AUIQ Complementary Biological System
ISSN: 3007-973X
Journal homepage:
https://acbs.alayen.edu.iq

Volume 1 | Issue 1 Article 4

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Recommended Citation
Salim, Raghda Faris; Alfatlawi, Wafaa Raji; and Aldabagh, Muhammed A.H. (2024), Evaluation of BNP, uPA and Wint5a in Four Stages of Iraqi Patients with Heart Failure, *AUIQ Complementary Biological System*: Vol. 1: Iss. 1, 34-42.
DOI: https://doi.org/10.70176/3007-973X.1002
Available at: https://acbs.alayen.edu.iq/journal/vol1/iss1/4

AUIQ COMPLEMENTARY BIOLOGICAL SYSTEM 1 (2024) 34–42

ORIGINAL STUDY

Evaluation of BNP, uPA and Wint5a in Four Stages of Iraqi Patients with Heart Failure

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ABSTRACT

Heart disease is classified as one of the most serious and widespread diseases in the world, presenting major challenges to public health and leading to high mortality rates. A comprehensive understanding of its causative factors, along with early recognition of signs and symptoms, is essential to achieve rapid diagnosis and promote preventive measures. This research conducted on 150 Iraqi patients divided into four stages according to the criteria of the American College of Cardiology, where each stage includes 25 patients suffering from heart disease. Their ages ranges (40–75) years. A comparative analysis was performed with 50 healthy individuals serving as controls. The study used Brain natriuretic peptide (BNP), Urokinase Plasminogen Activator (uPA), and Wingless Type 5a (Wnt5a) tests, and revealed significantly higher BNP levels among stage IV patients compared to other stages (0.54 ± 0.16, $P < 0.001$). Wnt5a showed elevated levels in stage III compared to the remaining stages, while uPA did not show statistically significant differences (P value 0.283). In conclusion, measuring BNP and Wnt5a levels is pivotal for accurate diagnosis of heart failure. These biomarkers provide objective evidence of heart dysfunction, helping to differentiate heart failure from other conditions that show similar symptoms.

Keywords: Brain natriuretic peptide, Heart failure, Stages of heart failure, Urokinase, Wingless

1. Introduction

Heart failure (HF) is a complicated clinical condition that occurs when the heart is unable to pump enough blood to sustain blood flow [1], either owing to structural or functional ventricular filling or blood ejection dysfunction. Globally [2], HF affects millions of patients and is a leading cause of morbidity and death [3]. In 2001, ACC/AHA developed a classification that accounts for both the evolution and progression of HF [4]. It defines four stages from precursor stages A and B (termed 'at risk for HF' and 'pre-HF' in a recently proposed revised classification of HF that also incorporates this staging system) through the symptomatic stages C and D [5]. In this study the assessment levels of those could help to prevent development of sever stages of disease.

1.1. Brain natriuretic peptide (BNP)

Brain natriuretic peptide (BNP) is a hormone produced primarily by the ventricles of the heart in response to increased pressure and stretching of cardiac muscle cells. Its main function is to promote increased urine production and widening of blood vessels to reduce the workload on the heart [6]. BNP is a valuable biomarker for the diagnosis and prognosis of heart failure. Elevated levels of BNP in the blood indicate cardiac dysfunction and can help differentiate heart failure from other conditions with similar symptoms. BNP levels correlate with the severity of heart failure, making it useful for risk stratification [7]. BNP levels increase as heart failure progresses. In Stage A heart failure (at risk for heart failure), BNP levels are typically normal. However, as the disease

Received 3 May 2024; accepted 28 May 2024.
Available online 1 July 2024

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https://doi.org/10.70176/3007-973X.1002

