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ASSESSMENT OF SEROLOGICAL VALUES OF NT-PRO BNP LEVELS IN CLINICALLY STABLE POST COVID PATIENTS IN THE DURATION OF 1 ½ YEAR TO 2 YEARS AFTER EXPOSURE TO COVID-19 INFECTION

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Abstract : study was carried out in 36 patients of 3 different groups regarding assessment of serological levels of NT proBNP. The test was carried out in three groups of patients.

Group A : 12 patients of mild catergory, Group B : 12 patients of moderate category, Group C : 12 patients of severe category.
The values we obtained after doing NT proBNP test were compared. It was observed that the values were raised in patients who required O2 support during covid 19 infection. Values in old patients and female patients are higher than the young patients and male patients.

Keywords: NT proBNP, COVID-19, SARS-CoV-2, DEATH.

Introduction: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in January 2020, leading to the COVID-19 pandemic, posed a global health crisis. Unlike its predecessors, SARS-CoV-2 exhibited a higher transmission rate and lower case fatality rate, resulting in a substantial loss of life . Severe COVID-19 cases were associated with various complications, including acute respiratory distress syndrome, cardiac injury, and renal dysfunction. Early identification of prognostic markers in these patients is crucial for improving clinical outcomes.

Biomarkers play a critical role in improving the drug development process as well as in the larger biomedical research enterprise. Understanding the relationship between measurable biological processes and clinical outcomes is vital to expanding our arsenal of treatments for all diseases, and for deepening our understanding of normal, healthy physiology. Since at least the 1980s, the necessity of using biomarkers as surrogate outcomes in large trials of major diseases, such as cancer and heart disease , has been widely discussed. The FDA continues to promote the use of biomarkers in basic and clinical research, as well as research on potential new biomarkers to use as surrogates in future trials . However, for all their potential to do good to speed drug development, to reduce exposure to ineffective experimental treatments, and so on biomarkers present substantial risks when trial designers confuse them with clinical endpoints.**[1]**

In recent years, biomarkers have gained prominence in diagnosing and assessing the risk of cardiovascular diseases. Among these, B-type natriuretic peptide (BNP) and its N-terminal fragment (NT-proBNP) have proven to be vital. NT-proBNP is primarily produced by the heart in response to myocardial wall stress and is excreted by the kidneys. It is measured in pg/ml or pmol/l and exhibits variations with sex and age .

In critically ill COVID-19 patients, cardiac biomarkers such as NT-proBNP have shown promise for risk stratification, as elevated levels of troponin and NT-proBNP have been associated with higher mortality rates. NT-proBNP is also an established tool for diagnosing heart failure, making it relevant in predicting adverse outcomes in COVID-19 patients. Higher plasma concentrations of BNP or NT proBNP are significantly associated with higher disease severity and increased mortality in COVID-19.**[2]**

Severe COVID-19 patients with high NT-proBNP levels tended to be older with increased cardiac injury markers and higher levels of systematic inflammation markers. Patients with high NT-

proBNP (> 88.64 pg/mL) level had lower cumulative survival rate. After adjusting for potential cofounders in separate modes, NT-proBNP presented as an independent risk factor of in-hospital death in patients with severe COVID-19.**[3]**

The diagnostic value of BNP and NT-proBNP is best investigated in patients with heart failure. In a large number of studies it has been consistently found that BNP and NTproBNP are elevated in patients with heart failure, and values were found to be related to disease severity as assessed by New York Heart Association (NYHA) functional class, left ventricular systolic ejection fraction, and left ventricular diastolic function.**[4]**

NT-proBNP showed a good predictive role for 30-day mortality, irrespective of the variant of concern involved. These biomarkers can be used as tools to identify high-risk non-critically ill COVID-19 hospitalized patients with additional comorbidities. Assessing them may represent a surrogate of invasive monitoring in a context of poor resource setting, may support the tailoring of medical therapy, and guide the allocation of available resources. Further large prospective studies should validate the additional value of these biomarkers compared to routinely collected clinical information.**[5]**

NT-proBNP is frequently elevated in COVID-19. It is strongly and independently associated with mortality after adjusting for relevant confounders, including chronic HF and acute HF. Therefore, its use may improve early prognostic stratification in this condition.**[6]**

