

## STUDY ON GAMMA GLUTAMYL TRANSFERASE CONCENTRATIONS IN PATIENTS WITH HEART FAILURE DUE TO ISCHEMIC HEART DISEASE

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### ABSTRACT

**Purposes:** Surveying serum Gamma Glutamyl Transferase levels followed by the grade of heart failure patients (according to the New York Heart Association - NYHA) due to ischemic heart disease and evaluating the relationship between serum Gamma Glutamyl Transferase levels with Heart failure staging and laboratory tests (NT-proBNP levels, (EF) ejection fraction) in heart failure patients due to ischemic heart disease.

**Method:** Study design: a cross - sectional descriptive study, including 140 patients were treated at the Department of Cardiology, Hue Central Hospital, from March 1st, 2021, to May 30th, 2022. They were divided into two groups: the group with heart failure (n = 70) and the control group without heart failure (n = 70).

**Result:** The serum Gamma Glutamyl Transferase concentration increased significantly in the group of patients with heart failure (56 U/l) compared with the control group (34 U/l) ( $p < 0.05$ ). The median value of serum Gamma Glutamyl Transferase concentrations in heart failure stages II, III, and IV in the study according to NYHA classification was 53 U/l, 56 U/l and 286 U/l, respectively. Serum Gamma Glutamyl Transferase levels were positively correlated with the severity of heart failure according to the NYHA class, ( $r = 0.49$ ;  $p < 0.001$ ). GGT had good value in predicting the severity of heart failure (AUC = 0.869; 95% CI: 0.767 - 0.938), the best cutoff GGT  $\geq 51$  U/l with sensitivity: 81.25%, specificity: 77.27%; Gamma Glutamyl Transferase concentration had a moderate positive correlation with NT-proBNP concentration ( $r = 0.42$ ;  $p = 0.0004$ ) and had a negative correlation with left ventricular ejection fraction (LVEF), ( $r = -0.3$ ;  $p = 0.013$ ).

**Conclusion:** With a high diagnostic value, giving fast and accurate results of Gamma Glutamyl Transferase levels in various degrees of chronic heart failure, the Gamma Glutamyl Transferase test should be used as a good support test in the diagnosis and prognosis in patients with heart failure due to ischemic heart disease.

**Keywords:** Gamma Glutamyl Transferase, heart failure, ischemic heart disease.

### I. INTRODUCTION

Heart failure is the final consequence of cardiovascular diseases, which is currently a huge and urgent challenge for human health. So, it should be the concern and priority of many managers and scientists.

Worldwide, the rate of patients with heart failure is more and more increasing and the frequency of heart failure increases with age. In the United States, heart failure is the cause of hospitalization for more than one million patients each year and 50.000 patient deaths annually. Also in the United

States, it is estimated that 4.9 million patients are treated for heart failure, 550.000 new heart failure patients annually. Heart failure is also a leading disease in the elderly. It is estimated that 6 to 10% of men or women over 65 have heart failure, and more than 80% of hospitalized heart failure patients are over 65 years old. Not only is it the most common disease, but it also occupies a leading position in the spending budget of the health sector [1].

Heart failure is not only the result of myocardial overload or damage but also the

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result of neurohumoral changes. In addition to classical morphological explorations in diagnosis, monitoring and prognosis, more recent interest has been focused on changes in serum concentrations of several biomarkers in patients with heart failure [2]. Today, assessing the degrees of heart failure and the effectiveness of treatment have been based on clinical signs and echocardiography. So, a more rapid and “non - invasive” method has been needed to diagnose and assess severity and prognosis in patients with heart failure.

Serum Gamma Glutamyl Transferase (GGT) is an analytical, inexpensive, easily performed and highly sensitive test that has traditionally been considered an indicator of hepatobiliary dysfunction and abuse of alcohol. Recent studies have shown its role in atherosclerosis and unstable plaque pathogenesis. Furthermore, epidemiological studies have identified a role for GGT in predicting the clinical progression of cardiovascular and cerebrovascular disease to life - threatening events such as myocardial infarction, stroke, and cardiovascular disease death, namely independent of the occurrence of liver disease, and alcohol consumption and as one of the risk factors. GGT is also correlated with cardiovascular risk factors, including diabetes, hypertension, dyslipidemia, and metabolic syndrome [3, 4]

In Vietnam, there had not been studies on GGT in cardiovascular disease and heart failure patients. Therefore, we conducted this study to investigate serum Gamma Glutamyl Transferase levels in patients with heart failure (according to the New York Heart Association - NYHA) due to ischemic heart disease and evaluated the correlation between serum Gamma Glutamyl Transferase levels with Heart failure stage and paraclinical symptoms (NT-proBNP levels, ejection fraction EF) in patients with heart failure due to ischemic heart disease.

