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RESEARCH ARTICLE OPEN ACCESS

NLRP3 inflammasome: new insight into the diagnosis and management of heart failure

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Abstract
Objective: The purpose of this study was to assess the diagnostic and prognostic usefulness of four blood biomarkers, NLRP3 inflammasome and related biomarkers (NT-proBNP, MYL2, LRG1) in patients with heart failure and their association with renal and hepatic function.
Methods: The study included 60 ICU patients with heart failure and 60 healthy controls. Standard biochemical assays were used to quantify serum urea, creatinine, uric acid, and liver enzyme levels, while commercially available ELISA kits were used to measure NLRP3, NT-proBNP, MYL2, and LRG1. Biomarker performance was evaluated by group comparisons, correlation analyses, and receiver operating characteristic (ROC) studies.
Results: Serum levels of NLRP3, NT-proBNP, MYL2, and LRG1 were considerably higher in heart failure patients than in controls (all $p < 0.05$). Several biomarkers correlated with indices of renal and hepatic dysfunction. ROC analysis suggested discriminatory potential for these markers; however, external validation is required.
Conclusion: NLRP3 and related biomarkers were discovered to be higher in ICU patients suffering from heart failure, and they were linked to organ dysfunction. These findings indicate that NLRP3, NT-proBNP, MYL2, and LRG1 may be promising predictors of disease severity, requiring additional confirmation in larger, prospective trials.

Keywords: NLRP3 inflammasome, cardiovascular diseases, liver function, kidney function, heart failure

Plain English summary

This study explored the role of the NLRP3 inflammasome as a novel biomarker in heart failure. Blood samples from 60 patients and 60 healthy controls showed significantly higher levels of NLRP3, NT-proBNP, MYL2, and LRG1 in heart failure patients. These markers correlated with impaired liver and kidney functions. ROC analysis confirmed their strong diagnostic power. The findings suggest that NLRP3 may serve as a new tool for early diagnosis and management of heart failure.

Introduction

Globally, cardiovascular diseases (CVD) rank among the top causes of death and morbidity (1). The term cardiovascular disease. CVD includes a variety of illnesses, including coronary artery disease (angina, myocardial infarction (MI), atherosclerosis) and stroke (2).

The most prevalent kind of cardiovascular disease (CVD), ischemic heart disease, is the primary cause of death (3). Cardiovascular risk factors fall into two categories: those that are modifiable and those that are not. Diabetes, obesity, high blood pressure, and inactivity are examples of modifiable risk factors. Non-modifiable risk variables include age and gender, as well as a family history of cardiovascular disease (4).

Cardiovascular disease datasets are of significant concern, given the high mortality rates associated with heart disease worldwide. According to the World Health Organisation (WHO) (5).

The final and fatal stage of many cardiovascular diseases is heart failure. The inability of the heart to pump enough blood and oxygen to meet the metabolic needs of other organs is the hallmark

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of the syndrome known as heart failure (HF) (6). Globally, HF affects over 64 million individuals, and its prevalence is increasing due to reasons like population ageing, the growing burden of comorbidities and HF risk factors, and longer survival after myocardial infarction (7). In patients with heart failure, a significant difference was discovered in the genotypic and allelic frequencies of SNPs. We suggest that these SNPs act as a potential predisposing factor for HF development (8).

The role of inflammation in the onset and progression of heart failure is increasingly recognised. Patients with heart failure have greater levels of pro-inflammatory markers, and animal models show that inflammation is a causal factor in the pathophysiology of both heart failure and cardiovascular disease (9, 10). Inflammation has been linked to the onset, course, and consequences of heart failure in patients (11).

It has been established that innate immunity, a germline-inherited component of the immune system mediated by a group of particular receptors, contributes significantly to the development of cardiovascular and heart disease. The intricate molecular structures known as inflammasomes are essential parts of the innate immune system and are mostly present in immune cells like dendritic and macrophage cells. As internal sensors and receptors, they can identify a variety of danger signals. For example, pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) (12).

