6 levels. Spectrophotometers were used to determine the lipid profile and renal tests. The levels of (BNP) were significantly higher among groups of patients However, the level of (BNP) was significantly higher in non-survive and severe, mild cases of COVID-19 groups compared with healthy group. Serum (BNP) levels were significantly high in non-survive (125.44 ± 21.27) compared sever Patients (113.59 ± 33.11) compared with mild/moderate case of patients group (59.11 ± 19.42) and healthy (26.6 ± 9.32) ($P < 0.001$). Indicating it to be an independent predictor in the coronavirus disease. Serum (BNP) levels were correlated a significant positively with Age, D-dimer, ferritin,,TG, LDL-C, and IL-6 levels. While, a significant negative correlated with TC, and Lymph.%. Serum (BNP) concentration were increased in sever and critical patients with COVID-19 compared with mild/moderate case. NT-proBNP might be an independent risk factor for in hospital death in patients with severe COVID-19.

**KEYWORDS:** COVID-19, "SARS-CoV-2", N-terminal pro B type natriuretic peptide, Severity

## 1. INTRODUCTION

The recent rapid spread of SARS-CoV-2 has garnered attention because of the seriousness of the issue. Cardiovascular problems have risen to prominence as a leading cause of morbidity and mortality in patients infected with coronavirus disease 2019 (COVID-19) [1], [2]. To determine which individuals with COVID-19 need close monitoring and urgent therapy, an early risk stratification is essential [1]. With limited people and material resources, as is common during COVID-19 surges [3]. this is critical Patients with COVID-19 have also been reported to have cardiac involvement in addition to respiratory dysfunction [4], [5].

Biomarkers of inflammations and immune-activations have been sought as a means of developing better

predictive models for the management of patients with the more severe forms of the disease, which is typically characterized by respiratory failure with or without multi-organ dysfunctions.

“COVID-19”patients' organs and systems have been shown to have considerable changes, which has led to the investigation of additional, organ-specific sbiomarkers. The presence sof myocardial injury sin “COVID-19”patientsswith or without a history of cardiovascular disease, such as myocarditis, sacute coronary syndromes, and arrhythmias, has been swell-documented [6]. During earlier historical epidemics, cardiovascular consequences of acute pneumonia, such as myocarditis and worsening of cardiac insufficiency, were widely reported [7].

Notably, cardiac abnormalities are independently related with an elevated risk of mortality in this population. While the exact mechanisms involved in the initiations and progression of COVID-19-relatedsmyocardial injury have yet tosbe explained, the predictive capacity of numerous circulating markers of myocardial damage, including creatine kinase (CK) and troponin, is increasingly being investigated [8], [9]. Heart failure, another cardiac consequence, has been found in approximately one-fourth of “COVID-19”patients and has-been associated with an elevated risk of unfavorable outcomes [10], [11].

Myocardial damage is a prevalent consequence of coronavirus disease 2019 (COVID-19) and has been linked to poor outcomes. The majority of studies and definitions, however, have concentrated on cardiac troponins and cardiac magnetic resonance imaging. Data relating natriuretic peptides are sparse [12] B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) are quantifiable plasma biomarkers that typically reflect hemodynamics cardiac stress and, as such, play a pivotal role in the diagnosis and management of hearts failure (HF). Moreover, they have demonstrated superior predictive accuracy compared to sophisticated multivariable risk ratings among patients with pulmonary disease [13].

Following “SARS-CoV-2” infection, embolism and pneumonia are also common side effects that might occur. Even though a variety of cardiovascular diseases have been linked to “COVID-19”(such as acute arterials thrombotic events, venous thromboembolic disease and arrhythmias) [14].

Patients with “COVID-19”who experience a myocardial damage during hospitalization, as revealed by cardiac troponin, may face a greater mortality risk than those who do not experience a myocardial injury, according to previous research [15], [16]. Retrospective studies from Europe and the United States [17], [18] have validated these findings. Patients with “COVID-19”may benefit from early diagnosis of cardiac involvement through the evaluation of cardiac biomarkers at the time of admission to the hospital. natriuretic peptide increase and these clinical manifestations may or may not be connected. It would also be excellent to identify natriuretic peptides as a powerful independent predictor for prognostic classification in “COVID-19”patients because of their wide availability and their ability to be tested both at hospital admission and throughout follow-up [12].