## **II. MATERIALS AND METHODS**

### **2.1. Research object**

Study 140 patients was treated at the Department of Cardiology, Hue Central Hospital, from March 1st, 2021, to May 30th, 2022, and was divided into two groups:

- Diseased group: including about 70 patients with heart failure (diastolic and systolic heart

failure) due to ischemic heart disease. Patients who are diagnosed with heart disease (hypertension, cardiomyopathy, valvular disease...), have clinical signs of heart failure (difficulty breathing, edema, hepatomegaly, distended neck veins...) are diagnosed as heart failure, and are graded according to NYHA criteria and the patient had coronary artery disease (Post sternal, transthoracic angina, pain radiating to shoulder, left arm, neck, and jaw accompanied by palpitations, anxiety, occurs with exertion, subsides with rest or nitrite, lasts several minutes and graded by the Canadian Heart Association (CCS))

- Control group: including about 70 patients without heart failure. Patients who come to the clinic or are hospitalized for other medical problems, have no clinical signs of heart failure, and the ejection fraction EF on echocardiography is within the normal range ( $EF \geq 60\%$ ), with the same age as the patients in the group of diseases included in the control group of the study.

Exclusion criteria: patients with a history of chronic obstructive pulmonary disease (COPD) or patients with pneumonia, severe infection, diabetes, chronic renal failure requiring dialysis, acute myocardial infarction, acute heart heart failure.

### **2.2. Research methods**

Cross - sectional descriptive research method. Convenient sample selection.

Research parameters: Hypertension was defined when the patient had a history of hypertension or systolic blood pressure  $\geq 140$  mmHg or diastolic blood pressure  $\geq 90$  mmHg. Diabetes: is defined when there is a history of diabetes or fasting blood glucose  $\geq 7$  mmol/l [5]. NYHA class of heart failure, grade IV was considered as severe heart failure. LVEF was classified in 3 groups: reduced EF ( $EF \leq 40\%$ ), mildly reduced EF ( $EF 41 - 49$ ), preserved EF ( $EF \geq 50\%$ ) [6].

**Table 1:** NYHA classification of heart failure [6]

|          |                                                                                                                                                                   |
|----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Grade I  | Does not restrict normal physical activity, does not cause fatigue, shortness of breath or palpitations                                                           |
| Grade II | Slight limitation of physical activity. The patient is well at rest. Ordinary physical activity leads to fatigue, palpitations, shortness of breath or chest pain |

|           |                                                                                                                                                         |
|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------------|
| Grade III | Limit a lot of physical activity. Although the patient is well at rest, only mild exercise has symptoms                                                 |
| Grade IV  | No physical activity without causing discomfort. Symptoms of heart failure occur immediately at rest. Just one physical exercise, the symptoms increase |

### III. RESULTS

There was no difference between the baseline risk factors between the diseased group and the control group, except that the frequency of diabetes patients in the diseased group (n = 22) was significantly higher than in the control group (n = 13),  $p < 0.05$  (table 2). Regarding subclinical characteristics, proBNP and GGT concentrations were higher in the diseased group than in the control group,  $p < 0.05$  (Table 3).

**Table 2:** General characteristics of the study sample

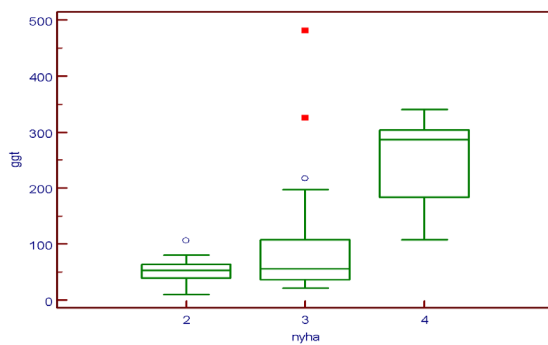
|                             | <b>Diseased group<br/>(n = 70)</b> | <b>Control group<br/>(n = 70)</b> | <b>p</b> |
|-----------------------------|------------------------------------|-----------------------------------|----------|
| Age (year)                  | 72.33 ± 14.20                      | 70.13 ± 10.07                     | > 0.05   |
| Gender (male - n)           | 42                                 | 48                                | > 0.05   |
| BMI (kg/m <sup>2</sup> )    | 22.17 ± 3.67                       | 22.36 ± 3.61                      | > 0.05   |
| Hypertension (n)            | 56                                 | 58                                | > 0.05   |
| Diabetes (n)                | 22                                 | 13                                | < 0.05   |
| Coronary artery disease (n) | 21                                 | 33                                | > 0.05   |
| Smoking (n)                 | 12                                 | 13                                | > 0.05   |