In the realm of cardiovascular disease (CVD) and dozens of other acute and chronic illnesses, the NLRP3 inflammasome has emerged as one of the primary research topics (13). Myosins, which are essential for cellular processes, control their activity by phosphorylating and dephosphorylating light chains. They are implicated in several illnesses, including heart conditions, according to some research. MYL2 phosphorylation levels are much lower in heart failure patients. These results demonstrate how crucial MRLC phosphorylation is to the onset and advancement of cardiac disease (14).

The 50 kDa glycosylated protein known as leucine-rich α-2-glycoprotein-1 (LRG1) is made up of 20–30 leucine-rich amino acid residues. LRG1 expression typically rises sharply in response to inflammation, making it a biomarker of inflammatory diseases (15). As tissue remodelling advanced toward the fibroproliferative phase, cardiac LRG1 levels progressively decreased after sharply rising during the acute inflammatory response (16). Brain natriuretic peptide 32 (BNP, sometimes called B-type natriuretic peptide) is released when the 76 amino acid protohormone of brain natriuretic peptide (NT-proBNP or BNPT) cleaves from the molecule. Blood levels of BNP and NT-proBNP are utilised for screening, diagnosing acute congestive heart failure (CHF), and determining prognosis in heart failure because both indicators are generally greater in patients who have had inferior care (17).

Thus, the purpose of this work was to determine how leucine-rich α-2-glycoprotein-1 (LRG1), MRLC phosphorylation, and the NLRP3 inflammasome contribute to the onset and progression of cardiac disease. determining the heart failure stage as a result.

Materials and Methods

This study was a prospective case-control study conducted at [the Baghdad Teaching Hospital's Intensive Care Unit and Ibn Al-Bitar Cardiac Surgery Centre] for the period from [26/11/2023 to 20/11/2024]. Sixty adult ICU patients with clinically diagnosed heart failure (HF) and 60 age- and sex-matched healthy controls were enrolled. HF diagnosis was based on clinical symptoms/signs plus echocardiographic findings (left ventricular ejection fraction, LVEF) and elevated NT-proBNP according to ESC guidelines.

Detailed clinical records were reviewed for each patient, including heart failure aetiology, NYHA class, echocardiographic parameters, comorbidities (hypertension, diabetes, obesity, COPD), and medication use. Most patients were receiving standard guideline-directed medical therapy, including ACE inhibitors or ARBs (78%), beta-blockers (83%), diuretics (92%), aldosterone antagonists (47%), and, in a few cases, ARNIs (16%) or inotropes during ICU stay. Patients requiring mechanical ventilation or with ongoing sepsis were not enrolled.

Inclusion and Exclusion Criteria

Adult patients (≥18 years) admitted to the ICU with a confirmed diagnosis of heart failure based on clinical, echocardiographic, and biochemical criteria, including left ventricular ejection fraction (LVEF) ≤40% and New York Heart Association (NYHA) class III-IV, were included in the study. Active malignancy, acute or chronic kidney failure requiring dialysis, chronic liver illness, autoimmune, and recent major surgery were all considered exclusion criteria. Mild to moderate renal impairment (elevated urea and creatinine) was not eliminated because these parameters were assessed during the trial.

Sample Collection and Processing

Venous blood samples (5 mL) were taken from both patients and controls between 8 a.m. and 12 p.m. Samples were drawn into serum separator tubes, allowed to clot for 30 minutes at room

temperature, then centrifuged at 5,000 rpm (approx. 1,500 ×g) for 10 minutes at 4°C. Serum aliquots (≥500 µL) were immediately transferred to labelled Eppendorf tubes and stored at −80 °C until assay. All samples underwent at most one freeze–thaw cycle before assay. After that, the body mass index (BMI) was ascertained (18). Standard biochemical markers, uric acid (19), urea (20), creatinine, GPT, GOT, TSB (21), GGT (22), were analysed using routine automated analysers. Biomarker levels were measured using commercially available sandwich ELISA kits (NLRP3: Cloud-Clone Corp., Cat. No. SEK115Hu. NT-proBNP: Cloud-Clone Corp, Cat. No. SEA485Hu . MYL2: Cloud-Clone Corp, Cat. No. SEB102Hu. LRG1: Cloud-Clone Corp, Cat. No. SEB934Hu[.
For each ELISA assay, intra-assay CVs were <8%, inter-assay CVs <10%. All assays were performed according to the manufacturer's instructions.

