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ORIGINAL ARTICLE

Validity of B-Type Natriuretic Peptide, Growth Differentiation Factor 15, and High-Sensitivity Troponin I Levels in Ischemic Heart Failure

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SUMMARY

Background: **Heart failure (HF) is a major medical, and epidemiological problems with ischemic heart disease (IHD) is the most common cause of HF. We aimed to assess the plasma B-type natriuretic peptide (BNP) levels, serum growth differentiation factor 15 (GDF15), and high-sensitivity troponin I (hsTnI) in HF patients with and without IHD.**

Methods: **The study included 120 HF patients, categorized into 51 patients with IHD and 69 patients without apparent IHD. Clinical and echocardiographic assessments of the included patients were performed. ELISA assays of plasma BNP and serum GDF15 were done, while serum hsTnI was measured using chemiluminescent immunoassay.**

Results: **There were significantly higher median values of serum levels for GDF15 (pg/mL) and hsTnI (pg/mL) among IHD group (1,630.5 and 141.8, respectively) compared to non-IHD group (895 and 14.3, respectively, $p < 0.05$ for both), with non-significant differences regarding to the BNP plasma levels ($p > 0.05$). In the IHD group, significant positive correlations were observed between GDF15 with both BNP ($r = 0.655$, $p = < 0.001$) and hsTnI ($r = 0.496$, $p = < 0.001$). Serum GDF15 at a cutoff of ≤ 717 pg/mL has the highest specificity [85.51% vs. 50.72% for BNP (at cutoff > 264 pg/mL) and 59.42% for hsTnI]. Additionally, hsTnI at a cutoff of > 45.2 pg/mL has the highest sensitivity (70.59% vs. 68.63% for BNP and 33.33% for GDF15) in discriminating heart failure with IHD from heart failure without IHD.**

Conclusions: **A multimarker approach, particularly GDF15 and hsTnI, is helpful in identifying HF patients with underlying IHD, thus enabling their proper management.**

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KEY WORDS

B-type natriuretic peptide, growth differentiation factor 15, high-sensitivity troponin I, heart failure, ischemic heart failure

LIST OF ABBREVIATIONS

eGFR - estimated glomerular filtration rate
INR - international normalization ratio

HDL-C - high density lipoprotein-cholesterol
LDL-C - low density lipoprotein-cholesterol
BNP - B-type natriuretic peptide
GDF15 - Growth differentiation factor15
hsTnI - High-sensitivity troponin I
+PV - positive predictive value
-PV - negative predictive value
AUC - area under curve
IHD - ischemic heart disease
ELISA - enzyme linked immunosorbent assay
AUC - area under curve
ROC - receiver operator characteristics
NYHA - New York heart association
PCI - percutaneous coronary intervention
CABG - coronary artery bypass grafting
BMI - body mass index
SBP - systolic blood pressure
DBP - diastolic blood pressure
LVEDD - left ventricular end diastolic diameter
LVESD - left ventricular end systolic diameter
IVS - interventricular septum
ACEI/ARBS - angiotensin-converting enzyme inhibitor/ angiotensin II receptor blockers

INTRODUCTION

Heart failure (HF) is a major medical and epidemiological issue, and new research shows that it is still associated with a high rate of morbidity and mortality, both in acute and chronic HF. Early detection of high-risk patients can have a positive impact on outcome, and biomarkers are rapidly becoming acknowledged as valuable clinical tools in this regard [1]. Ischemic heart disease (IHD) is the most common cause of HF [2]. The monitoring of circulating biomarkers has become an integral feature of HF management [3].

The use of B-type natriuretic peptide (BNP) as a biomarker for HF has changed the standard of care for HF patients substantially. It is now a common part of conventional HF care to include it in determining the diagnosis and prognosis [4]. There has been a wave of interest in novel HF biomarkers, fueled by the success of natriuretic peptides and an accumulation of data addressing the pathophysiology of HF development and progression [5].

The transforming growth factor family includes growth differentiation factor 15 (GDF15), originally known as macrophage-inhibitory cytokine. Most tissues, including the myocardium, lung, kidney, brain, liver, and gut, express low levels of GDF15. Increased expression of this cytokine can be induced by myocardial stretch, volume overload, and experimental cardiomyopathy, as well as oxidative stress, inflammatory cytokines, and ischemia/ reperfusion, implying that plasma levels of this cytokine are linked to circulatory stress as well as myocardial dysfunction [6].

The intrinsic myocyte protein high-sensitivity troponin I (hsTnI) has been linked to myocyte turnover [7]. The current research aimed to compare the circulating levels of BNP, GDF15, and hsTnI in heart failure patients with and without ischemic heart disease and also to find out the possible correlations between the measured biomarkers and their characteristic performance in discriminating heart failure with and without ischemic heart disease.