As a biomarker for the diagnosis and estimate of prognosis in cardiac insufficiency, NT-proBNP is an excellent indicator of cardiac dysfunction. The goal of this study was to determine if the severity of “COVID-19”was related to the patient's serum NT-proBNP level at arrival.

## 2. MATERIALS AND METHODS

The study comprised 90spatients (min.-max.ages:45-65 years) infected with COVID-19 who were admitted to AL- Amal Hospital for communicable disease in Najaf, Iraq. During the period from Dec., 2021 to June, 2022, after receiving approval from the Iraqi Ministry of Health and Environment's Ethics Committee, and

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all participants gave informed consent before the study began. These patients were diagnosed by quantitative RT-PCRsand chest X-ray or CT scan at the7-12 days after the onsets of symptoms. Patients were divided too three subgroups: (40) mild/moderate COVID-19 if they had fever, respiratory manifestations, and radiological evidence of pneumonia, (30) severe case, and (20) critically ill after then dead.

COVID-19 patients were collected as admission and the diseases severity was assessed using Murray scores [19] a patient was considered to have sever COVID-19, if he or she met any of the following:

1. Repertory distraction (≥ 30 /min)
2. Resting oxygen saturated ≤ 90% or
3. Arterial oxygen (PaO2) / fractions of inspired oxygen ≤ 300 mmHg. or
4. Repertory failure requiring mechanicals ventilation and requires intensive care unit (ICU), and critical patient dead considered as Non-survived.

This study was authorized by the local medical ethics committee, and all participants provided informed permission prior to the start of the trial. The patients were registered and given a file to record their information, including name, age, sex, weight, and height.

As a control group, ninety apparently healthy subjects were selected. Their age and sex distributions was comparable to that of the patients.

Exclusion criteria include volunteers with any chronic diseases, including diabetes, cardiovascular disease, and long-term oral corticosteroid medication, cancer and renal disease patients, as well as smokers, pregnant, those with systemic immunological disease, and those with thyroid gland disease were all excluded.

Medical syringes were used to collect fivesmilliliters of venoussblood fromseach patient and controlsgroup. Two milliliters were placed in EDTA tubes for CBC analysis, and the remaining blood was placed in gel tubessand left at room temperature for 10 to 15 minutessfor coagulation before being centrifuged for 10 minutes at (3000 x g) to provide the serum. Eppendorf tubes were used to isolate and store at (-20 $^{o}$C) the sera until biochemical analysis could be performed.

Completesblood count (CBC) wassmeasured by using auto hematology analyzer (linear, Spain). The concentration of (NT-proBNP), (IL-6) assays were determined in serum samples by Enzyme linked immune sorbent assay (ELISA) (Melsin, Chain) generally measured within the first 24–48 h from admission. Also, the total cholesterol (TC), triglycerides (TG), High density lipoprotein –Cholesterol (HDL-C), Creatinine (Cr), and blood urea nitrogen (BUN) were measured by using colorimetric methods kits (Cobas, Roche). Serumsferritin, and D-dimer levels were measured by fluorescencesimmunoassay (FIA) (ichromaTM).

## 3. RESULTS and DISCUSSION

### *3.1 Demographic Characteristics of Patients and Control groups*

The demographic and clinical features of the study groups, which included (mean ± SD) of the 90 patients recruited in this study to compared with 90 healthy volunteers. Patients groups divided according to "COVID-19"severity to three sub- groups as shown in table (1) and figure (1).