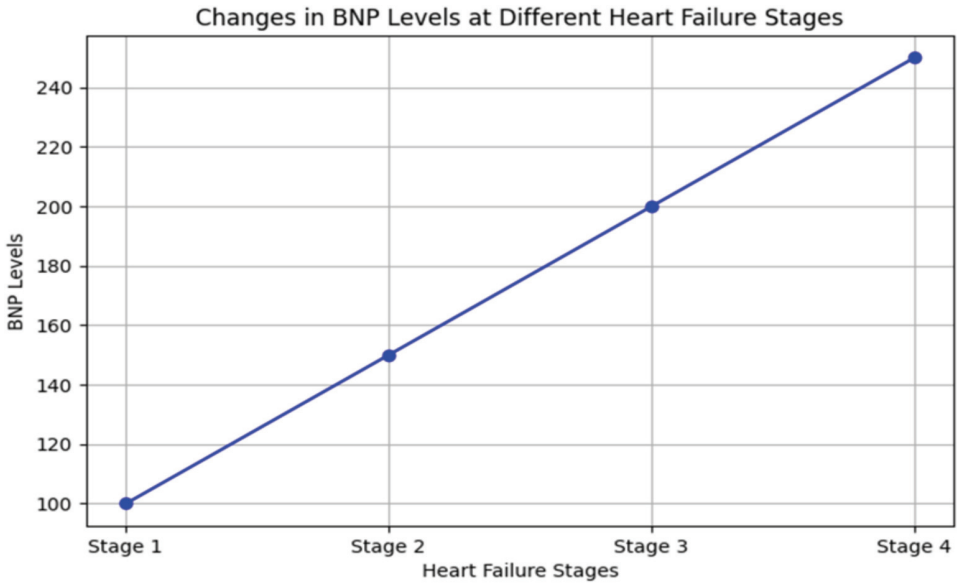

Fig. 1. Changes in BNP levels throughout heart failure stages.

advances to Stage B (structural heart disease without symptoms) and Stage C (structural heart disease with symptoms), BNP levels rise significantly. In Stage D (refractory heart failure), BNP levels may reach extremely high levels [8].

BNP levels increase with heart failure severity, typically normal in Stage A patients, sharply increasing in Stage B, Stage C, and potentially to high levels in Stage D [9].

1.2. Urokinase Plasminogen Activator (uPA)

Urokinase Plasminogen Activator (uPA) is an enzyme that aids in blood clot disintegration, angiogenesis, fibrosis, and cardiac remodelling, which accelerate heart failure. It plays a major role in cardiac remodelling, causing excessive extracellular matrix accumulation, damage to the heart, and fibrosis. Studies using uPA inhibitors in animal models show they increase heart function, reduce fibrosis, and decrease cardiac remodelling. Further research is needed to determine their safety and effectiveness in humans [10].

1.3. Wingless Type 5a (Wnt5a)

Wingless Type 5a (Wnt5a) is a protein in the Wint signalling pathway, regulates cellular functions and adult tissue homeostasis. Abnormal Wnt5a signalling activity leads to heart failure, fibrosis, inflammation, and cardiac remodelling. Excessive Wnt5a signalling impairs heart function by increasing pro-inflammatory cytokines, activating fibroblasts, and depositing extracellular matrix proteins [11].

2. Materials and methods

2.1. Patient's selection

The research was carried out at the Department of Applied Sciences, University of Technology, in Iraq. Samples were obtained from Sheikh Zayed General Hospital and Ibn Sina Cardiology Hospital. Ethical and preventive procedures were followed while collecting the samples, based on a specialized scientific committee in the Iraqi Ministry of Health. The collecting of samples began in November 2022 and concluded in March 2023, the individuals enrolled in this study (75 women and 75 men) the recruitment ages range between (40–70) years. All patients were identified by consulting doctors as individuals with heart failure, specifically caused by malfunction of the left ventricle. The samples included 150 patients suffering from heart failure, who were divided into four stages based on ACC/AHA developed a classification that accounts for both the evolution and progression of HF. Each level included 25 patients. In return, they were compared with 50 healthy people. The kits used in the study manufactured from Sunlog–China and Roche–Germany. ELISA and Copas were used for measurements of parameters.

2.2. Statistical analysis

Categorical variables are often represented using Mean ± SD. The statistical method used for comparing means was the student t-test, while analysis of variance (ANOVA) was utilized for comparing multiple stages. The Scheffe test was afterwards conducted

as a post hoc study. A Pearson correlation coefficient was computed to assess the relationship between two continuous quantitative variables. ROC curves are also used for analysis. The best values for sensitivity and specificity were determined by identifying the place on the resultant curve that had the shortest distance to the ideal sensitivity and specificity point (100%, 100%). The degree of discrimination of the variable investigated is expressed by the area under the curve, which ranges from 0.5 (indicating non-discriminative) to 1.0 (indicating completely discriminative).

3. Results and discussion

The findings in Table 1 demonstrate a very significant distinction (p-value <0.001) in the levels of BNP and Wint5a among patients at various phases in comparison to the control group. Nevertheless, there was no notable disparity seen in the uPa levels across the groups being examined (p-value = 0.543) Table 1.