**Table 3:** Paraclinical characteristics of the study sample

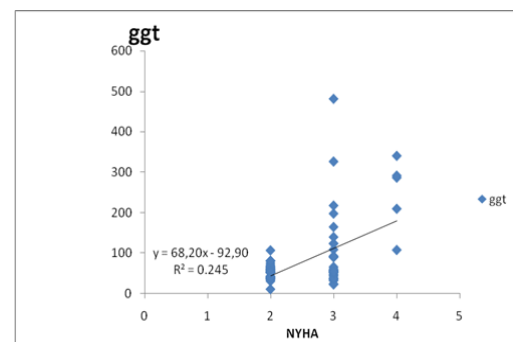
|                    | <b>Diseased group<br/>(n = 70)</b> | <b>Control group<br/>(n = 70)</b> | <b>p</b> |
|--------------------|------------------------------------|-----------------------------------|----------|
| CT (mmol/L)        | 4.29 ± 1.58                        | 4.24 ± 1.19                       | > 0.05   |
| TG (mmol/L)        | 1.62 ± 1.09                        | 1.93 ± 1.04                       | > 0.05   |
| HDL (mmol/L)       | 0.97 ± 0.44                        | 1.03 ± 0.35                       | > 0.05   |
| LDL (mmol/L)       | 2.65 ± 1.29                        | 2.36 ± 0.98                       | > 0.05   |
| NT-proBNP(pg/mL) * | 2262                               | 144.6                             | < 0.05   |
| GGT (U/l) *        | 56                                 | 34                                | < 0.05   |

\*: non - normally distributed variable was presented as median

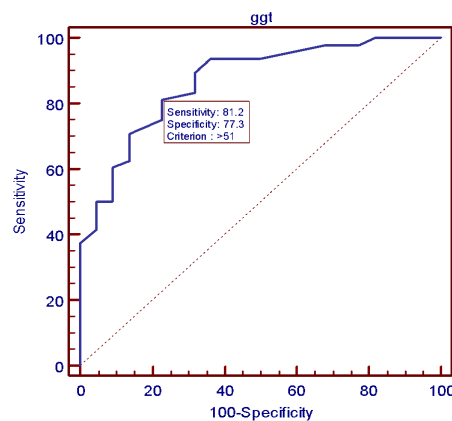
GGT concentration in NYHA class IV group was higher than other grades of heart failure ( $p < 0.05$ ) (Figure 1). There was a moderate correlation between the degree of heart failure and the GGT concentration ( $r = 0.49$ ,  $p < 0.05$ ) (Figure 2). Analysis of the ROC curve to determine the best cutoff of GGT for severe heart failure, a GGT concentration greater than 51 U/l predicts severe heart failure with sensitivity: 81.25% and specificity: 77.27% (Figure 3).



**Figure 1:** GGT levels according to the grade of heart failure NYHA

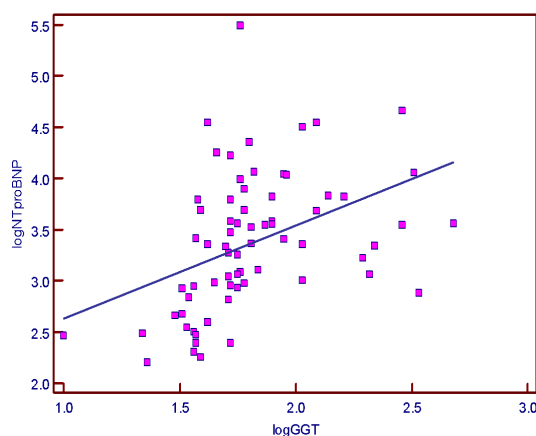


**Figure 2:** Correlation between the grade of heart failure and serum GGT

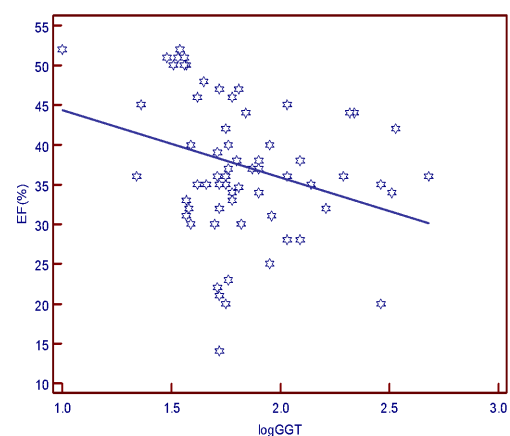


**Figure 3:** ROC curve of GGT in predicting severity of heart failure  
AUC = 0.869 (95% CI: 0.767 - 0.938)

The concentration of Gamma Glutamyl Transferase has a moderate positive correlation with the concentration of NT-proBNP ( $r = 0.42$ ;  $p = 0.0004$ ) (Figure 4) and has a negative correlation with the ejection fraction index. LVEF ( $r = -0.3$ ;  $p = 0.013$ ) (Figure 5).