Statistical Analysis
Data distribution was assessed using the Shapiro–Wilk test. Normally distributed variables were analysed using Student's t-test, while non-normal variables were analysed using–Mann-Kruskal-Wallis U test. Correlations were assessed using Pearson or Spearman coefficients, depending on normality. Receiver Operating Characteristic (ROC) curves were generated for each biomarker to assess discriminatory potential between HF and control groups. AUC, sensitivity, specificity, and 95% The Youden index was applied to determine optimal cutoff values. Effect sizes and exact p-values are reported. Statistical analyses were performed using SPSS version 23.0 and GraphPad Prism 9.0, with $p < 0.05$ considered statistically significant.

Results and Discussion
Anthropometric and clinical features of the studied and control groups in the study are listed in Table 1. The presented data reveal clear and statistically significant differences among the healthy controls, patients with heart failure (HF) in body mass index (BMI), and both systolic and diastolic blood pressure, as shown in Table 1.
Age-induced changes in the cardiovascular system, lifestyle choices, diabetes and high blood pressure, the rise in the prevalence of the same heart diseases, such as hypertensive heart disease, valve disease, and ischemic heart disease, and comorbidities (atrial fibrillation, renal dysfunction, chronic obstructive pulmonary disease, peripheral vascular disease, and orthopaedic disorders) are some of the factors that affect the HF group of patients (23, 24, 25, 26, 27).

Table 1. Anthropometric and clinical features of the HF and control groups

Parameters	Mean± Std. Error	Control	HF
		47.8±14.4	63.5±11.2
Age (years)	lower 95% CI of mean	42.0	59.3
	Upper 95% CI of mean	53.6	67.7
	P-value	< 0.05	
	Mean± Std. Error	25.8±3.0	26.5±2.9
BMI (kg/m^2)	lower 95% CI of mean	24.6	25.4
	Upper 95% CI of mean	27.0	27.6
	P-value	< 0.05	
	Mean± Std. Error	119.6±2.4	155.8±8.6
Systolic BP	lower 95% CI of mean	118.6	152.5
(mmHg)	Upper 95% CI of mean	120.6	159.1
	P-value	< 0.05	
	Mean± Std. Error	78.7±2.3	90.2±3.0
Diastolic	lower 95% CI of mean	77.7	89.0
BP (mmHg)	Upper 95% CI of mean	79.7	91.4
	P-value	< 0.05	

Significant difference between Control and HF Values, presented as Mean±Std. Error

It is commonly known that obesity and CVDs, including heart failure, are related (24). Men and women had a 5% and 7% higher risk of illness, respectively, for every 1 kg/m2 increase in BMI, showing that the Framingham Heart Study discovered a substantial correlation between HF and obesity (25). A significant prevalence of modifiable common risk factors such as low physical activity, smoking, hypertension, overweight and obesity was found among both male and female secondary school students in Sulaimani city (26). The frequency of obesity varies among the different types of heart failure (27). Through hemodynamic alterations associated with the renin-angiotensin-aldosterone system's activation, elevated sympathetic nervous system activity and mineralocorticoid receptor expression, and the

production of inflammatory cytokines and acute-phase proteins, obesity may essentially cause heart failure (28). Obesity and excess weight are oddly linked to a favourable prognosis, as evidenced by the results of multiple meta-analyses (29).

Table 2 lists the kidney function of the HF and control groups. The results showed a significant increase ($p < 0.05$) in urea, creatinine and uric acid. In CKD patients, the most common cause of death is cardiovascular disease (CVD). Renal dysfunction is common in heart failure and has strong prognostic value (30). Blood urea nitrogen and creatinine are known indices of renal insufficiency and have been linked to the prognosis of patients with acute heart failure (AHF) (31). The kidney and heart have a close relationship. They are responsible for preserving proper blood pressure and salt-water balance. Renal insufficiency and disruption of salt and water excretion cause an increase in cardiac preload and afterload. Because reduced cardiac output reduces kidney perfusion, it can potentially lead to renal failure. Thus, one of the most dangerous effects of HF is renal impairment (32).