MATERIALS AND METHODS

Study design and participants

This case-control study was carried out on 120 HF patients from both sexes, categorized into 51 patients with IHD and 69 patients without apparent IHD. They were recruited from Aswan and Qena University hospitals after approval of the ethical committee of the University Hospitals and after taking a written consent from every participant. The study period was from January 2018 to December 2020 and was conducted according to the guidelines laid down in the Declaration of Helsinki. Patients with hepatic or renal disease, as well as those who refused to participate in the study, were excluded.

Clinical assessment and data collection

Ischemic heart disease was considered in HF patients in a variety of ways: patients who have had a previous MI or have had coronary artery revascularization (either with percutaneous coronary intervention "PCI" or coronary artery bypass grafting "CABG") were considered to have IHD. Furthermore, in patients who are candidates for revascularization (either by PCI or CABG), the presence of typical angina implies a clinical diagnosis of IHD, which can be confirmed by coronary angiography after an abnormal stress test or in the setting of an acute coronary syndrome (unstable angina or heart attack) [8]. All patients were subjected to a detailed history taking including: age, gender, BMI [weight (kg)/ height (m^2)], and smoking habits. Past history of drugs, operations, blood transfusion, and hospitalization or CCU admission was recorded. Presence of co-morbidities (diabetes mellitus, hypertension, and other co-morbidities) was recorded. The New York Heart Association (NYHA) graded the HF severity based on clinical symptoms [9,10]. All patients underwent transthoracic echocardiography utilizing a two-dimensional (2D) cardiovascular ultrasound system (using Vivid 3, 2005, Germany, syncmaster 450 MB). The electrocardiogram (ECG) was utilized to determine whether there was any cardiac ischemia, chamber enlargement, or arrhythmia. Coronary angiography performed for ischemic heart failure included selective catheterization of the left coronary artery and the right coronary artery (RCA), combined with intra-arterial injection of radiopaque contrast media, allowing radiographic imaging of the coronary arterial system. After accessing the blood stream through the femoral or radial artery, the procedure uses X-ray imaging to visualize the coronary arterial system.

Laboratory work up

1. Complete blood counts "CBC", sodium, potassium and calcium, urea, creatinine, INR, serum albumin and lipid profile; will be taken from the patients' files.
2. Estimated glomerular filtration rate (eGFR); as an indicator of renal function estimated from serum creatinine using a formula that accounts for the influence of age on creatinine production, which was validated in patients with HF, and described in detail in modification of diet and renal disease (MDRD) [11]. MDRD equation: 186 x (creatinine/88.4)-1.154 x (age)-0.203 x (0.742 if female) x (1.210 if male).
3. Five milliliter fasting venous blood samples were drawn from an antecubital vein of the included individuals, divided into two tubes, 2 mL on EDTA tube and centrifuged at 3,500 rpm for 15 minutes and the separated plasma was aliquoted and stored at -80℃ using 1 mL cryotubes until time of biochemical assay of plasma BNP. The remaining 3 mL was evacuated into serum separator gel tubes where the samples were allowed to clot for 30 minutes before centrifugation at 3,500 rpm for 15 minutes. The separated sera were transferred and divided into aliquots using 1 mL cryotubes and stored at -80℃ until the time of biochemical analysis of serum GDF-15 and hsTnI. All samples were measured in a single assay to avoid repeated freeze-thaw cycles. Expected values in healthy individuals for serum GDF-15 and hsTnI are (248.5 - 492.25 and 1.35 - 2.2 pg/mL, respectively).
4. Commercially available ELISA assay kits were used for biochemical assays of BNP and GDF-15, according to manufacturer protocols using a microplate ELISA reader (EMR-500, Labomed, Inc., USA): For the plasma BNP assay, the kit was supplied by Elabscience, USA, with catalog No. E-EL-H0598. For the serum GDF-15 assay, the kit was supplied by Elabscience, USA, with catalog No. E-EL-H00 80. Expected values for plasma BNP in healthy individuals are 11.5 - 17.34 pg/mL.

5. **Serum hsTnI assay**
   The Access hsTnI assay was performed on a single Beckman Coulter immunoassay analyser (Beckman Coulter, Brea, CA, USA) and the same lot of reagent, calibrators, and controls were used throughout the study. Kit item number B52699, Kit Lot Number: 922146. The Beckman Coulter Access hsTnI assay has excellent analytical sensitivity and precision characteristics close to zero [12]. Access hsTnI is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum based on chemiluminescent sandwich immunoassay principle using an automated immunoassay system (Access 2 system, USA, model BR-12178B).