**Table (1):** Demographic and clinical characteristics of the patient's categories and control groups

| Variables | Covid-19 Patients Groups | Healthy | P. value |
|---|---|---|---|

| | Dead Mean ± SD | Severe Mean ± SD | Mild / moderate Mean ± SD | group Mean ± SD | |
|---|---|---|---|---|---|
| **No.** | **20** | **30** | **40** | **90** | **……..** |
| **No. (Male/Female)** | **(12/8)** | **(20/10)** | **(28/12)** | **(54/36)** | **.....** |
| **Age, (years)** | **67.20 ± 1.64** | **57.11 ± 4.64** | **57.20 ± 5.21** | **57.26 ± 5.76** | **A= 0.03 B= 0.001 C= 0.001 D= 0.001** |
| **BMI, ($Kg/m^2$)** | **30.11 ± 1.25** | **27.87 ± 3.24** | **26.60 ± 3.43** | **24.81 ± 3.43** | **A= 0.04 B= 0.01 C= 0.07 D= 0.001** |
| **SBP , (mmHg)** | **140.60 ± 43.34** | **136.34 ± 22.33** | **132.33 ± 10.44** | **130.83 ± 6.52** | **A= 0.03 B= 0.01 C= 0.01 D= 0.001** |
| **DBP, (mmHg)** | **76.40 ± 31.532** | **79.94 ± 15.69** | **80.33 ± 4.90** | **80.83 ± 5.09** | **A= 0.05 B= 0.06 C= 0.05 D= 0.05** |
| **SpO2** | **82.32 ± 3.52** | **89.71 ± 1.69** | **95.89 ± 3.693** | **99.57 ± 0.019** | **A= 0.001 B= 0.0001 C= 0.01 D=0.01** |
| **Lymph.%** | **10.24 ± 2.750** | **10.26 ± 1.62** | **10.79 ± 5.87** | **23.26 ± 5.62** | **A= 0.73 B= 0.0001 C= 0.0001 D=0.001** |
| **Neutro.%** | **90.96 ± 5.81** | **85.26±11.62** | **76.43±10.82** | **44.48±10.18** | **A= 0.01 B= 0.001 C= 0.001 D=0.001** |
| **NLR** | **8.88 ± 1.94** | **8.06 ± 1.62** | **7.21 ± 2.12** | **2.15 ± 0.53** | **A= 0.06 B= 0.0001 C= 0.0001 D=0.001** |
| **Urea , (mg/dL)** | **17.08 ± 8.66** | **20.10 ± 3.58** | **11.39 ± 6.08** | **3.73 ± 0.54** | **A= 0.35 B= 0.25 C= 0.56 D= 7.64** |
| **Creatinine, (mg/dL)** | **1.34 ± 0.82** | **0.96 ± 0.42** | **0.79 ± 0.02** | **0.78 ± 0.04** | **A= 0.61 B= 0.73 C= 0.71 D= 0.00** |
| **TG , (mg/dL)** | **125.0 ± 47.75** | **242.0 ± 48.33** | **288.16±57.11** | **297.0 ± 60.22** | **A=0.86 B=0.72 C=0.36 D=0.00** |

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| | | | | | |
|---|---|---|---|---|---|
| **TC, (mg/dL)** | **179.0 ± 24.30** | **176.21 ±24.47** | **170.11 ±14.51** | **156.22 ± 29.81** | **A=0.80<br>B=0.44<br>C=0.09<br>D=0.00** |
| **HDL-C, (mg/dL)** | **44.40 ± 10.88** | **36.33 ± 10.93** | **32.16 ± 19.37** | **28.32 ± 9.24** | **A= 0.72<br>B= 0.95<br>C= 0.65<br>D= 0.05** |
| **VLDL-C, (mg/dL)** | **25.40 ± 10.81** | **48.83 ±10.03** | **57.66 ± 19.23** | **59.63 ± 24.44** | **A=0.86<br>B= 0.72<br>C=0.36<br>D= 0.00** |
| **LDL-C, (mg/dL)** | **110.66 ± 17.60** | **92.33 ± 22.74** | **86.16 ± 10.85** | **69.0 ± 27.40** | **A =0.96<br>B= 0.29<br>C= 0.07<br>D= 0.08** |
| **D-Dimer, (ng/mL)** | **5573.02 ± 2722.22** | **3868.03 ± 2223.61** | **712.6 ± 300.90** | **266.14 ± 87.07** | **A =0.001<br>B= 0.0001<br>C =0.0001<br>D=0.001** |
| **Ferritin, (ng/mL)** | **1338.64 ± 686.43** | **1097.17 ± 628.21** | **651.54 ± 46.96** | **105.92 ± 34.73** | **A= 0.001<br>B =0.0001<br>C= 0.0001<br>D=0.001** |
| **IL-6, ( pg/mL)** | **831.2 ± 133.51** | **802.9 ± 147.76** | **362.50 ± 65.05** | **148.95 ± 51.59** | **A= 0.001<br>B=0.0001<br>C= 0.0001<br>D=0.001** |
| **NTproBNP, (pg/mL)** | **125.44 ± 21.27** | **113.59 ± 33.11** | **59.11 ± 19.42** | **26.6 ± 9.32** | **A= 0.0001<br>B =0.0001<br>C=0.0001<br>D=0.001** |