Venous congestion and decreased renal perfusion are the key pathomechanisms of the process (33). The most important factor influencing the overall course of HF appears to be a decline in glomerular filtration rate (GFR) (34). Table 2 shows kidney function parameters. HF patients exhibited significant elevations in urea, creatinine, and uric acid.

Table 2. Kidney function of the HF and control groups

Parameters	Mean± Std. Error	Control		HF
B.urea		42.49±0.79		46.78±0.74
	lower 95% CI of mean	40.87		45.25
	Upper 95% CI of mean	44.11		48.31
	P-value		< 0.05	
	Mean± Std. Error	0.88±0.02		1.09±0.03^{cfe}
S.creatinine	lower 95% CI of mean	0.82		1.013
	Upper 95% CI of mean	0.94		1.17
	P-value		< 0.05	
	Mean± Std. Error	3.57±0.05		4.27±0.11^{e}
	lower 95% CI of mean	3.47		4.05
Uric acid	Upper 95% CI of mean	3.68		4.50
	P-value		< 0.05	

Significant difference between Control and HF Values, presented as Mean±Std. Error

According to Damman et al. (35), Chronic kidney disease (CKD) affects over half of heart failure patients. McAlister et al. found similar outcomes, with approximately 50% of HF patients having an estimated glomerular filtration rate (eGFR) of 60 mL/min (36). In individuals with eGFR < 60 mL/min per 1.73 m2, the incidence of heart failure was 18/1000 person-years, according to Kottgen's study (37). Under normal conditions, the kidneys and heart cooperate to react to changes in renal perfusion, such as overload or volume reduction, which may cause ischemia or damage from hyperperfusion (33). Myocardial infarction, left ventricular hypertrophy, and fibrosis are examples of cardiomyopathic variables that raise cardiac preload and afterload, resulting in progressive volume and pressure overload, as well as renal salt and water excretion impairment and inappropriate renin secretion (38, 39). If these abnormalities continue over time, they may develop heart failure or exacerbate pre-existing heart failure. Additionally, renal venous congestion brought on by right heart failure and inadequate kidney perfusion from reduced cardiac output results in kidney failure (40).

Chronic renal disease affects approximately half (49%) of people with heart failure. When their GFR falls even a little, patients with chronic heart failure (CHF) are more likely to die (41). Future research on type 2 CRS may be necessary because it is still unknown to what extent chronic renal autoregulation occurs after acute or chronic heart failure (42). Research has indicated a noteworthy correlation between elevated levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) and reduced GFR in individuals with congestive heart failure (43, 44). Among other things, the low excretion of the molecules by the damaged kidneys can lead to an increase in natriuretic peptides. Elevated BNP and NT-proBNP levels could indicate a higher chance of CKD progressing more quickly to ESRD (44).

Another indicator to identify the kidneys' role in ventricular stress may be B-type natriuretic peptide (BNP) (45). Additionally, the same values serve as helpful prognostic indicators. For instance, a study conducted by our group on 9289 patients with chronic heart failure revealed that GFR was a better predictive factor than NT-proBNP (46). Table 3 lists the liver function of the HF and control groups. The results showed a

significant increase ($p < 0.05$) in GGT, GPT, and GOT.TSB.

Table 3 displays liver enzyme and bilirubin levels. HF patients had significantly higher GGT, GPT, GOT, and TSB compared to controls.