Statistical analysis

Data entry and data analysis were done using SPSS version 19 (Statistical Package for Social Science). Data were presented as a number, percentage, the mean and standard deviation for parametric data, and the median and inter-quartile range for non-parametric data. Chi-squared test and Fisher's exact test were used to compare qualitative variables. Mann-Whitney test was used to compare between two quantitative variables and Kruskal-Wallist test was used to compare between more than two quantitative variables for non-parametric data. Independent *t*-test was used to compare between two quantitative variables for parametric data. Spearman's correlation was done to measure the correlation between quantitative variables in case of non-parametric data. Medcalc Program was used to calculate sensitivity, specificity, positive and negative predictive values. p-value was considered statistically significant when < 0.05.

RESULTS

Demographic and clinical data of the included patients

The study included 120 HF patients from both genders, categorized into 51 patients with IHD [37 (72.5%) males and 14 (27.5%) females], and 69 patients without IHD [25 (36.2%) males and 44 (63.8%) females] with significant male predominance in the IHD group, $p < 0.001$; male to female ratio was 2.6 in the IHD group. The mean ± SD of age of the IHD group was 59.82 years ± 12.06 which was significantly older than the mean age of the non-IHD patients which was 52.35 ± 16.75, $p = 0.032$. The BMI of IHD patients (36.97 ± 4.49) was significantly higher than non-IHD group (32.72 ± 7.22), $p = 0.001$ (Table 1).

Smoking, diabetes mellitus, hypertension, and dyslipidemias were significantly more frequent cardiovascular risk factors among the IHD group [37 (72.5%), 36 (70.6%), 37 (72.5%), and 51 (100%), respectively] compared to the non-IHD patients [14 (20.3%), 20 (29%), 27 (39.1%), and 27 (39.1%), respectively], $p < 0.001$ for all, (Table 1). The various etiologies of HF in the non-IHD group included dilated cardiomyopathy [19 (27.5%)], decompensated core pulmonale [15 (21.7%)], valvular heart disease [14 (20.3%)], hypertensive heart failure and HF due to congenital heart disease [6 (8.7%) for each], and peri-partum cardiomyopathy [4 (5.8%)].

There were significantly lower mean systolic and diastolic blood pressures among non-IHD patients (103.33 mmHg ± 22.34 and 67.54 ± 13.33, respectively) compared with the IHD group (118.24 ± 14.38 and 74.9 ± 10.84, respectively, and $p < 0.00$, and $p = 0.002$, respectively. Both patient groups included HF of various NYHA classes (I, II, III, and IV) with nonsignificant differences regarding the frequency of each class among the included patient groups or in the ejection fraction

Table 1. Demographic and clinical characteristics of heart failure patients with ischemic heart disease compared to heart failure patients without ischemic heart disease.

Variables	Ischemic heart failure patients (n = 51)	Non-ischemic heart failure patients (n = 69)	p-value
Age (years)	59.82 ± 12.06	52.35 ± 16.75	0.032 *
Gender (No., %)			
Males	37 (72.5%)	25 (36.2%)	< 0.001*
Females	14 (27.5%)	44 (63.8%)	
BMI "kg/m^2"	36.97 ± 4.49	32.72 ± 7.22	0.001 *
Cardiovascular risk factors (No., %)			
Smoking	37 (72.5%)	14 (20.3%)	< 0.001 *
Diabetes mellitus	36 (70.6%)	20 (29%)	< 0.001 *
Hypertension	37 (72.5%)	27 (39.1%)	0.001 *
Dyslipidemias	51 (100%)	27 (39.1%)	< 0.001 *
Heart rate (beat/min, mean ± SD)	94.16 ± 11.06	96.91 ± 11.54	0.163
SBP (mmHg, mean ± SD)	118.24 ± 14.38	103.33 ± 22.34	< 0.001 *
DPB (mmHg, mean ± SD)	74.9 ± 10.84	67.54 ± 13.33	0.002 *
NYHA class (No., %)			
Class - I	14 (27.5%)	16 (23.2%)	0.604
Class - II	14 (27.5%)	15 (21.7%)	
Class - III	5 (9.8%)	26 (37.7%)	
Class - IV	18 (35.3%)	12 (17.4%)	
Ejection fraction (%, mean ± SD)	45.41 ± 10.49	47.07 ± 12.45	0.397
Echocardiographic parameters (mean ± SD)			
LVEDD (cm)	5.76 ± 0.95	5.52 ± 1.03	0.154
LVESD (cm)	4.58 ± 1.02	4.35 ± 1.06	0.161
Wall motion abnormalities (No., %)			
Anterior wall dyskinesias	40 (78.4%)	28 (40.6%)	< 0.001 *
Lateral wall dyskinesias	12 (23.5%)	28 (40.6%)	0.077
IVS dyskinesias	33 (64.7%)	32 (46.4%)	0.075
Inferior wall dyskinesias	34 (66.7%)	31 (44.9%)	0.029 *
Diastolic dysfunction	51 (100%)	55 (79.7%)	0.002 *
Medications (No., %)			
Diuretics	48 (94.1%)	59 (85.5%)	0.230
Inotropes	3 (6.1%)	30 (43.5%)	< 0.001 *
ACEI/ARBS	16 (32.7%)	11 (15.9%)	0.052
Anti-platelets	45 (88.2%)	29 (42%)	< 0.001 *
Anticoagulants	13 (25.5%)	34 (49.3%)	0.014 *
Digitalis	8 (15.7%)	15 (21.7%)	0.555
Beta-blockers	27 (52.9%)	10 (14.5%)	< 0.001 *
Nitrates	29 (56.9%)	16 (23.2%)	< 0.001 *
Ca channel blockers	0 (0%)	3 (4.3%)	0.366
Statins	31 (60.8%)	15 (21.7%)	< 0.001 *