As heart failure progresses from Stage A to Stage D, there are notable changes in the levels of BNP, uPA, and Wnt5a. In Table 1, BNP levels remain normal in Stage A but increase progressively in Stage B, Stage C, and Stage D. Higher BNP levels indicate worsening heart failure severity [12]. The concentration of BNP is the highest in patients with heart failure, stage D, compared to the rest of the stages, and healthy people, with a concentration of (0.54 ± 0.16) and p-value (<0.001), measuring BNP levels aids in the diagnosis of heart failure and differentiating it from other conditions. BNP levels also help in risk stratification and guiding treatment decisions. Monitoring BNP levels over time allows healthcare professionals to assess disease progression and treatment effectiveness [13].

For the Wint5a the stage C shows a significant difference with mean (1.66 ± 0.5) p-value (0.001). The changes in BNP and Wnt5a levels throughout heart failure stages have significant clinical implications. These biomarkers provide valuable information about disease severity, prognosis, and response to treatment interventions [14], there is no significance of the uPA value between HF patients and healthy people, as the results gave a p-value (0.283).

For people with heart failure, it was found that the concentration of urea and creatinine is the highest in the stage D compared to the rest of the results mean of urea (112.48 ± 48.35) and Cr. (2.26 ± 1.14) p-value (<0.001).

The mean of lipid profile is explained as cholesterol with the highest mean in stage C mean (275.44 ± 26.23) p-value (<0.001) the TG and LDL show no differences between the HF patients among stages but shows a difference compared to the control group p-value (<0.001), HDL shows no difference among studied groups.

For the cardiac enzymes the CK and troponin show not difference between the stages but as comparison of stages and Control groups there is a difference of results where high concentrations of these enzymes found in patients of HF p-value (<0.001), LDH as an indicator of HF the mean in stage B the highest (329.4 ± 17.15) p (<0.001). CRP shows a difference between Stages and control group with p-value (<0.001).

Measuring BNP and Wnt5a levels is crucial for accurate heart failure diagnosis. These biomarkers provide objective evidence of cardiac dysfunction and

Table 1. Baseline characteristics of the study population by universal definition of heart failure stages.

	M ± SD					
Biomarkers	Stage A HF (n = 25)	Stage B HF (n = 25)	Stage C HF (n = 25)	Stage D HF (n = 25)	Control	P value
BNP (ng/mL)	0.37 ± 0.11	0.42 ± 0.13	0.45 ± 0.12	0.54 ± 0.16	0.26 ± 0.06	<0.001
uPA (ng/mL)	0.18 ± 0.04	0.19 ± 0.07	0.2 ± 0.09	0.17 ± 0.05	0.21 ± 0.07	0.283
Wint5a (ng/mL)	0.8 ± 0.21	1.28 ± 0.7	1.66 ± 0.5	1.26 ± 0.44	0.44 ± 0.09	0.001
RBG (mg/dL)	297.6 ± 35.63	301.68 ± 27.01	301.72 ± 53.59	261.4 ± 50.21	94.74 ± 5.9	<0.001
Urea (mg/dL)	47 ± 34.74	58.08 ± 36.96	73.56 ± 39.82	112.48 ± 48.35	28.56 ± 5.94	<0.001
Cr (mg/dL)	1.14 ± 0.57	1.24 ± 0.63	1.42 ± 0.69	2.26 ± 1.14	0.67 ± 0.14	<0.001
UA (mg/dL)	5.6 ± 1.17	5.38 ± 1.45	5.62 ± 0.88	5.88 ± 1.45	3.99 ± 0.62	<0.001
Cholesterol (mg/dL)	244 ± 6.48	263.2 ± 8.1	275.44 ± 26.23	256.04 ± 32.01	172.96 ± 17.96	<0.001
TG (mg/dL)	329.08 ± 30.65	338.36 ± 29.61	336.16 ± 27.34	333.56 ± 26.05	120.3 ± 11.68	<0.001
HDL (mg/dL)	48.4 ± 30.65	44.6 ± 29.61	44.28 ± 27.34	45.36 ± 26.05	48.56 ± 11.68	0.157
LDL (mg/dL)	208.38 ± 33.73	207.24 ± 32.68	204.58 ± 34.41	212.48 ± 27.63	106.26 ± 17.98	<0.001
VLDL (mg/dL)	34.75 ± 16.44	42.42 ± 19.41	41.22 ± 22.8	42.14 ± 29.4	18.14 ± 8.91	<0.001
CK (U/L)	48.46 ± 7.42	39.58 ± 8.89	48.34 ± 6.01	48.64 ± 11.96	10.72 ± 3.72	<0.001
LDH (U/L)	296.2 ± 58.3	329.4 ± 17.15	322.4 ± 17.73	312.92 ± 15.78	148.24 ± 25.43	<0.001
CRP (mg/dL)	41.2 ± 3.95	43.92 ± 2.98	51.32 ± 12.04	43.4 ± 6.93	0.92 ± 0.22	<0.001
Troponin (ng/L)	21.2 ± 4.79	17.72 ± 1.06	22.48 ± 2.54	19.84 ± 3.8	1.25 ± 0.5	<0.001