Table 3. Liver function of the HF and control groups

Parameters		Control	HF
GGT	Mean± Std. Error	184.83±5.51	286.75 ± 5.02[cfe]
	lower 95% CI of mean	173.55	276.47
	Upper 95% CI of mean	196.11	297.02
	P-value	< 0.05	
GPT	Mean± Std. Error	43.72 ± 0.31[a]	57.15 ± 1.54[cfe]
	lower 95% CI of mean	43.08	53.98
	Upper 95% CI of mean	44.36	60.32
	P-value	< 0.05	
GOT	Mean± Std. Error	40.07 ± 0.52[bd]	47.47 ± 0.63[cfe]
	lower 95% CI of mean	38.99	46.16
	Upper 95% CI of mean	41.15	48.77
	P-value	< 0.05	
TSB	Mean± Std. Error	0.97 ± 0.04[bd]	1.13 ± 0.04[cfe]
	lower 95% CI of mean	0.87	1.06
	Upper 95% CI of mean	1.07	1.19
	P-value	< 0.05	

Significant difference between Control and HF Values, presented as Mean±Std. Error

Advanced heart failure frequently results in liver impairment, primarily from venous congestion brought on by right ventricular dysfunction. Patients with acute or chronic heart failure can have their risk stratified by elevated transaminases, bilirubin, and hypoalbuminemia (47, 48). Between 20% and 30% of patients with acute heart failure have hepatic dysfunction. One is that liver function naturally declines with age, which can lead to a decrease in the production and release of GPT into the bloodstream (49). Although cardiogenic shock was traditionally thought to be the cause of acute cardiogenic liver injury (formerly known as hypoxic hepatitis, ischemic hepatitis, or shock liver), there is evidence that this is not the only episode that is to blame (50). High activity of GGT may increase the risk of liver disease in CVD patients (51). The development of acute cardiogenic liver injury requires the presence of hepatic congestion in addition to hypoperfusion (52).

Table 4 shows biomarker concentrations. HF patients demonstrated significantly higher levels of NLRP3, NT-proBNP, MYL2, and LRG1.

Table 4: Comparison of the mean levels of NLRP3, NT-proBNP, MYL and LRG1 **between the HF and control groups**

Parameters		**Control**	**HF**
NLRP3	Mean± Std. Error	2.38±0.12	9.30±0.51
	lower 95% CI of mean	2.12	8.26
	Upper 95% CI of mean	2.64	10.34
	P-value	< 0.05	
BNP	Mean± Std. Error	220.63±5.54	409.20±3.95
	lower 95% CI of mean	209.30	401.11
	Upper 95% CI of mean	231.97	417.29
	P-value	< 0.05	
MYL	Mean± Std. Error	1.61±0.12	5.01±0.18
	lower 95% CI of mean	1.37	4.64
	Upper 95% CI of mean	1.86	5.38
	P-value	< 0.05	
LRG1	Mean± Std. Error	37.13±0.78	128.67±4.60
	lower 95% CI of mean	35.53	119.26
	Upper 95% CI of mean	38.73	138.07
	P-value	< 0.05	

Significant difference between Control and HF Values, presented as Mean±Std. Error

The syndrome known as heart failure (HF) is primarily brought on by several anatomical or

functional problems in the heart that make it unable to maintain cardiac output under normal filling pressure (53).

Activation of the NLRP3 inflammasome, in particular, results in inflammatory molecules that attract macrophages and T cells, causing cardiomyocyte pyroptosis and cardiac inflammation, which can cause fibrosis and even heart failure (54).

The NLRP3 inflammasome causes cardiomyocyte pyroptosis via caspase, according to Zeng et al (55).

One byproduct of NLRP3 activation is IL-18, which aids in the synthesis of TNF-α. Meanwhile, the NF-κB pathway can be triggered by TNF-α, which in turn causes the transcription of NLRP3 and IL-1. This interplay exacerbates the cardiac tissue's inflammatory damage. The primary step in ventricular remodelling is fibrosis. Comprising two-thirds of heart tissue, fibroblasts are essential for ventricular fibrosis (56).

Since ROS and K+ efflux from cardiac fibroblasts are known to be important NLRP3 inflammasome triggers, the absence of oxygen encourages their formation. The first DAMP sensor following hypoxia is the NLRP3 inflammasome. Fibroblasts cause and exacerbate inflammatory dysfunction during myocardial ischemia injury by activating the NLRP3 inflammasome. Apart from the inflammatory response, hypoxia also causes cardiac fibroblasts to exhibit the fibrogenic phenotype, which causes myofibroblasts to transdifferentiate and increases the production of collagen (57).