*** $p < 0.05$ is significant.**

Table 2. Routine laboratory data of heart failure patients due to ischemic etiology compared to heart failure patients due to other etiologies.

Variables	Ischemic heart failure patients (n = 51)	Non-ischemic heart failure patients (n = 69)	p-value
Hemoglobin (g/dL, mean ± SD)	12.58 ± 1.35	12.44 ± 2.29	0.315
eGFR (mL/min/1.73 m^2, mean ± SD)	117.59 ± 43.33	82.8 ± 15.88	< 0.001 *
S. creatinine (mg/dL, mean ± SD)	0.76 ± 0.22	0.88 ± 0.11	0.003 *
Blood urea (mg/dL, mean ± SD)	43.12 ± 16.34	48 ± 23.33	0.391
Ionized calcium (mg/dL, mean ± SD)	1.06 ± 0.08	1 ± 0.08	< 0.001 *
Potassium (mEq/L, mean ± SD)	3.98 ± 0.52	4.23 ± 0.68	0.003 *
Sodium (mEq/L, mean ± SD)	137.26 ± 4.1	135.74 ± 7.04	0.263
Albumin (g/dL, mean ± SD)	3.98 ± 0.51	3.8 ± 0.65	0.115
INR (mean ± SD)	1.24 ± 0.44	1.75 ± 1.38	0.075
Lipid profile (mean ± SD)			
Triglycerides (mg/dL, mean ± SD)	271.29 ± 40.77	197.54 ± 41.4	< 0.001 *
Total cholesterol (mg/dL, mean ± SD)	272.55 ± 14.8	201.62 ± 36.43	< 0.001 *
HDL-C (mg/dL, mean ± SD)	28.75 ± 6.64	42.71 ± 10.11	< 0.001 *
LDL-C (mg/dL, mean ± SD)	157.31 ± 19.07	112.64 ± 19.08	< 0.001 *

*** p < 0.05 is significant.**

Table 3. Comparison of the circulating levels of the specific measured biochemical markers among heart failure patients due to ischemic etiology compared to heart failure patients due to other etiologies.

Variables	Ischemic heart failure patients (n = 51)	Non-ischemic heart failure patients (n = 69)	p-value
BNP (pg/mL)			0.297
Median	315.5	272	
Interquartile range "IQR"	106 - 610.5	163 - 480.5	
GDF15 (pg/mL)			< 0.001 *
Median	1,630.5	895	
Interquartile range "IQR"	1,317 - 2,003	717 - 1,391	
hsTnI (pg/mL)			< 0.001 *
Median	141.8	14.3	
Interquartile range "IQR"	74.3 - 699.2	6.4 - 48.25	

*** p < 0.05 is significant.**

Table 4. Correlations between the circulating levels of the specific measured biochemical markers with each other among heart failure patients.

Heart failure patients with ischemic heart disease (n = 51)		
Specific measured biomarkers	GDF15 (pg/mL)	hsTnI (pg/mL)
BNP (pg/mL)	r = 0.655	r = 0.115
	p ≤ 0.001 *	p = 0.423
hsTnI (pg/mL)	r = 0.496	
	p = < 0.001 *	

*** p < 0.05 is significant.**

Table 5. Characteristics performances of plasma BNP (pg/mL), serum GDF15 and hsTnI (pg/mL) for discriminating heart failure with ischemic heart disease from heart failure without ischemic heart disease.