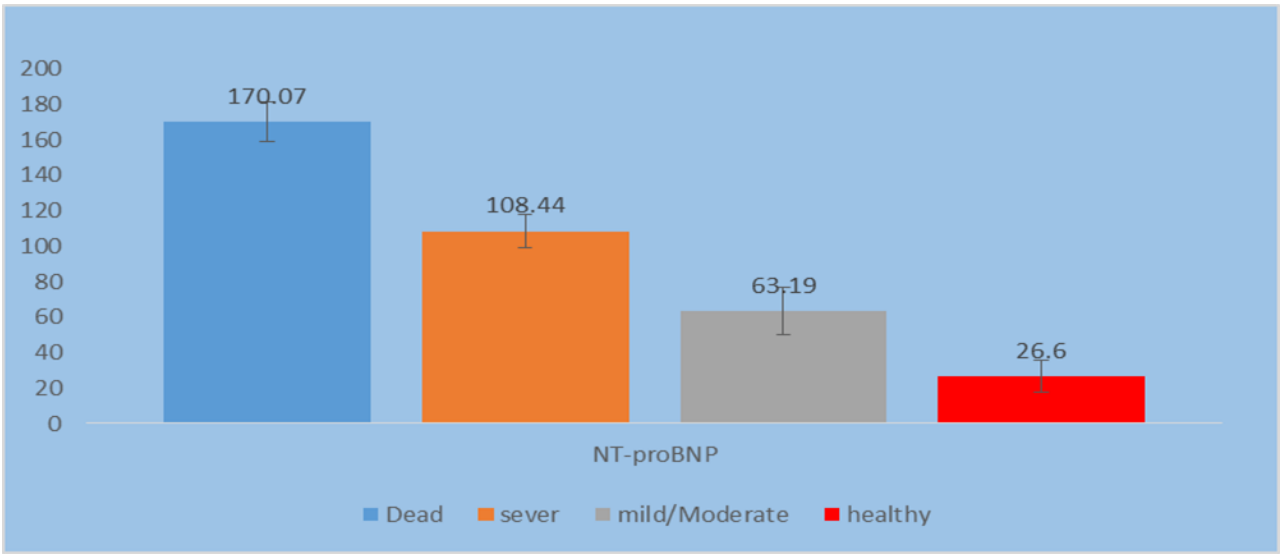

**Figure (1):** comparison of serum level NT proBNP in categories of COVID-19 patients severity

Data represented as Mean ± SD: standard deviation, BMI: body mass index, SBP: Systolic blood pressure, DBS diastolic blood pressure, NLR: Neutrophil% to Lymphocyte % ratio, BNP, IL-6: A= p. value (severe cases +mild/moderate cases), B= p. value (Severe cases + healthy group) and C= p. value (mild/moderate cases + healthy group), D= p. value (dead cases + healthy group) A= p-value (dead+ sever), B=p-value (dead+ moderate), C= p-value (sever+ moderate) D =p-value (total patients +healthy.)

