Original Article

Study the Association of NT-proBNP and TNF-α with Acute Decompensated Heart Failure with Reduced Ejection Fraction

Sumaya Nadhim Mohammed, Abdulrahman Mohammed Geeran, Sami Mukhlif Mishlish[1]

Department of Microbiology, [1]Department of Medicine, College of Medicine, University of Anbar, Ramadi, Iraq

Abstract

Background: In Western nations, acute decompensation of heart failure (ADHF) is the most frequent cause of hospitalization for people over the age of 65 years. Due to the high death rate, it places a heavy cost on both patients and the health care system. **Objective:** The investigation's objective is to check the level of NT-proBNP and TNF-α and check if it is associated with heart failure (HF) with reduced ejection fraction (HFrEF). **Materials and Methods:** About 60 patients whose average age is 25–94 years were taken from both genders after the clinical diagnosis by a specialist to cases who were referred to the Ibn Al-Baitar Specialized Center for Cardiac Surgery and Ramadi Teaching Hospital, and 30 healthy people were taken as a control. The levels of NT-proBNP and TNF-α had been planned to be detected from the sera taken from the patients and controls by ELISA technique. **Results:** The mean level of NT-proBNP (54.89 ± 8.54) and TNF-α (30.974 ± 6.016) in patients were both significantly higher than those in controls (23.921 ± 4.051, 10.2 ± 2.386) respectively. **Conclusion:** This study showed that patients with ADHF had elevated levels of NT-proBNP and TNF-α.

Keywords: NT-proBNP, TNF-α, acute decompensated heart failure (ADHF)

Introduction

Acute decompensated heart failure (ADHF) is common cause of hospitalization and mortality worldwide. Decompensated hemodynamics are the result of cardiac and vascular failure caused by a range of etiologies and triggers.[1] Heart failure with reduced ejection fraction (HFrEF) or heart failure with preserved ejection fraction (HFpEF) and predominance of left vs. right ventricular dysfunction are two ways to categorize heart failure (HF).[2,3] Prevalence of HF follows an exponential pattern, and it rises with age. Over 65 years of adults (6%–10%) suffer from heart failure. Each year, nearly 1 million hospitalizations in the United States have HF as their primary diagnosis, making it the most frequent reason for people over 65 to be admitted.[4,5] A cardiac neurohormone called N-terminal proBNP is released from the heart in response to an increase in intracardiac volume or pressure,[6] Increasing its levels would make it easier to distinguish between cardiac and respiratory causes of dyspnea. The heart releases B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) in response to neurohormonal activation and transmural wall stress. They are frequently utilized as biomarkers in HF for prognostication and diagnosis,[7] NT-proBNP concentrations and key physiological indicators in HFrEF, such as left ventricular ejection fraction, left atrial volume index, and diastolic function.[8] Because of its delayed clearance from the circulation, NT-proBNP concentrations are often higher in human plasma and serum. Standardization is preferable for NT-proBNP assays since they use the same antibody for detection as opposed to BNP assays, which use separate antibodies.[9] TNF-α, inflammation, is crucial in the development of numerous forms of cardiovascular disease. The systemic inflammatory

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Address for correspondence: Ms. Sumaya Nadhim Mohammed, Department of Microbiology, College of Medicine, University of Anbar, Ramadi 31001, Iraq.
E-mail: som21m0012@uoanbar.edu.iq

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state, while promoting atherogenesis and coronary artery disease, can also hasten the onset of diastolic heart failure. On the other hand, cardiac inflammation arises in response to non-ischemic cardiac injury, which frequently results in pathogenic alterations in the heart tissue that lead to systolic dysfunction, and it occurs in post-ischemic myocardial events.[10] Anti-inflammatory therapy has thus been advocated as a way to safeguard the circulatory system and heart.[11] One of the strongest pro-inflammatory cytokines is tumor necrosis factor (TNF), hence it was chosen as the initial target in the cytokine-targeted strategy.[12] The aim of the study is to check the level of NT-proBNP and TNF-α and check if it is associated with HFrEF.