Cutoff	Sensitivity	Specificity	+PV	-PV	Accuracy	AUC
BNP > 264 pg/mL	68.63	50.72	50.7	68.6	59.58	0.551
GDF15 ≤ 717 pg/mL	33.33	85.51	63	63	59.42	0.511
hsTnI > 45.2 pg/mL	70.59	59.42	56.2	73.2	65.01	0.611

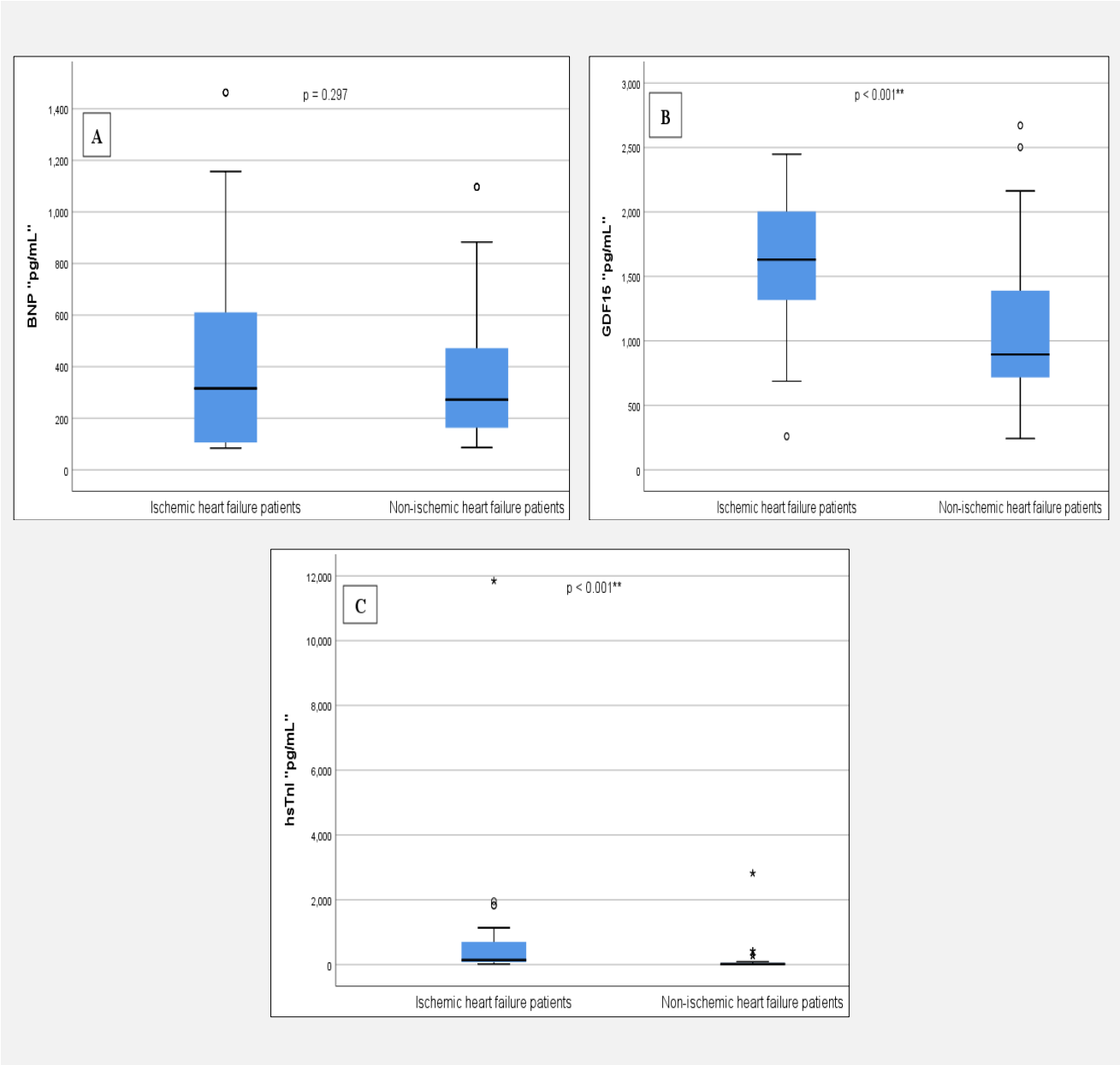

Figure 1. (A) Plasma levels (median, IQR) of BNP, (B) serum levels (median, IQR) of GDF15, and (C) hsTnI in heart failure patients with ischemic heart disease compared with heart failure patients without ischemic heart disease.