**Figure 4:** Correlation between NT-proBNP concentration and GGT concentration



**Figure 5:** Correlation between LVEF and GGT concentration

#### IV. DISCUSSION

Chronic heart failure is a very common syndrome worldwide and is associated with significant morbidity and mortality. In addition

to traditional risk factors, biomarkers of nervous system activity, inflammation, metabolism, and renal and hepatic dysfunction are associated with severity and disease progression.

Serum Gamma Glutamyl Transferase (GGT) analysis is a highly sensitive, inexpensive and easy test. This is considered an indicator of hepatobiliary dysfunction and alcoholism. Recent studies have also shown the role of GGT in the pathogenesis of atherosclerosis and atherosclerotic plaques [7]. Furthermore, epidemiological studies have demonstrated GGT in predicting cardiovascular and cerebrovascular disease risk factors, such as myocardial infarction, stroke, and cardiovascular mortality, independent of the occurrence of liver disease, and alcohol intake particularly. GGT also correlates with the most cardiovascular risk factors, including diabetes, hypertension, dyslipidemia, and metabolic syndrome.

In our study, the more severe the heart failure, the higher the GGT concentration. Several studies have consistently shown that serum GGT levels, mainly within the normal range, are most strongly associated with cardiovascular risk factors and predict the development of cardiovascular disease, hypertension, stroke, and type 2 diabetes. In patients with stable symptoms of heart failure, elevated serum GGT levels were significantly associated with the severity of heart failure [8,9]. Although the underlying mechanism for this association is unknown, several explanations for this phenomenon can be considered. Congestion in the liver is a clear mechanistic explanation for the increased levels of GGT in heart failure. Many studies have suggested that severe heart failure often leads to a congestive state of the liver, thereby causing liver enzyme stasis with high concentrations of GGT and bilirubin or local ischemia, and cytokine release may be involved in this process. However, there is still no convincing evidence for a definite or exclusive correlation between GGT, right atrium and pulmonary artery pressure, and severity of decreased cardiac output. Therefore, besides hepatic obstruction and/or ischemia, other factors that contribute to elevated GGT in heart failure must also be considered. Also, GGT is a marker of increased oxidative stress has been linked to the pathogenesis of coronary arterial disease by way of oxidant/antioxidant imbalance and inflammation [10].

According to our study, GGT concentration has a negative correlation with left ventricular ejection

fraction index LVEF with a correlation coefficient of  $r = -0.3$ . This further demonstrates that the more the heart function (specifically the left ventricle) declines, the more severe the heart failure is, leading to congestive liver conditions due to heart failure. It is a problem that has caused an increase in GGT. Our results are consistent with the results of foreign authors, especially the results of Gerhard Poelzl et al.: with the correlation coefficient between EF and GGT being  $r = -0.1$  and  $p < 0.05$  [7].

In our study, NT-proBNP and GGT concentration had a moderate positive correlation with a correlation coefficient of  $r = 0.42$ . NT-proBNP is a biomarker, and the mechanism of secretion of (NT-Pro) BNP is primarily from myocardial wall tension, increased ventricular filling pressure, and volume overload [11,12]. (NT-Pro) Plasma BNP is increased in patients with heart failure and is positively correlated with left ventricular filling pressure [13]. Therefore, for patients with severe heart failure corresponding to the higher NYHA class of heart failure, the greater the secretion of NT-ProBNP. Thus, along with the gradual increase of heart failure according to the NYHA class, NT-ProBNP also increased in a significant way. Therefore, NT-proBNP levels are correlated with GGT levels in patients with heart failure. This is especially meaningful in assessing the severity of heart failure based on NT-ProBNP and GGT, thereby having appropriate attitudes and indications for treatment as well as prognosis for patients.

## V. CONCLUSION

With a high diagnostic value, giving fast and accurate results of Gamma Glutamyl Transferase levels in various degrees of chronic heart failure, the Gamma Glutamyl Transferase test should be used as a good support test in the diagnosis and prognosis in patients with heart failure due to ischemic heart disease.

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### *Study on gamma glutamyl transferase concentrations...*

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