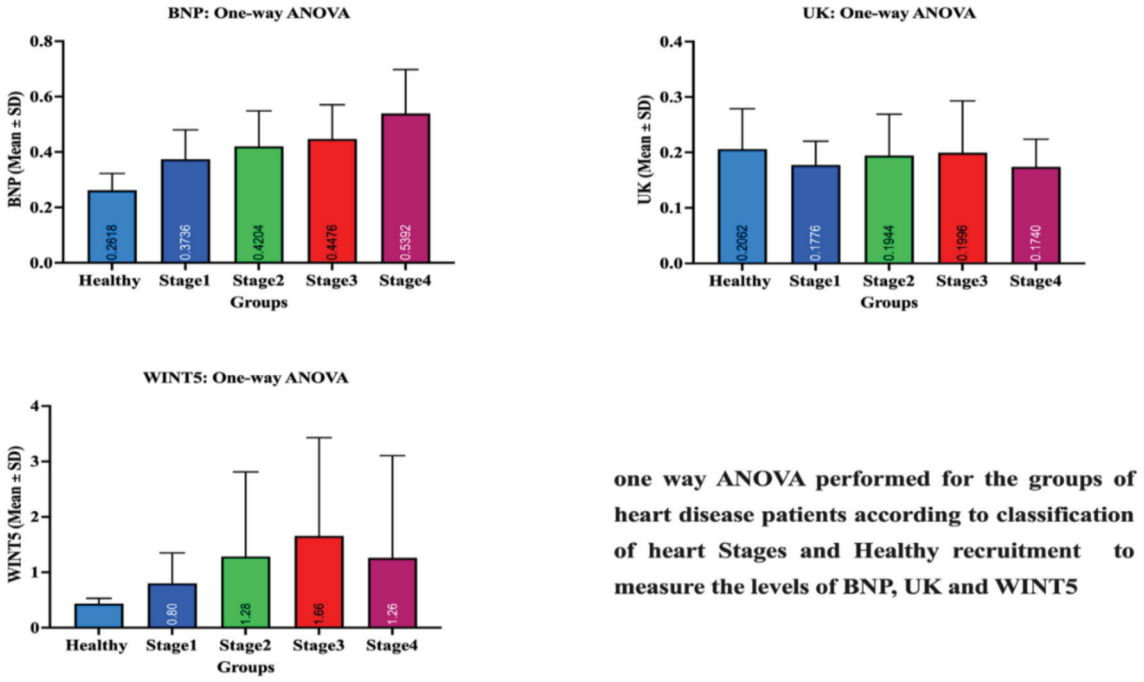

Fig. 2. ANOVA test for stages of heart failure.

help differentiate heart failure from other conditions with similar symptoms. Incorporating these biomarkers into diagnostic algorithms enhances diagnostic accuracy and improves patient outcomes [15].

Regarding to ROC curves in Fig. 3 BNP levels reflect the underlying pathophysiology of heart failure. As cardiac dysfunction worsens, the heart compensates by producing higher levels of BNP. Monitoring BNP