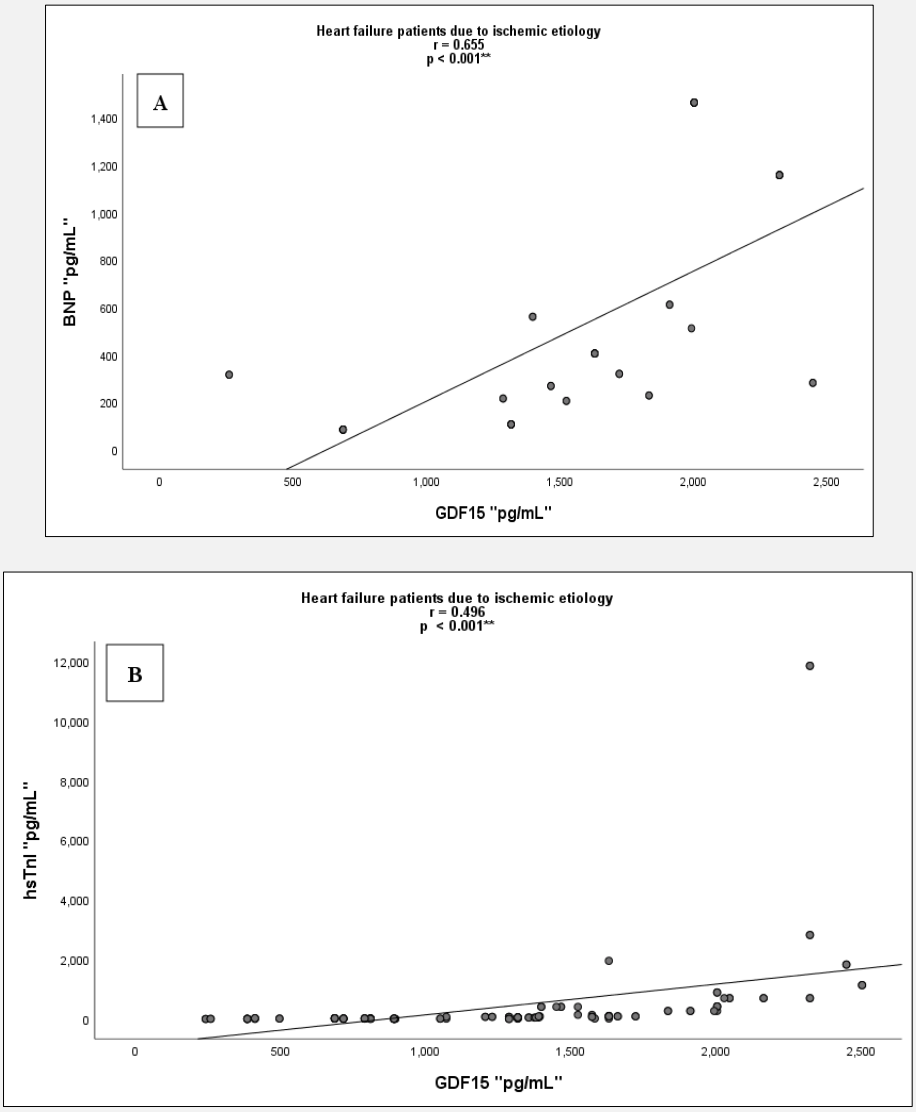

Figure 2. Positive correlation between GDF15 and BNP levels (A) among ischemic heart failure patients (r = 0.655, p < 0.001) and positive correlation between serum GDF15 and hsTnI (B) among ischemic heart failure patients (r = 0.496, p < 0.001).

(EF) or left ventricular end systolic (LVESD) or diastolic (LVEDD) diameters ($p > 0.05$ for all). Thus, we avoid the differences in both the clinical severity and echocardiographic parameters (EF, LVESD, and LVEDD) between the study groups as well as possible confounding factors that may affect the circulating studied marker levels. There were significantly higher frequencies of dyskinesias (anterior and inferior walls) and diastolic dysfunction among HF patients with IHD compared to non-IHD ($p < 0.05$ for all), (Table 1). Percutaneous coronary intervention "PCI" was present in 11 (21.6%) patients with HF and IHD.

As regards the frequencies of various coronary angiographic lesions among HF patients with IHD, right coronary artery (RCA) lesion was present in 32 (62.7%) patients, left anterior descending artery (LAD) lesion was present in 31 (60.8%) patients, while the least frequent one was left circumflex artery (LCX) lesion which was present in 19 (37.3%) patients. It should be noted that the patient may have more than one lesion. Anti-platelets (88.2%), β-blockers (52.9%), nitrates (52.9%), and statins (60.8%) were more frequent medications among ischemic heart failure patients with less frequent use of inotropes and anticoagulants compared to the non-IHD