The patients' mean age according to severity of "COVID-19"(57.11 ± 4.64 years; 58.20 ± 5.21 years) none significantly when compared with control groups age (57.26 ± 5.76 years). In the three disease severity categories, sex distributions (males more than females). "COVID-19"patients with severe illness have considerably higher mean BMI than patients with mild/moderate disease (27.87 ± 3.24 and 26.60 ± 3.43 $kg/m^2$, respectively; p = 0.04). The data of serum ferritin, D-Dimer,TG, and (IL-6) activity levels were significantly higher (1338.64 ± 6868.43), (5573.02 ± 2722.22), (242.00 ± 48.33), (176.21 ±24.47) and (802.9± 147.76) respectively. In "COVID-19"patients with severesdisease, based on clinical assessment or the necessity for hospitalizations or mechanical breathings or ICUstransfer, NT-proBNP levels were considerablysgreater than in patients with mild disease or those survived duringsfollow-up. D-dimer, a coagulation marker, is higher in individuals with covid-19, particularly in cases of severe disease. In table (2) shown a significant correlation between serum (NT-proBNP) levels with SpO2 neutrophils%, TG, TC, HDL-C, VLDL-C, LDL-C, D-sdimer, and ferritins levels in "COVID-19"patientssgroup.

**Table (2):** Correlation between serum (NT-proBNP) Level with clinical Parameters in "COVID-19"patients group

| variables | r | P. value |
|---|---|---|
| **Age (years)** | 0.061 | 0.164 |
| **BMI , ($kg/m^{2)}$** | -0.027 | 0.365 |
| **SBP , (mmHg)** | 0.14 | 0.071 |
| **DBP , (mmHg)** | 0.084 | 0.119 |
| **SpO2** | -0.59 | 0.0001 |
| **Lymph.%** | -0.11 | 0.238 |
| **Neutro.%** | 0.39 | 0.012 |
| **N/L Ratio** | 0.23 | 0.074 |
| **Urea, (mg/dL)** | 0.018 | 0.559 |
| **Creatinine, (mg/dL)** | 0.001 | 0.908 |
| **TG (mg/dl)** | -0.46 | 0.001 |
| **TC, (mg/dl)** | -0.42 | 0.001 |
| **HDL-C,(mg/dL)** | .-0.38 | 0.01 |
| **VLDL-C,(mg/dL)** | -0.57 | 0.124 |
| **LDL-C,(mg/dL)** | 0.33 | 0.438 |
| **D-Dimer, (ng/mL)** | 0.35 | 0.02 |
| **Ferritin, ( ng/mL)** | 0.47 | 0.001 |
| **IL-6, (pg/mL)** | 0.39 | 0.001 |

Data represented as Pearson Correlation Coefficient (r),BMI: body mass index, SBP: Systolic blood

pressure, DBS diastolic blood presser F: females, M: male TG: triglyceride, HDL-C: High .density lipoprotein .cholesterol, TC: total cholesterol, LDL-C: low density lipoprotein -cholesterol VLDL-C: Very Low Density Lipoprotein-Cholesterol, IL-6 : Interleukin 6

For the first time, in patients with severe COVID-19, researchers found a link between serum NT-proBNP levels and in-hospital death risk. “COVID-19”patients with high NT-proBNP levels were more likely to be older, have more cardiac damage signs, and have higher levels of systemic inflammatory markers [20]. While the inactive NT-proBNP has no biological effect, BNP binds to the guanylyl cyclase-coupled natriuretic receptors A and B, causing major physiological changes. There is an increase in the production of cyclic guanosine monophosphate (CGMP), which causes diuresis, snatriuresis, inhibition of the reninsangiotensin-aldosteronessystem, inhibition of fibrosis, cell apoptosis and inflammation (including suppression of superoxide generation by neutrophils), sand improvement in myocardial relaxation [21], [22].

It's worth noting that no human research have found any correlation betweensBNP levels and cyclic guanosines monophosphate concentrations. The reductions of neutrophil-inducedssuperoxidesproduction by nicotinamide adenine dinucleotide phosphates oxidase, which is mediated by BNP, is also hindered in the contexts of acute heart failures even when BNP concentrations are elevated [23]. BNP-related inhibition of superoxide release, albeit partially restored by pharmacological treatment, may lead to persistent tissue inflammation in heart failure, regardless of the presence or absence of COVID-19. NT-proBNP has a higher molecular mass, a longer half-life (>60 vs. 15–20 min), a higher degree of in-vivo glycosylation, and a lower degree of intra-individual biological variation compared to BNP [24].