The high NT-proBNP in patients was thought to be caused by the complex interplay between underlying conditions, relative ischemia, sympathetic system activation, systemic inflammation, and pathogen-mediated direct cardiovascular system injury. However, in the current investigation, the threshold for diagnosing heart failure (450 pg/mL for patients under 50, 900 pg/mL for patients between 50 and 75, and 1800 pg/mL for patients over 75) was much lower than the cutoff value of NT-proBNP to predict the unfavorable outcome of severe COVID-19 patients. It was indicated that heart failure brought on by the virus or hypoxia could not entirely account for the predictive effect of plasma NT-proBNP in severe COVID-19 patients**.[7]**

The best cut-off value of NT-proBNP for predicting in-hospital death was 88.64 pg/mL with the sensitivity for 100% and the specificity for 66.67%. Patients with high NT-proBNP values (> 88.64 pg/mL) had a significantly increased risk of death during the days of following-up compared with those with low values (≤88.64 pg/mL). After adjustment for potential risk factors, NT-proBNP was independently correlated with in-hospital death**.[8]**

Extensive research has been conducted on biomarkers associated with coronavirus disease 2019 (COVID-19) in both healthy individuals and those with various conditions, particularly heart diseases. However, there is a limited investigation into the relationship between widely used cardiac biomarkers known as natriuretic peptides, including Brain natriuretic peptide (BNP), N-Terminal Pro-B-Type Natriuretic Peptide (NT-proBNP), and Atrial natriuretic peptide (ANP), and

COVID-19 infection specifically in patients with heart failure. These natriuretic peptides assess the hemodynamic stress on the heart wall and have the potential to serve as biomarkers for evaluating the severity of COVID-19 infection in heart failure patients.**[9]**

NT-proBNP provides the prognostic information in patients with HF with preserved ejection fraction (HFpEF) as in those with HFrEF. An expert panel composed of cardiologists mainly from Asia Pacific region was convened to discuss the utility of NT-proBNP in HF prognostication.**[10]**

Higher plasma concentrations of BNP or NT-proBNP are significantly associated with higher disease severity and increased mortality in COVID-19.**[14]** People with COVID19 infections who are transferred to intensive care units have a significant incidence of thrombosis and venous thromboembolism, which may be indicative of a bad prognosis.Instances of clots leading to pulmonary embolisms and ischaemic events (strokes) within the brain found as complications leading to death in people infected with COVID19 suggest that blood vessel dysfunction and clot formation may play a significant role in mortality. A series of vasoconstrictive reactions within the body, including pulmonary vasoconstriction, which may be the mechanism by which oxygenation declines during pneumonia, may be set off by infection. Furthermore, brain tissue samples from persons who died with COVID19 showed damage to arterioles and capillaries.

COVID-19 may also cause substantial structural changes to blood cells, sometimes persisting for months after hospital discharge.A low level of blood lymphocytes may result from the virus acting through ACE2-related entry into lymphocytes.**[11]**

Some early studies suggest 10% to 20% of people with COVID-19 will experience symptoms lasting longer than a month. A majority of those who were admitted to hospital with severe disease report long-term problems including fatigue and shortness of breath. On 30 October 2020, WHO chief Tedros Adhanom warned that "to a significant number of people, the COVID virus poses a range of serious long-term effects." He has described the vast spectrum of COVID-19 symptoms that fluctuate over time as "really concerning". They range from fatigue, a cough and shortness of breath, to inflammation and injury of major organs – including the lungs and heart, and also neurological and psychologic effects. Symptoms often overlap and can affect any system in the body. Infected people have reported cyclical bouts of fatigue, headaches, months of complete exhaustion, mood swings, and other symptoms. Tedros therefore concluded that a strategy of achieving herd immunity by infection, rather than vaccination, is "morally unconscionable and unfeasible".**[12]**

Serum NT-proBNP levels of COVID 19 patients can be used to predict the prognosis of covid which can help in early diagnosis and management of complications**.[15]**

Normal range of NT proBNP:

Normal range of NT proBNP is lower than 125 pg/ml for adults younger than 75 years and lower than 450 pg/ml for adults 75 years or older.**[13]**

Objective: This study aims to evaluate the assessment of serological values of NT-proBNP levels in post COVID-19 patients who have achieved the non diseased status(healthy status) for more than $1^{1/2}$ year.

Methods: A total of 36 post-COVID-19 patients were included in the study. They were categorized into three groups:

1. Group A (Mild Category individuals): 12 post covid patients who did not require oxygen support during their treatment while covid 19 exposure.
2. Group B (Moderate Category individuals): 12 post covid patients who required oxygen support up to 6 liters per minute during their treatment while covid 19 exposure.
3. Group C (Severe Category individuals): 12 post covid patients who required more than 6 liters per minute of oxygen support during their treatment while covid 19 exposure. Patients aged between 16 and 60 years, both male and female, were included.
4. Mode of blood Sample collection:
   NT proBNP levels are assessed by the means of blood sample testing. Venous blood is collected in a edta bulb (purple cap) and given in the lab for investigation.
   The sample was collected in two methods:
   I. Collect blood sample when the patient is in resting position.
   II. Collect the blood sample after doing workout for 15-20 minutes.