Materials and Methods

The patients and control groups

The patients

This study included 60 ADHF patients whose ages ranged from 25 to 94. All patients' names, ages, genders, occupations, addresses, and medical histories were gathered. These patients were chosen from the Ramadi Teaching Hospital and the Ibn Al-Baitar Specialized Center for Cardiac Surgery. Each case was chosen after a cardiologist performed a clinical evaluation. For the collection of blood samples, 30 volunteers who appeared to be in good health but had no prior history of ADHF were chosen as the control group. The patient groups were matched based on age, sex, place of residence, and environment. Participants in the study gave their signed, informed consent.

Specimens

Blood specimen

About 5 mL of blood was drawn by venipuncture from patients and the control group, and after sterilizing the skin with an antiseptic solution, the blood was placed into a plastic tube. The serum was separated from the blood samples after centrifuging them at 3000 rpm for 5 min. The serum samples used for the immunological assays were stored in tubes at −20°C.[13]

Determination the level of NT-proBNP and TNF-α in serum by ELISA

The frozen serum samples are defrosted, allowed to cool at room temperature, centrifuged for a short period of time at 2000 rpm, and then subjected to the ELISA procedure. The SUNLONG Biotech (Ltd.) company, HangZhou, China produces the immunological kits used for measuring NT-proBNP and TNF-α in serum.

Ethical approval

The University of Al-Anbar Governorate's Medical Ethics Committee in Ramadi, Iraq, gave its approval to this study (approval number 47, May 7, 2023). Following the Helsinki declaration, all participants in the study—whether they were patients or their parents—provided written informed consent.

Statistic evaluation

The statistical program SPSS-22 (Statistical Package for the Social Sciences), which is readily available, is used for data analysis. Simple frequency and percentage metrics are used to represent the data. The one-way analysis of variance (ANOVA) and Chi-square test were used to assess the significance of variations in various percentages (quality data). Every time the *P* value for the relevance check was equal to or lower than the *P* value for the relevance check (0.05), statistical significance was considered.

Results

This study included 60 patients with ADHF with reduced ejection fraction. About 19 (31.6%) were female and 41 (68.3%) were male. As a control group, 30 healthy individuals were included in the study.

Three age groups were created for the ADHF patients, whose ages ranged from 25 to 94 years. The findings show that men were more common in all age groups. The highest frequency was found in the age range 46–65 compared to all other age groups, according to a recent study, as seen in Table 1.

The concentration of NT-pro BNP in the serum of patients and control groups

Serum human NT-proBNP was identified in all serum samples from patients and controls, though at varying amounts, and this was true for both patients and controls. According to the study's findings, patients with acute decompensated heart failure (ADHF) had higher serum NT-proBNP concentrations than control groups; the mean level of circulating NT-proBNP in the ADHF patients' serum was 54.89 ± 8.54 compared to 23.921 ± 4.051 ng/mL, with a significant difference between the two groups (*P* value = 0.00032), as shown in Table 2.

The concentration of NT-proBNP in patients according to gender, age groups, and residence

The mean and SD value of NT-proBNP concentration before treatment in female was (59.96 ± 6.36) and

Table 1: Distribution of ADHF patients according to the ages

Age groups	Total no.	Male	Female	%
25–45	14	10	4	23.3
46–65	27	20	7	45
65 <	19	11	8	31.7
Total	60			100

Table 2: The mean and SD of NT-proBNP concentration in serum of patients and controls

Parameter	NT-proBNP (mean + SD)
Patient	A 54.89 ± 8.54
Control	B 23.921 ± 4.051
P value	0.00032

Table 3: The amount of NT-proBNP present in patients according to gender

Parameter gender	NT-proBNP before treatment (mean + SD)	NT-proBNP after treatment (mean + SD)
Female (19)	A 59.96 ± 6.36	B 34.36 ± 4.76
Male (41)	B 52.854 ± 5.96	A 53.79 ± 7.74
P value	0.00007	0.00098

Table 4: The concentration of NT-proBNP of patients according to resident

Parameter resident	NT-proBNP before (mean + SD)	NT-proBNP after (mean + SD)
Rural (16)	A 61.67 ± 6.01	B 43.93 ± 6.22
Urban (44)	B 50.252 ± 6.497	A 63.11 ± 8.61
P value	0.00087	0.00003

in male was (52.854 ± 5.96) ng/mL with *P* value = 0.00007, while the mean and SD value of NT-proBNP concentration after treatment in female was (34.36 ± 4.76) and in male was (53.79 ± 7.74) with (*P* value = 0.00098). There is a sizable discrepancy, as demonstrated in Table 3.