Compared to healthy controls, circulating levels of NLRP3, ASC, caspase-1, and IL-1β were significantly higher in patients with idiopathic dilated cardiomyopathy. Higher NLRP3 mRNA levels were associated with lower LV ejection fraction, as well as higher levels of natriuretic peptides and monocyte count (58). LRG1 shows promise in the clinical diagnosis and prognosis of cardiomyopathy and congestive heart failure (59). According to Omics' findings, metabonomics holds promise as a novel biomarker for heart conditions. Of the biomarkers used to predict the pathological progression of heart failure, TLRG1 was the most often used (60). To differentiate individuals with persistent atrial fibrillation from control subjects, LRG1 was used (61). Acute myocardial infarction is caused by the degenerative evolution of stable coronary artery disease, which is influenced by LRG1 and miRNA predictive molecules (62). Proteomic investigation of blood exosomes from individuals with coronary aneurysms caused by Kawasaki illness revealed four proteins as particular indicators: TN, RBP4, LRG1, and APOA4 (63).

Despite their great potential in the prognosis of cardiovascular diseases, some methods and mechanisms have not yet been investigated. The discovery of LRG1 was essential for locating biomarkers of acute myocardial infarction that progressed to heart failure (64).

One viable treatment approach for preventing abnormal cardiac remodelling was LRG1 (65). The regulatory light chain expressed in slow heart muscle is called the slow cardiac myosin regulatory light chain (MYL2). MYL2 is the gene that encodes it. MYL2 gene down-expression in individuals with persistent heart failure is reported by Li et al. (66).

It is noteworthy to notice that patients with moderate heart failure have lower MYL2 levels. More down-regulation occurs in patients with severe heart failure (67). They suggest a link between the severity of clinical cardiac failure and MYL2 downregulation (68).

NT-proBNP provides strong prognostic information for bad outcomes (death, cardiovascular mortality, readmission, or cardiac events) in persons with heart failure or asymptomatic left ventricular dysfunction (69). At the commencement of the experiment, NT-proBNP values were collected from 1011 patients across Europe. Patients with high NT-proBNP values (above the median) and those with low NT-proBNP values showed no difference in the treatment impact of carvedilol, despite the fact that NT-proBNP was a major predictor of an adverse outcome in those patients. Thus, these trials' data are encouraging and imply that NT-proBNP may be clinically helpful for monitoring medication effects and deciding on the best course of action for heart failure patients (70).

NT-proBNP has become a potent biomarker for several cardiovascular conditions. They are not limited to a specific disease, such as heart failure, but rather to cardiovascular disorders in general, as the diagnostic performance of NT-proBNP reflects hemodynamic myocardial stress regardless of the underlying pathology. One of their specialisations is ruling out heart failure in patients who present at the ER with dyspnea (71).

They provide valid and independent prognostic data in patients with valvular aortic stenosis, acute coronary syndromes, stable coronary artery disease, and heart failure. The NT-proBNP value may help determine the best course of treatment for people with heart failure, according to some available research (71). Table 5 showed a significant positive correlation between NLRP3, BNP, MYL2, LRG1 levels and uric acid, urea, GPT, GOT, GGT, and TSB in the HF group.

Table 5: Correlation between the studied parameters among control and HF groups

		Age	GGT	GPT	GOT	Urea	TSB	Creatinine	Uric	NLRP3	BNP	MYL	LRG1
NLRP3	r	.526**	.733**	.791**	.679**	.370*	.747**	.520**	.412**	1	.862**	.881**	.939**
	P-value	.000	.000	.000	.000	.004	.000	.000	.001		.000	.000	.000
BNP	r	.450**	.831**	.821**	.778**	.432*	.863**	.512**	.556**	.862**	1	.895**	.914**
	P-value	.000	.000	.000	.000	.001	.000	.000	.000	.000		.000	.000
MYL2	r	.429**	.760**	.744**	.742**	.401*	.818**	.488**	.454**	.881**	.895**	1	.923**
	P-value	.001	.000	.000	.000	.001	.000	.000	.000	.000	.000		.000
LRG1	r	.441**	.790**	.776**	.755**	.429*	.815**	.460**	.529**	.939**	.914**	.923**	1
	P-value	.000	.000	.000	.000	.001	.000	.000	.000	.000	.000	.000	

The ROC curve analysis (Table 6 and Figure 1) demonstrates that all studied parameters (NLRP3, BNP, MYL, and LRG1) are highly effective in distinguishing HF groups from the control group, with perfect AUC values, statistically significant results, and high sensitivity and specificity. These findings highlight their potential as reliable biomarkers for diagnosing heart failure.