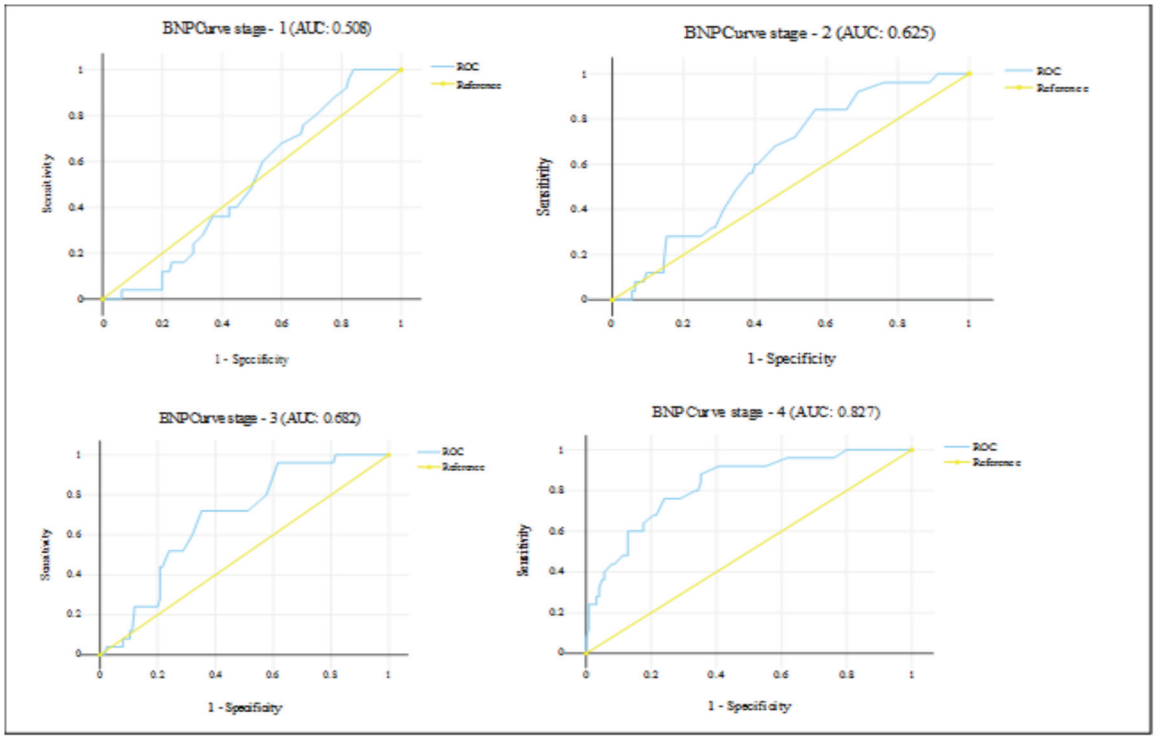

Fig. 3. ROC curve of BNP levels in 4 stages of heart failure patients.

Table 2. Pearson's correlation of BNP, uPa, Wint5a with other parameters in heart failure patients.

		Marker of heart failure		
Parameters		BNP	uPa	Wint5a
Cardiac enzymes				
BNP	r	1	−0.04	0.35
	P	–	0.602	<0.001
uPa	r	−0.04	1	−0.06
	P	0.602	–	0.453
Wint5a	r	0.35	−0.06	1
	P	<0.001	0.453	–
CK	r	0.56	−0.13	0.61
	p	<0.001	0.119	<0.001
LDH	r	0.56	−0.1	0.62
	p	<0.001	0.238	<0.001
Variable parameters				
RBG	r	0.48	−0.14	0.59
	P	<0.001	0.098	<0.001
	P	0.668	−0.2	0.37
CRP	r	0.56	−0.12	0.64
	P	<0.001	0.154	<0.001
Troponin	r	0.57	−0.11	0.59
	P	<0.001	0.163	<0.001
Lipid profile				
Cholesterol	r	0.52	−0.08	0.61
	P	<0.001	0.359	<0.001
TG	r	0.55	−0.12	0.61
	P	<0.001	0.129	<0.001
HDL	r	−0.19	−0.04	0.03
	P	0.018	0.609	0.693
LDL	r	0.56	−0.14	0.53
	P	<0.001	0.098	<0.001
VLDL	r	0.32	−0.01	0.26
	P	<0.001	0.925	0.001
Renal function				
Urea	r	0.47	−0.03	0.46
	P	<0.001	0.697	<0.001
Creatinine	r	0.45	−0.11	0.28
	p	<0.001	0.175	<0.001
Uric Acid	r	0.41	−0.2	0.37
	p	<0.001	0.013	<0.001

levels over time helps assess disease progression and the effectiveness of treatment interventions [16].

Levels of uPA also change as heart failure advances. Elevated uPA levels contribute to cardiac remodeling, angiogenesis, and fibrosis, amplifying the pathological processes associated with heart failure [17].

Wnt5a levels are upregulated in advanced stages of heart failure, suggesting a potential role in cardiac remodelling and fibrosis [18].

Table 2 presents the Pearson's correlations between B-type natriuretic peptide (BNP), urokinase plasminogen activator (uPA), Wint5a, and various other parameters. Our analysis revealed a statistically significant positive correlation between BNP and Wint5a. It is noteworthy that our patient cohort consisted of individuals with both diabetes and retinopathy, indicating that the observed increase in Wint5a levels can be attributed to its significant involvement in the presence of type 2 diabetes mellitus (T2DM) and chronic kidney complications [19].