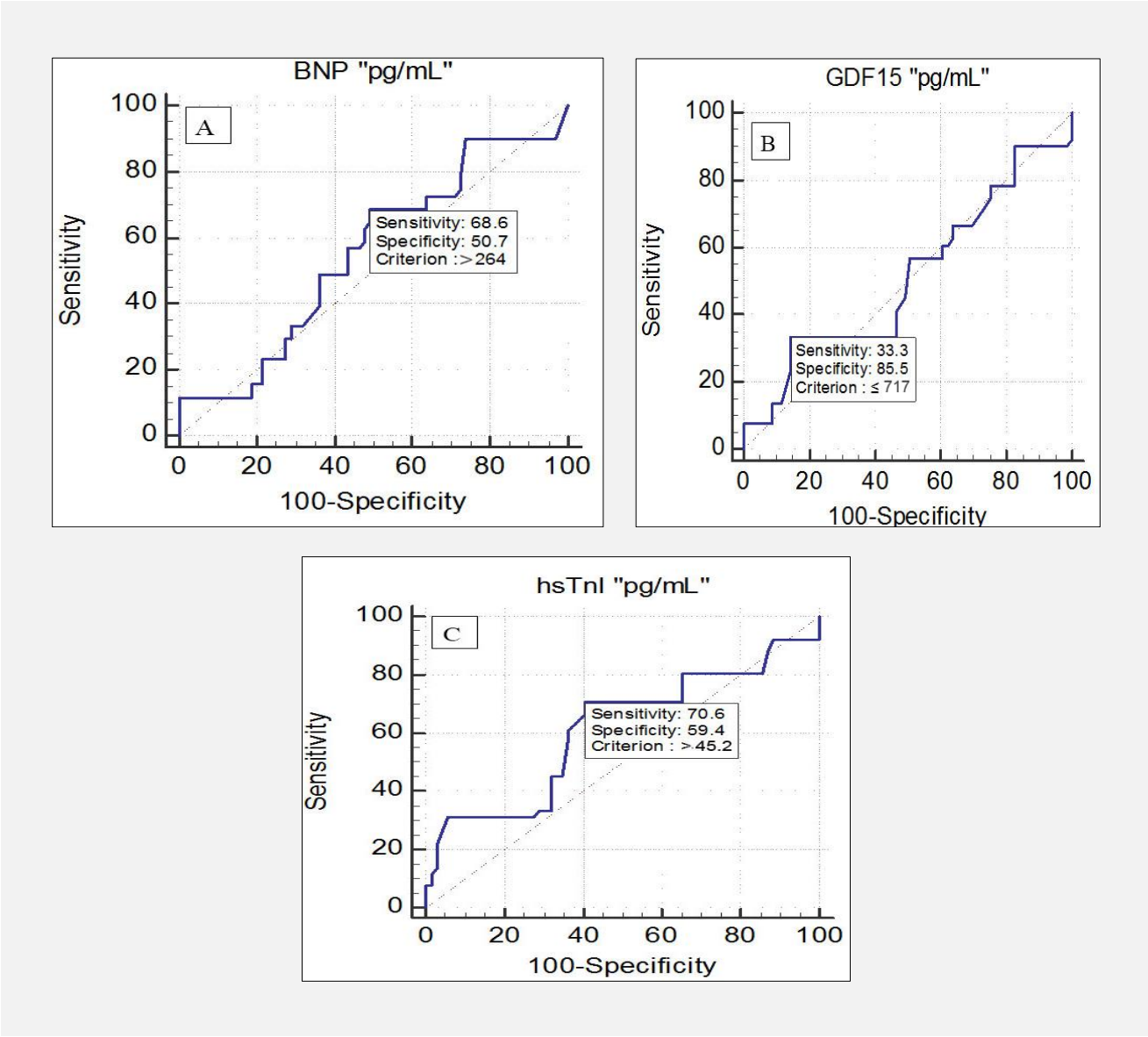

Figure 3. Receiver operator characteristics (ROC) curves of (A) plasma BNP, (B) serum GDF15, and (C) hsTnI for discriminating ischemic heart failure from heart failure due to other etiologies.

group ($p < 0.05$ for all), (Table 1).

Routine laboratory data of the included patients

There were significantly higher mean values of eGFR (mL/min/1.73 m^2), triglycerides (mg/dL), total cholesterol (mg/dL), LDL-C (mg/dL) and significantly lower mean values of creatinine (mg/dL) and HDL-C (mg/dL) among ischemic heart failure patients (117.59 ± 43.33, 271.29 ± 40.77, 272.55 ± 14.8, 157.31 ± 19.07, 0.76 ± 0.22, and 28.75 ± 6.64, respectively) compared to the non-IHD group (82.8 ± 15.88, 197.54 ± 41.4, 201.62 ± 36.43, 112.64 ± 19.08, 0.88 ± 0.11, and 42.71 ± 10.11, respectively) with $p < 0.05$ for all), (Table 2).