In patients who had a high NT-proBNP level (> 88.64 pg/mL), the cumulative survival rate was decreased. In patients with severe COVID-19, NT-proBNP was revealed to be an independent predictor of in-hospital death after controlling for putative cofounders in distinct modes [25]. Studies have shown that NT-proBNP can predict mortality in patients with community-acquired pneumonia (CAP) [25]. For 30-day mortality prediction, NT-proBNP cut-off values of 1434.5 pg/mL and 1795.5 pg/mL were shown to be optimal. Complex combinations between preexisting disorders, relative ischemia, upregulation of the sympathetic system, systemic inflammation and direct pathogen-mediated injury to the cardiovascular system were thought to be responsible for the higher NT-proBNP in these cases [20].

A lower cutoff value for severe COVID-19 patients was used to predict poor outcomes, although this was still higher than the threshold used to diagnose heart failure (450 pg/mL for patients under 50 years old, 900 pg/mL for those between 50 and 75 years old, or 1800 pg/mL for those over 75 years old). The predictive value of plasma NTproBNP in COVID-19 patients with severe heart failure could not be fully attributed to virus-induced heart failure or hypoxia [26]. The significance of plasma in health and disease: a deeper knowledge Elevated NT-proBNP in severe COVID-19 patients may aid doctors in making appropriate decisions to lessen the likelihood of a negative result [27]. Increased cardiac stress results in the release of NT-proBNP.

Patients with COVID-19 had higher BNP/NT-proBNPsvalues than those without, which suggests that heart failure and related complications are a common occurrence in this population. There are numerous indicators that can assist the doctor in making an early diagnosis of heart disease and initiating pharmacological and other non-pharmacological treatments [28]. There needs to be more research to see if assessing BNPs/NT-proBNPsmay also be addedsinto “COVID-19”patient-specific prognostic algorithms [29]. Standardized mean differences(SMD) of BNP/NT-proBNP and D-dimer, myoglobin, LDH and

proscalcitonin have beensfound to besassociated withsindicators of pro-coagulantsactivity, tissue injury, and severe sepsis [30]. These indicators, on the other hand, have been found to have a significant impact on the severity and consequences of COVID-19. BNPs/NT-proBNP maysprovide complementing, rather than duplicate, informationsregarding the occurrence of cardiacs problems in individuals with COVID-19 [31].

NT-proBNP isssecreted in response to increased myocardialswall stress [32]. Chronic kidneys disease and proinflammatory moleculesssuch as interleukins1, C-reactive protein (CRP), lipopolysaccharide (LPS), as well as acute renal damage regulate it. According to the study, an elevated level of NT-proBNP was linked to an increased risk of cardiac, renal, and systemic inflammation [33], [34].

Existing evidence shows that unreported factors may have contributed to the observed heterogeneity in the SMD and patient and study characteristics that are not related to D-dimer, smyoglobin, LDH, or procalcitoninsconcentrations. The association betweensthe SMD values and the existencesof new onset vs. acute in chronic heart failure, asswell as information about the precise analytical procedures employed to determine BNP and NT-proBNPs concentrations, are examples of such variables [35], [36]. Univariate Cox proportional-hazards regression showed that these decision makers also contributed to the overall in-hospital mortality risk. However, after accounting for these variables in multivariate Cox, NTproBNP was found to be an independent risk factor. NT-predictive proBNP's value could be an indicator of the overall severity of "SARS-CoV-2" infection [37].

## 4. CONCLUSION

Finally, in COVID-19, higher levels of serum NT-proBNP are associated with both increased disease severity and increased mortality. If these cardiac biomarkers may be used to develop early prediction markers that aid in the early management and monitoring of this patient group, more research must be carried out.

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## 6. REFERENCES

[1] Z. Wu and J. M. McGoogan, "Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China," JAMA .2020, 323, 13 : 1239–42.