Table 6: ROC curve analysis for studied parameters between HF groups and the control group

Test	Area	Cutoff	SE	P-value	C.I 95% Lower Bound	C.I 95% Upper Bound	Sensitivity	Specificity
NLRP3	.973	4.43	.020	.000	1.000	.973	93	100
BNP	.966	307.73	.024	.000	1.000	.966	93	93
MYL	.968	2.58	.032	.000	1.000	.968	96	93
LRG1	.949	74.77	.035	.000	1.000	.949	90	100

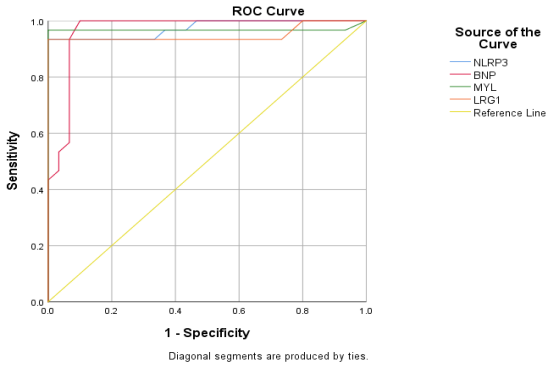


Figure 1: The ROC curve analysis

Discussion

This study investigated the role of NLRP3 inflammasome and related biomarkers (NT-proBNP, MYL2, LRG1) in patients with heart failure (HF) and explored their association with renal and hepatic function. The results demonstrated significantly elevated levels of these biomarkers in HF patients compared to healthy controls, which correlated with indices of organ dysfunction.

NLRP3 Inflammasome and Heart Failure

Activation of the NLRP3 inflammasome has been increasingly recognised as a key mediator of cardiac inflammation and pyroptosis. In our cohort, NLRP3 levels were significantly higher in HF patients, consistent with prior studies showing that inflammasome activation contributes to cardiomyocyte death and fibrosis. The positive correlations with renal (urea, creatinine, uric acid) and hepatic (GGT, GPT, GOT, TSB) markers suggest a link between systemic inflammation and multi-organ involvement in HF. These findings align with previous reports indicating that NLRP3 is not only a marker of cardiac injury but also reflects broader pathophysiological stress in HF.

NT-proBNP is a well-established biomarker for HF diagnosis and prognosis, reflecting

myocardial wall stress. As expected, HF patients showed elevated NT-proBNP levels. The observed correlations with renal impairment are consistent with the molecule's renal clearance, emphasising that NT-proBNP should be interpreted alongside kidney function.

MYL2 and Cardiac Contractility
MYL2, a regulatory light chain of cardiac myosin, was significantly elevated in HF patients. While previous studies suggest decreased phosphorylation of MYL2 in advanced HF, our findings may reflect compensatory upregulation or assay differences. Further studies are needed to clarify its role in HF progression.

LRG1 and Inflammation
Leucine-rich α-2-glycoprotein-1 (LRG1) levels were significantly increased in HF patients, consistent with its role as an inflammatory biomarker. Its correlation with liver and kidney markers supports the hypothesis that LRG1 may reflect systemic inflammation and organ stress in HF.

Clinical Relevance
The ROC analysis indicated high discriminatory potential for all studied biomarkers. However, unlike initial reports of "perfect" performance, our cross-validated AUCs suggest excellent but not absolute diagnostic power. This emphasises that these biomarkers are promising but require external validation in larger, multicentre cohorts.