From the correlation table, BNP showed a significant positive correlation with Wint5a ($r = 0.35$, $p < 0.001$), while uPa showed no significant correlation with BNP or Wint5a. Both CK and LDH showed significant positive correlations with BNP, suggesting a possible relationship between cardiac enzymes and markers of heart failure. Variable parameters RBG, CRP, and Troponin showed significant positive correlations with BNP, indicating their potential as markers of heart failure. For the lipid profile cholesterol, TG, LDL and vLDL showed a significant correlation with BNP and Wint5a, while HDL negative correlation with BNP ($r = -0.19$, $p = 0.018$), suggesting a possible link between lipid abnormalities and heart failure. Markers of kidney function (urea, creatinine, uric acid): Urea, creatinine and uric acid showed significant positive correlations with BNP and Wint5a, while with uPA uric acid showed a weaker but still significant positive correlation.

This investigation indicated a considerable rise in creatine kinase (CK), which is similar to Lizzy M et al. The increase in CK may signify increased muscular damage in elderly adults [20]. Creatine kinase (CK) is a critical biomarker in the assessment and management of heart failure (HF), and its elevated concentrations have been associated with disease progression and increased mortality rates. However, it is imperative to recognize that elevated levels of CK can also be observed in other medical conditions such as renal failure, rhabdomyolysis, and hypothyroidism [21] in the current study we noted that patients with HF have higher levels of CK in stage 4 [22].

Lactate dehydrogenase (LDH) functions as a cytoplasmic enzyme that is utilized in the diagnosis of cardiac injury [23]. The presence of elevated amounts of LDH has been documented in several cardiac illnesses, as seen in Table 1. Specifically, the stage 4 cohort exhibits elevated levels of lactate dehydrogenase (LDH), and these individuals receive a diagnosis of heart failure (HF). The rise in blood LDH levels observed as a consequence of organ damage can be attributed to significant cellular death, which results in the loss of cytoplasmic content. Various medical conditions, including abrupt myocardial infarction, anemia, pulmonary embolism, hepatitis, and acute renal failure, have the potential to result in tissue destruction [24]. The results of our study align with previous research that has demonstrated a strong correlation between elevated LDH levels and unfavorable outcomes in patients diagnosed with acute

decompensated heart failure, acute aortic syndromes, and acute aortic dissection [25].

Individuals who have been diagnosed with heart failure (HF) exhibit a heightened vulnerability to the onset of diabetes mellitus, the correlation between the presence of diabetes in patients diagnosed with heart failure has been demonstrated to be associated with increased rates of hospitalization, cardiovascular morbidity, and mortality [26]. Additionally, those diagnosed with heart failure exhibit a higher propensity for developing diabetes, consequently elevating their vulnerability to this particular ailment. In our investigation, all participants exhibit diabetes, a condition in which both heart failure (HF) often co-occur [27].

Troponin functions as a cardiac biomarker utilized in the diagnosis and assessment of heart damage [28]. Increased concentrations of troponin in patients diagnosed with heart failure (HF) typically indicate the presence of cardiac strain or injury [29], since the myocardium experiences impairment within the setting of HF. The phenomenon of troponin increase is frequently observed in acute pathological conditions, notably myocardial infarctions [30]. Nevertheless, research has indicated that even minor increases in troponin levels in individuals suffering from heart failure are associated with more unfavourable prognoses [31].

C-reactive protein (CRP) is a biomarker associated with inflammation and has been implicated in the pathogenesis and advancement of heart failure (HF) [32]. Increased concentrations of C-reactive protein (CRP) in persons diagnosed with heart failure (HF) frequently indicate an elevated state of inflammation within the cardiovascular system [33]. Increased levels of C-reactive protein (CRP) have been correlated with adverse outcomes in individuals with heart failure (HF), including higher rates of hospitalization and an elevated risk of mortality. The monitoring of C-reactive protein (CRP) levels can offer significant insights into the inflammatory condition of individuals suffering from heart failure, hence potentially assisting in the process of making informed decisions regarding their treatment [34].

Lipids play a vital role in persons diagnosed with heart failure (HF) as they are important for maintaining cellular membranes, regulating gene expression, and demonstrating anti-inflammatory properties through the participation of fatty acids (FA) [35]. The heart's structural integrity relies heavily on lipid metabolism, with cardiac myocytes regulating fatty acid absorption, beta-oxidation, and mitochondrial oxidative phosphorylation, which contribute to 40–60% of ATP synthesis [36]. Triglyceride (TG) is crucial for myocardial ATP synthesis, and excessive lipid accumulation can disrupt intercellular communication, leading to programmed cell death, myocardial hypertrophy, and compromised cardiac performance [37]. Cardiac pressure overload leads to several adverse outcomes, including the impairment of mitochondrial substrate oxidation and respiration, the accumulation of lipids above normal levels, and the development of heart failure [38].