The concentration of NT-proBNP of patients according to resident

There is significant difference was found in NT-proBNP concentrations before treatment between rural patients (61.67 ± 6.01) and urban patients (50.252 ± 6.497) with *P* value = 0.00087 while the concentration of NT-proBNP after treatment was (43.93 ± 6.22) in rural patients and (63.11 ± 8.61) in urban patients with (*P* value = 0.00003) as shown in Table 4.

The level of NT-proBNP in patients according to age groups

There were significant differences in NT-proBNP values between age groups of patients with ADHF, the higher levels of NT-proBNP before and after were found in age group (>65 years), (56.71 ± 6.73 vs 71.08 ± 9.35) ng/mL, respectively as shown in (Table 5). Sometimes the level of plasma NT-proBNP is increased by beta-blockers, cardiac glycosides, and vasopeptidase inhibitors, and this may contribute to the usefulness of these agents in HF. In addition, the NT-proBNP rate returns to normal level after treatment in about 1 week.[14,15]

Table 5: The concentration of NT-proBNP of patients according to age groups

Parameter age group	NT-proBNP before (mean + SD)	NT-proBNP after (mean + SD)
25–45 years (14)	B 43.83 ± 4.39	B 56.12 ± 4.45
46–65 years (27)	A 56.47 ± 6.11	C 48.98 ± 9.85
<65 years (19)	A 56.71 ± 6.73	A 71.08 ± 9.35
P value	0.00064	0.0008

Table 6: The mean and SD of TNF-α concentration in serum of patients and controls

Parameters	TNF-α (mean + SD)
Patient	A 30.974 ± 6.016
Control	B 10.2 ± 2.386
P value	0.00005

Table 7: The concentration of TNF-α of patients according to gender

Parameters gender	TNF-α before (mean + SD)	TNF-α after (mean + SD)
Female (19)	B 11.774 ± 1.312	B 18.733 ± 1.732
Male (41)	A 32.059 ± 4.792	A 31.018 ± 3.948
P value	0.00071	0.00052

The concentration of TNF-α in the serum of patients and control groups

Serum human TNF-α was identified in all serum samples from patients and controls, though at varying amounts, and this was true for both patients and controls. According to the study's findings, patients with acute decompensated heart failure (ADHF) had higher serum TNF-α concentrations than control groups; the mean level of circulating TNF-α in the ADHF patients' serum was 30.974 ± 6.016 ng/mL compared to 10.2 ± 2.386, with a significant difference between the two groups (*P* value = 0.00005), as shown in Table 6.

The concentration of TNF-α in patients according to gender, age groups, and residence

The mean and SD value of TNF-α concentration before treatment in female was 11.774 ± 1.312 and in male was 32.059 ± 4.792 with *P* value = 0.00071 while the mean and SD value of TNF-α concentration after treatment in female was 18.733 ± 1.732 and in male was 31.018 ± 3.948 *P* value = 0.00052. As demonstrated in Table 7, there is a sizable difference.

Table 8: The concentration of TNF-α of patients according to resident

Parameter resident	TNF-α before (mean + SD)	TNF-α after (mean + SD)
Rural (16)	A 32.51 ± 7.56	A 38.497 ± 3.786
Urban (44)	A 30.733 ± 4.286	A 39.684 ± 4.081
P value	0.258	0.314

Table 9: The concentration of TNF-α of patients according to age groups

Parameter age groups	TNF-α before treatment (mean + SD)	TNF-α after treatment (mean + SD)
25–45 years (14)	B 21.4 ± 1.672	B 18.296 ± 2.027
46–65 years (27)	A 44.5 ± 5.61	B 22.132 ± 4.278
<65 years (19)	C 16.726 ± 3.333	A 77.07 ± 11.51
P value	0.000075	0.00006

The concentration of TNF-α of patients according to resident

There is no significant difference was found in TNF-α concentrations before treatment between rural patients (32.51 ± 7.56) and urban patients (30.733 ± 4.286) with *P* value = 0.258 while the concentration of TNF-α after treatment was 38.497 ± 3.786) in rural patients and 39.684 ± 4.081 in urban patients with *P* value = 0.314 as shown in Table 8.