[2] D. Wang, B. Hu, C. Hu et al., "Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China," JAMA .2020, 323, 11 : 1061–69.

[3] Guan W-J, Ni Z-Y, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med .2020; 382 : 1708–20.

[4] Stefanini GG, Azzolini E, Condorelli G. Critical organizational issues for cardiologists in the "COVID-19"outbreak: a frontline experience from Milan, Italy. Circulation. 2020; 141 : 1597–9.

[5] Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with "COVID-19"in Wuhan, China. JAMA Cardiol. 2020 ; 5 : 802.

[6] Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. "COVID-19"and cardiovascular disease: from basic

mechanisms to clinical perspectives. Nat Rev Cardiol. (2020) 17 : 543–58.

[7] V. F. Corrales-Medina, D. M. Musher, S. Shachkina, and J. A. Chirinos, “Acute pneumonia and the cardiovascular system,” The Lancet.(2013), 381, 9865 : 496–505.

[8] Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of cardiac injury with mortality in hospitalized patients with “COVID-19”in Wuhan, China. JAMA Cardiol. (2020) 5 : 802–10.

[9] Yang J, Liao X, Yin W, Wang B, Yue J, Bai L, et al. Elevated cardiac biomarkers may be effective prognostic predictors for patients with COVID-19: a multicenter, observational study. Am J Emerg Med.(2021) , 39 : 34–41.

[10] Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al.. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. (2020), 368: 1091.

[11] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al.. Clinical course and risk factors for mortality of adult inpatients with “COVID-19”in Wuhan, China: a retrospective cohort study. Lancet. (2020) 395 : 1054–62.

[12] Caro-Codón J, Rey JR, Buño A, Iniesta AM, Rosillo SO, Castrejon-Castrejon S, Rodriguez-Sotelo L, Martinez LA, Marco I, Merino C, Martin-Polo L. Characterization of NT-proBNP in a large cohort of COVID-19 patients. European journal of heart failure. (2021)23(3) : 456-64.

[13] Gachpazan M, Mohammadinejad A, Saeidinia A, Rahimi HR, Ghayour-Mobarhan M, Vakilian F, Rezayi M. A review of biosensors for the detection of B-type natriuretic peptide as an important cardiovascular biomarker. Analytical and Bioanalytical Chemistry. (2021) Oct ; 413(24) : 5949-67.

[14] Baldini T, Asioli GM, Romoli M, Carvalho Dias M, Schulte EC, Hauer L, Aguiar De Sousa D, Sellner J, Zini A. Cerebral venous thrombosis and severe acute respiratory syndrome coronavirus-2 infection: a systematic review and meta-analysis. European journal of neurology. (2021) Oct; 28(10) : 3478-90.

[15] Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol (2020)5:811.
[16] Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with “COVID-19”in Wuhan, China. JAMA Cardiol.(2020)5:802.

[17] Lala A, Johnson KW, Januzzi JL, et al. Prevalence and impact of myocardial injury in patients hospitalized with “COVID-19”infection. J Am Coll Cardiol. (2020), 76 : 533–46.

[18] Lorente-Ros A, Monteagudo Ruiz JM, Rincón LM, Ortega Pérez R, Rivas S, Martínez-Moya R, Sanromán MA, Manzano L, Alonso GL, Ibáñez B, Zamorano JL. Myocardial injury determination improves risk stratification and predicts mortality in COVID-19 patients. Cardiol J. 2020; 27(5) : 489-96.

[19] Murray, J. F., M. A. Matthay, J. M. Luce, and M. R. Flick. .An Expanded Definition of the Adult Respiratory Distress Syndrome. Am Rev Respir Dis. (1988) 138, 720-723.

[20] Yang, Yang, et al. Exuberant elevation of IP-10, MCP-3 and IL-1ra during “SARS-CoV-2” infection is associated with disease severity and fatal outcome Med Rxiv (2020).03.02.20029975.

[21] Mohsin, H. S., Ali, H. A., and Al-Tu'ma, F. J. Assessment of von Willebrand Factor/ADAMTS13 Ratio and Vitamin K Levels as Predictor Markers for Severity of "COVID-19"Patients. Journal of Contemporary Medical Sciences, (2021). 7(5) : 303 – 307.