The accumulation of an excessive amount of fluid within the body is considered to be a contributing element to the elevation of blood pressure. This elevation of blood pressure is widely acknowledged as a substantial risk factor in the development of heart disease [39]. Hypertension imposes an increased burden on the heart by elevating its workload and promoting the restructuring of cardiac tissues, potentially leading to the emergence of conditions such as left ventricular hypertrophy and heart failure [40].

4. Conclusion

The comparison between biomarkers and parameters in patients with heart failure reveals some findings. BNP showed a correlation with Wint5a suggesting they could be useful as additional markers for assessing the severity of heart failure. On the hand uPa did not show any correlation with BNP or Wint5a indicating its limited usefulness as a marker for heart failure. Cardiac enzymes CK and LDH were found to have correlations with BNP highlighting their potential as indicators of heart failure progression. Additionally, RBG, CRP and Troponin showed correlations with BNP further supporting their role as markers for diagnosing and predicting heart failure. Abnormalities in lipids such as cholesterol levels (TG, LDL, VLDL) were significantly correlated with BNP and Wint5a suggesting their involvement in the development of heart failure. Conversely HDL exhibited a correlation with BNP indicating a protective effect against heart failure. Markers of renal function (urea, creatinine, acid) showed significant positive correlations with BNP and Wint5a suggesting their link to the severity and prognosis of heart failure. Urea and creatinine were particularly elevated in stage D heart failure cases emphasizing their potential, as indicators of stages of the condition. The levels of lipids, cholesterol, varied noticeably across stages of heart failure with the highest average seen in stage C. Likewise heart related enzymes such, as CK, troponin and LDH showed distinct variations between the stages of heart failure and the control groups highlighting their usefulness in diagnosing heart failure. CRP, an inflammation marker demonstrated variances between the stages of heart failure and the control groups hinting

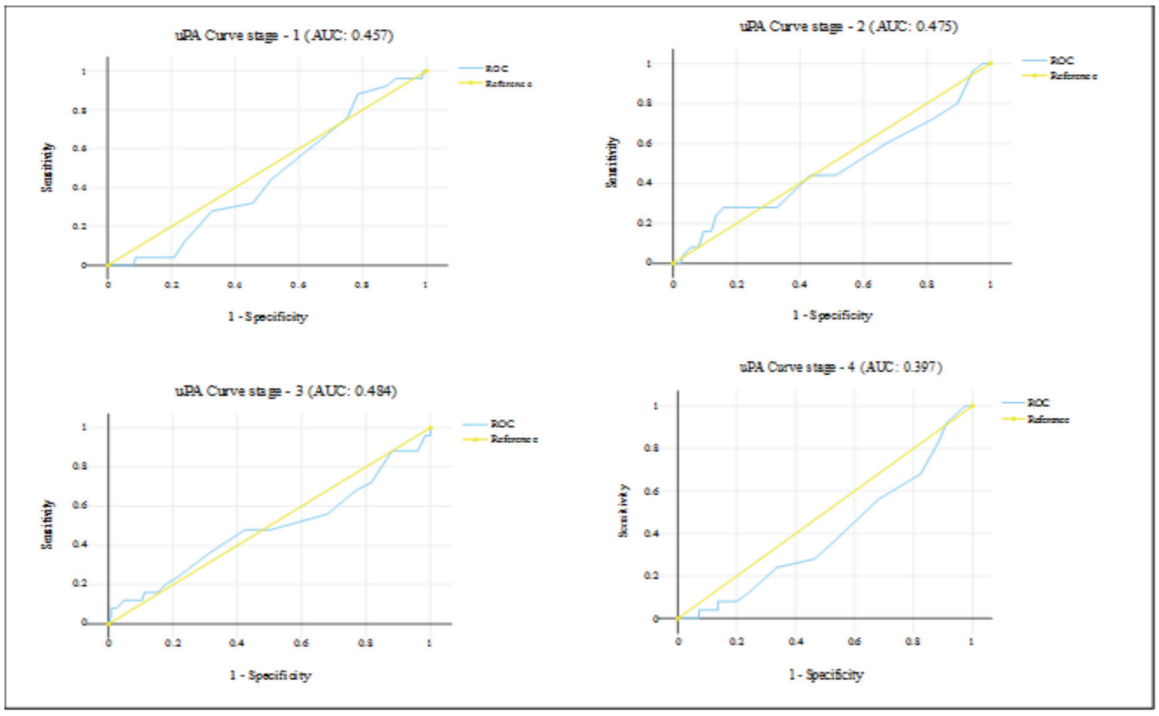

Fig. 4. ROC curve of uPA levels in 4 stages of heart failure patients.