The concentration of TNF-α of patients according to age groups

There were significant differences in TNF-α values between age groups of patients with ADHF, the higher level of TNF-α before was found in age group (46–65 years) and the higher level of TNF-α after was found in age group (>65 years), (44.5 ± 5.61 vs 77.07 ± 11.51) respectively as shown in Table 9.

Discussion

According to age groups of patients, previous studies were agreed with recent study.[16,17] These results may be due to the fact that a person's chance of having a heart attack normally rises with age. This is brought on by various physical modifications to the circulatory system and the heart in general. One of these modifications is the accumulation of fatty deposits, which can occur on the artery walls. Another is the hardening of the arteries, thickened heart walls, weak heart valves, and increased sodium sensitivity. Men are more likely than women to develop macrovascular coronary artery disease and myocardial infarction, both of which are known risk factors for developing HFrEF.[18]

According of NT-proBNP concentration in serum of patients and controls, previous studies were agreed with recent study.[19-21] These results may be due to NT-proBNP can more accurately reflect ventricular dysfunction than other natriuretic peptides because it is principally produced and released in the ventricle in response to ventricular hemodynamic changes.[22] Additionally, it is known to strongly relax blood vessels and promote natriuresis.[23]

Another previous study was agreed with recent study[24] that shown the level of NT-proBNP affected with gender. The majority of research discovered that males had lower baseline NT-proBNP levels than females.[25,26] Numerous studies have demonstrated that patients with HFpEF have much lower natriuretic peptide levels than patients with HFrEF.[27,28]

In a recent investigation, we discovered an inverse relationship between NT-proBNP levels and hematocrit, which is lower in women than in males.[29] Other theories include the lower plasma renin levels in women[30] or the potential impact of female sex hormones on the natriuretic peptide gene expression.[31] These results may be due to strong clinical evidence suggests that testosterone may reduce cardiac natriuretic peptide levels, likely via increasing neprilysin activity. This effect may account for the difference between NT-proBNP levels in men and women.[32,33]

According of NT-proBNP with residence, previous study was agreed with recent study.[34] This result may be due to the nature of nutrition tending to consumption of animal derivatives which rich with cholesterol and fats.

Previous study was Sugiharto *et al*[35] that shown the level of NT-proBNP after increase in urban. This result may be due to urban residents both men and women have greater rates of instances than rural residents do. Men and women who lived in urban regions had a higher chance of acquiring heart disease than those who lived in rural areas, according to the odds ratio data used to estimate the risk. Different eating habits in urban and rural cultures were to blame, according to various articles. It has a significant impact on heart disease cases. The food in metropolitan areas contributed to increased rates of obesity, diabetes, inactivity, unbalanced nutrition, and air pollution.[36] In addition, bad eating habits in metropolitan areas may contribute to heart disease.[37] Urban neighborhoods' high rates of heart disease were also a result of the smoking habit among residents.[38] In cities, high-intensity work habits can cause stress and heart disease. The use of more forms of transportation for activities outside the home, such as traveling to the market, offices, and other places, contributes to low levels of physical activity in metropolitan areas.[37]

Medications for HF, such as beta-blockers, ACE inhibitors, and diuretics, can lower blood levels of BNP or NT-proBNP.[39]

In another study was agreement[40-42] that shown age-related increases in NT-pro-B-type natriuretic peptide (NT-proBNP). This result may be due to acute myocardial infarction patients 65 years of age and older who have primary coronary intervention with stent implantation (PCI) in accordance with recommendations had a better 12-month prognosis than those who receive conservative care, age left ventricular ejection fraction, and the NT-proBNP level measured in the acute phase of myocardial infarction in patients over 65 are significant prognostic indicators of survival probability and progress of the disease in the medium-term monitoring period. The earliest phases of the disease as well as after 6 and 12 months of surveillance showed improved left ventricular function and reduced NT-proBNP levels in patients over 65 who had invasive treatment in the acute phase of myocardial infarction. Age, left ventricular function, and the existence of comorbidities such as HF all influence the patient's NT-proBNP level during the acute phase of myocardial infarction.[41,43]