[22] Kamel, S. H., Al-Tu'ma, F. J. and Al-Saegh, R. M.. Angiotensin-Converting Enzyme Receptor Genotype and its Activity Level as Potential Predictors of the Severity "COVID-19"among Iraqi Patients. Journal of Contemporary Medical Sciences) 2021) : 7(6) : 384 – 91.

[23] Potter LR, Yoder AR, Flora DR, Antos LK, Dickey DM. Natriuretic peptides: their structures, receptors, physiologic functions and therapeutic applications. Handb Exp Pharmacol. (2009) 191: 341–66.

[24] Liu S, Ngo DT, Chong CR, Amarasekera AT, Procter NE, Licari G, et al.. Suppression of neutrophil superoxide generation by BNP is attenuated in acute heart failure: a case for 'BNP resistance'. Eur J Heart Fail. (2015) 17 : 475–83.

[25] Clerico A, Zaninotto M, Passino C, Plebani M. New issues on measurement of B-type natriuretic peptides. Clin Chem Lab Med. (2017) 56 : 32–9.

[26] Noman Wisam, Abdulameer, Hanaa Addai Ali, Ahmed Beseem Mahdi, and Rahman S Zabibah et al. "The Association between Serum Levels of Ferritin and D-Dimer with Liver Function Tests in Patients with COVID-19" Clin Schizophr Relat Psychoses15S (2021).

[27] Shaha KB, Manandhar DN, Cho JR, Adhikari A, KC MB. "COVID-19"and the heart: what we have learnt so far. Postgraduate Medical Journal. 2021 Oct 1;97(1152) : 655-66.

[28] Abdeen Y, Kaako A, Alnabulsi M, Okeh A, Meng W, Miller R. The prognostic effect of brain natriuretic peptide levels on outcomes of hospitalized patients with COVID-19. Avicenna Journal of Medicine. 2021 Jan;11(01) : 20-6.

[29] Zhang Y, Coats AJS, Zheng Z, Adamo M, Ambrosio G, Anker SD, et al.. Management of heart failure patients with COVID-19: a joint position paper of the Chinese Heart Failure Association & National Heart Failure Committee and the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. (2020) 22 : 941–56

[30] Paliogiannis P, Mangoni AA, Dettori P, Nasrallah GK, Pintus G, Zinellu A. D-Dimer Concentrations and "COVID-19"severity: a systematic review and meta-analysis. Front Public Health. (2020) 8 : 432

[31] Ghahramani S, Tabrizi R, Lankarani KB, Kashani SMA, Rezaei S, Zeidi N, et al.. Laboratory features of severe vs. non-severe "COVID-19"patients in Asian populations: a systematic review and meta-analysis. Eur J Med Res. (2020) 25 : 30.

[32] Qin JJ, Cheng X, Zhou F, Lei F, Akolkar G, Cai J, et al.. Redefining cardiac biomarkers in predicting mortality of inpatients with COVID-19. Hypertension. (2020) 76 : 1104–12.

[33] Saenger AK, et al. Specificity of B-type natriuretic peptide assays: cross-reactivity with different BNP, NT-proBNP, and proBNP peptides. Clin Chem. 2017; 63 : 351–8.

[34] Myhre, Peder L., et al. "SARS-CoV-2 viremia is associated with inflammatory, but not cardiovascular biomarkers, in patients hospitalized for COVID-19." Journal of the American Heart Association 10.9 (2021): e019756.

[35] He, Xingwei, et al. "Factors associated with acute cardiac injury and their effects on mortality in patients with COVID-19." Scientific reports 10.1 (2020) : 1-9.

[36] Lee JS, Ko SH, Lee J, Jeong KY. The relationship between body mass index and N-terminal pro-B-type natriuretic peptide in community-acquired pneumonia. European Journal of Clinical Nutrition. 2021 Jul; 75(7) :1088-98.

[37] Gao, Lei, et al. "Prognostic value of NT-proBNP in patients with severe COVID-19." Respiratory research 21.1 (2020): 1-7.