Results:

Observations for NT-proBNP Levels in Post-COVID-19 Patients:

Group A - Mild Category (No O2 Support Required):

Sr.no	Name of the participants	Age	sex	Observed serological NT proBNP values of the participants in the sample collected in resting position and before 12 noon.	Observed serological NT proBNP values of the participants in the sample collected after 5-10 minutes after the exertion of climbing of the staircase from ground floor to 3rd floor.

1.	H1	22	F	<20	<20
2.	H2	50	F	22.00	36.00
3.	H3	42	F	40.00	53.00
4.	H4	26	F	<20	20.00
5.	H5	23	M	<20	<20
6.	H6	60	M	M	50.00
7.	H7	37	<20	<20	<20
8.	H8	28	M	M	<20
9.	H9	57	<20	<20	<20
10.	H10	42	M	M	<20
11.	H11	29	<20	<20	<20
12.	H12	39	M	M	<20

Group B - Moderate Category (O2 Support up to 6 L/min):

Sr.no	Name of the participants	Age	Sex	Observed serological NT proBNP values of the participants in the sample collected in resting position and before 12 noon.	Observed serological NT proBNP values of the participants in the sample collected after 5-10 minutes after the exertion of climbing of the staircase from ground floor to 3rd floor.
1)	R1	36	F	<20	<20
2)	R2	43	F	<20	<20
3)	R3	46	F	100.00	255.00
4)	R4	47	M	<20	45.00

5)	R5	35	M	<20	22.00
6)	R6	37	M	<20	37.00
7)	R7	57	M	<20	24.00
8)	R8	48	M	55.00	61.00
9)	R9	53	F	49.00	29.00
10)	R10	45	F	<20	87.00
11)	R11	45	M	<20	186.00
12)	R12	42	M	<20	58.00

Group C - Severe Category (O2 Support > 6 L/min):

Sr.no	Name of the participants	Age	Sex	Observed serological NT proBNP values of the participants in the sample collected in resting position and before 12 noon.	Observed serological NT proBNP values of the participants in the sample collected after 5-10 minutes after the exertion of climbing of the staircase from ground floor to 3rd floor.
1.	P1	45	F	87.00	103.00
2.	P2	60	M	<20	7325.00
3.	P3	54	M	31.00	74.00
4.	P4	55	M	<20	<20

5.	P5	58	M	512.00	116.00
6.	P6	50	M	<20	<20
7.	P7	50	M	<20	91.00
8.	P8	45	M	87.00	110.00
9.	P9	55	M	<20	125.00
10.	P10	37	M	<20	97.00
11.	P11	32	M	<20	28.00
12.	P12	43	F	<20	91.00

Summary of Findings:

1. In the Mild Category, 9 out of 12 patients had NT-proBNP levels <20 pg/ml, indicating normal values.
2. In the Moderate Category, 2 out of 12 patients had NT-proBNP levels <20 pg/ml, 8 patients had levels between 20 to 125 pg/ml, and 2 patients had levels above 125 pg/ml.
3. In the Severe Category, 2 out of 12 patients had NT-proBNP levels <20 pg/ml, 8 patients had levels between 20 to 125 pg/ml, and 2 patients had levels above 125 pg/ml. Notably, one patient had an exceptionally high NT-proBNP level (7325.00 pg/ml).

Conclusion:

1. Increased NT proBNP levels found in Patients requiring oxygen support during COVID-19 infection.
2. NT proBNP levels were found increased in Females and older individuals.
3. NT-proBNP provides valuable prognostic information in patients and can be a useful tool for early intervention and risk assessment.
4. Notably, one patient had an exceptionally high NT-proBNP level (7325.00 pg/ml) which is almost 16 times of 450 pg/ml which is the normal serological value of NT proBNP level

at the age more than 75 years. Therefore further research can be carried out to explore this finding which may lead to establish the potential of serological NT-proBNP levels as a diagnostic parameter for clinical assessments of myocardial stress in the patients/healthy individuals of various age groups.

CONFLICT OF INTEREST –NIL

SOURCE OF SUPPORT -NONE

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