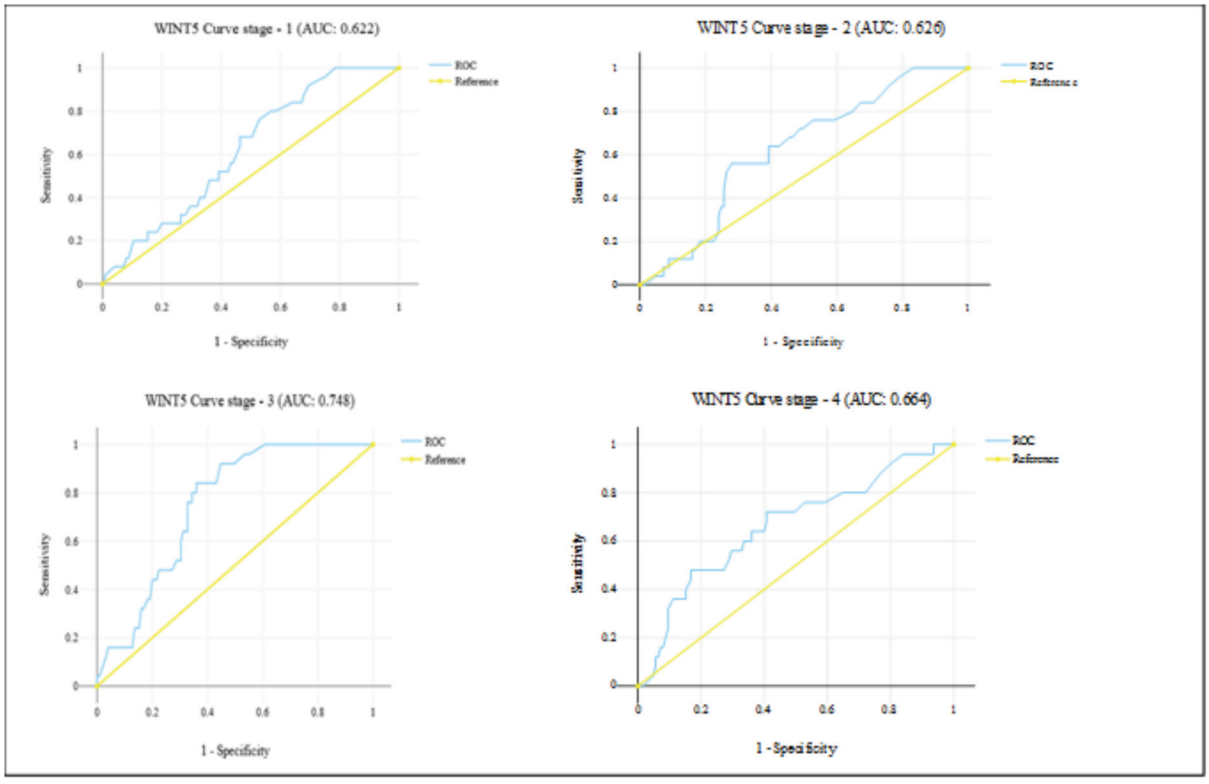

Fig. 5. ROC curve of Wint5a levels in 4 stages of heart failure paients.

at its possible involvement, in the development and prognosis of heart failure. The changes in BNP and Wnt5a levels throughout heart failure stages have significant clinical implications. These biomarkers provide valuable information about disease severity, prognosis, and response to treatment interventions. The Wint5a at stage C shows a significant difference among groups. Through the results, it was shown that Wint5a could be an early screening for heart failure in the third stage before it develops into the fourth stage, and this can help us in early diagnosis and taking the necessary precautions in terms of treatment.

Acknowledgments

The authors offer thanks and gratitude to University of Technology, applied science department, Applied Chemistry Branch for their endless support and complete this research and Shaikh Zayed Hospital to getting samples and ethical approvement of patients.

Ethical responsibilities of authors

The project was approved by the applied science department of University of Technology–Iraq.

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