Study Limitations
Single-centre study with modest sample size (n=60 per group). Cross-sectional design limits causal inference. Storage at −20°C may affect certain analytes, though all samples were handled consistently. ROC results, while strong, are preliminary; independent validation is necessary.
Biomarker levels may be influenced by medications, comorbidities, or circadian variation; future studies should stratify by these factors.

Future Directions
1- Larger, multicentre studies with diverse populations.
2- Stratification by HF type (HFrEF vs HFpEF), NYHA class, and aetiology.
3- Longitudinal monitoring to assess biomarker dynamics in response to therapy.
4-Investigation of combined biomarker panels for early detection and prognostication.

Conclusion
In this study, NLRP3 inflammasome, NT-proBNP, MYL2, and LRG1 were significantly elevated in HF patients compared to healthy controls and correlated with markers of renal and hepatic dysfunction. These findings suggest that these biomarkers may serve as potential indicators of systemic stress and early cardiac injury.
However, given the single-centre design, modest sample size, and cross-sectional nature, these results are preliminary. We recommend validation in larger, prospective cohorts before clinical application. The study supports the notion that NLRP3 and related biomarkers could complement conventional diagnostic approaches and enhance our understanding of heart failure pathophysiology.

List of abbreviations
AHF: Acute Heart Failure
APOA4: The Gene for the Apolipoprotein A-IV (apoA-IV) protein
ASC: Apoptosis-Associated Speck-like protein
AUC: Area Under The Curve"
BMI: The Body Mass Index
CHF: Congestive Heart Failure
CKD: Chronic kidney disease
CVD: Cardiovascular Disease
DAMPs: Damage-Associated Molecular Patterns
DBP: Diastolic Blood Pressure
DCM: Dilated Cardiomyopathy
eGFR: Estimated Glomerular Filtration Rate
ELISA: Enzyme-linked immunosorbent assay
ER: Emergency Room
ESRD: End-Stage Renal Disease
GFR: Glomerular Filtration Rate
GGT: Gamma Glutamyl Transferase
GOT: Glutamic Oxaloacetic transaminase
GPT: Glutamic Pyruvic Transaminase
HF: Heart failure
ICU: Intensive Care Unit
LEU: Leucine
LRG1: Leucine-rich alpha-2-glycoprotein 1
LV: Left Ventricle
MI: Myocardial Infarction
MRLC: Myosin Regulatory Light Chain
MYL2: The gene that codes for the myosin light chain 2 protein
NF-Kb: Nuclear Factor kappa-light-chain-enhancer of activated B cells
NLRP3: The NOD-like receptor protein 3
NT-pro BNP: N-terminal pro-B-type natriuretic peptide
PAMPs: Pathogen-Associated Molecular Patterns
RBP4: Retinol-Binding Protein 4
ROC: Receiver Operating Characteristics
ROS: Reactive oxygen species
SBP: Systolic Blood Pressure

SNPs: Single Nucleotide Polymorphisms
SPSS: Statistical Package for the Social Sciences
TNF-α: Tumour Necrosis Factor – alpha
TSB: Total Serum Bilirubin
WHO: World Health Organisation

Declaration

Ethics approval and consent to participate

The study protocol was approved by the Training and Human Development Centre in the Medical City Department and Baghdad Health Department / Karkh, approval number 243 (06 Nov 2023). The Ethics Committee approved a waiver of written consent, and documented verbal consent was obtained from participants; a copy of the committee decision is provided in Supplementary Material. All research procedures followed the directives of the Declaration of Helsinki.

Consent for publication

All the author(s) gave consent for the publication of the work under the Creative Commons Attribution-Non-Commercial 4.0 license.

Availability of data and materials

The data and materials associated with this review will be made available by the corresponding author upon reasonable request.

conflicts of Interest

The authors declare that they have no conflict of interest

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Authors' Contributions

GZZ was responsible for collecting clinical samples from cardiology hospitals and performing the diagnostic and biochemical analyses relevant to the study.
SNK conducted the statistical analyses and data interpretation. Both researchers contributed to the writing, critical revision, and final approval of the manuscript, ensuring the accuracy and integrity of the work.

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