Previous studies were[44,45] that shown the level of TNF-α increase in patients with ADHF. This result may be due to a responsive tissue repair mechanism that is, thought to have positive benefits via mediating cardiac remodeling is the rise in the pro-inflammatory cytokine profile. Increasing research suggests that the anti-inflammatory response typically follows the acute pro-inflammatory stage to heal the injury.[46] However, due to the varied and distinctive characteristics of cardiac stress, the pro-inflammatory response is amplified as a result of localized smooth muscle damage linked to an increase in leukocyte extravasation that lengthens the pro-inflammatory cycle.[47] Chronic inflammation results from the protracted pro-inflammatory process that, if left unchecked by the anti-inflammatory systems, is supported in part by the ongoing cardiac stress brought on by co-morbid illnesses like hypertension, diabetes, etc.[48] The prevailing theory that HF development results from detrimental signaling mediated by pro-inflammatory cytokines released by the heart in addition to the secondary effects accrued from circulating cytokines is supported by increasing evidence.[49]

TNF-α increase in male, that may be due to short treatment time in female which leading to increase the TNF-α and decrease it or decline a level in a short time compare with male and previous study was in line. Hormonal differences, including lower estrogen levels in males, may influence the inflammatory response and TNF-alpha levels. Estrogen has been shown to have anti-inflammatory effects, and the absence of this hormone in males may contribute to higher TNF-alpha production. Genetic and biological differences between males and females can affect immune responses and inflammatory pathways. Variations in genes involved in the regulation of TNF-alpha production and signaling may contribute to gender differences in TNF-alpha levels. Lifestyle factors, including smoking, alcohol consumption, and dietary habits, may differ between males and females and can influence inflammation and TNF-alpha levels.[50]

TNF-α is no significant difference with residence, that may be due to the fact that the immune response induce in a same degree in both rural and urban individuals that explain the recent finding.[51]

Recent research found significant differences in the levels of TNF-α (before and after) with age groups and previous study was in line.[52] In HF, TNF-alpha is often overproduced and contributes to chronic inflammation. It has several detrimental effects on the heart, such as promoting cell death (apoptosis) of cardiac muscle cells, reducing the heart's ability to contract, and inducing adverse remodeling of the cardiac tissue. These effects can worsen HF signs and causes the progression of the disease. Regarding the age group of 46–65 years, HF commonly occurs in this population. As individuals age, there is a natural increase in the prevalence of cardiovascular risk factors, such as hypertension, diabetes, and coronary artery disease. These factors can contribute to the development of HF.[53]

Before treatment, elevated levels of TNF-alpha in individuals within the 46–65 age group with HF can indicate a higher degree of inflammation and disease severity. Higher TNF-alpha levels are associated with worse prognosis and increased mortality in HF patients. The excessive production of TNF-alpha in this age group can exacerbate the existing cardiac dysfunction and lead to a more pronounced decline in heart function.[54,55]

TNF-α increased in age group above 65 years due to persistent inflammation: Aging is associated with chronic low-grade inflammation, known as inflammaging.[56] Inflammation is a key player in the development of HF, and TNF-alpha is a key mediator of this inflammatory response. Even after treatment, TNF-alpha levels may remain elevated in older individuals, contributing to ongoing inflammation and disease progression. Treatment response variability: The response to HF treatments, including medications like angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and aldosterone antagonists, can vary among individuals. In older patients, the efficacy of these treatments may be influenced by factors such as age-related physiological changes, comorbidities, and drug interactions. TNF-alpha can impact treatment response by interfering with the beneficial effects of these medications. The use of multiple medications, known as polypharmacy, in older patients may interact with TNF-alpha and modulate its effects.[57-59]

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Conflicts of interest
There are no conflicts of interest.

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