Comparison of the circulating levels of BNP, GDF15 and hsTnI among heart failure patient groups

There were significantly higher median values of serum levels for GDF15 (pg/mL) and hsTnI (pg/mL) among ischemic heart failure patients (1,630.5 and 141.8, respectively) compared to those with heart failure due to other etiologies (895 and 14.3, respectively) ($p < 0.05$ for both), with non-significant differences regarding the BNP plasma levels (pg/mL) among the two patient subgroups (315.5 vs. 272, respectively) ($p > 0.05$), (Table

3, Figure 1A, B, and C).

Correlations between the circulating levels of BNP, GDF15, and hsTnI among heart failure patients with ischemic heart disease

Among ischemic heart failure patients, there were significant positive correlations between serum GDF15 with both plasma BNP ($r = 0.655$, $p = < 0.001$) and serum hsTnI ($r = 0.496$, $p = < 0.001$) with a lack of correlation between BNP and hsTnI levels ($r = 0.115$, $p = 0.423$), (Table 4, Figure 2A and B). There were no significant correlations between the studied markers among HF patients without IHD, $p > 0.05$.

Characteristic performances of plasma BNP, serum GDF15, and hsTnI for discriminating heart failure with ischemic heart disease from heart failure without ischemic heart disease

Serum GDF15 at cutoff ≤ 717 pg/mL has the highest specificity [85.51% vs. 50.72% for BNP (at cutoff > 264 pg/mL) and 59.42% for hsTnI]. Additionally, hsTnI at cutoff > 45.2 pg/mL has the highest sensitivity (70.59% vs. 68.63% for BNP and 33.33% for GDF15) and AUC (0.611 vs. 0.551 for BNP and 0.511 for GDF-15) in discriminating heart failure with IHD from heart failure without IHD, with non-significant differences between the three markers regarding to their AUC ($p > 0.05$), (Table 5, Figure 3A, B, and C).

DISCUSSION

Heart failure is a global pandemic that affects at least 26 million people and is becoming more common [13]. Since the 1990s, cardiovascular disease (CVD) has been the main cause of mortality in Egypt [14]. CVD accounted for 46.2% of total mortality in Egypt in 2017 [15]. HF poses a significant and growing public health burden, given the aging of the population and the effectiveness in extending the survival of people who have had coronary events.

In the present research, HF patients were categorized into two subgroups according to the apparent etiology, the first group was HF with ischemic heart disease (ischemic HF) and the other group was heart failure without ischemic heart disease (heart failure due to other etiologies, non-ischemic HF). Ischemic HF frequently occured with older age, male gender, and higher BMI values compared to non-IHD group. Smoking, DM, hypertension, and dyslipidemias were significant and frequent cardiovascular risk factors for ischemic heart failure. Anterior and inferior wall hypokinesias and diastolic dysfunction were highly frequent among ischemic heart failure. Anti-platelets, β-blockers, nitrates, and statins (lipid lowering drugs) were more frequent medications among ischemic heart failure patients with less frequent use of inotropes and anticoagulants. These data were in line with Tominaga et al. [16], Gheisari et al. [17], and Cesaroni et al. [18] who reported similar findings.

Our findings revealed significantly higher eGFR, triglycerides, total cholesterol, LDL-C, and significantly lower mean values of creatinine and HDL-C among ischemic heart failure patients. Many investigators were in line with our findings who reported that hypercholesterolemia, hypertriglyceridemia, high LDL-C, and low HDL as common findings in IHD [19-22]. HF can induce a reduction in cardiac output and a decrease in renal perfusion, which has become the predominant driver of renal dysfunction in HF, according to pathophysiological characteristics [23,24].

In cases of cardiovascular injury, such as pressure overload, myocardial infarction, heart failure, and atherosclerosis, GDF-15 levels may be significantly elevated [25]. The current study findings revealed significantly higher serum levels for GDF15 among ischemic heart failure patients compared to the non-IHD group. Similarly, after a myocardial infarction in mice, the infarcted area shows a rapid and long-lasting production of GDF-15, whereas the noninfarcted myocardium shows a lesser and more temporary induction [26]. In patients with acute myocardial infarction, GDF-15 is expressed in the heart [27]. GDF-15 expression in the heart has been seen in mice models of pressure overload, hypertrophic or dilated cardiomyopathy [28-30], suggesting that GDF-15 and BNP share similar upstream regulatory stimuli. Despite the fact that GDF-15 is highly expressed in infarcted human hearts [27], a study revealed no indication of GDF-15 expression in the myocardium of individuals with advanced nonischemic HF [31]. GDF-15 has been proposed as a biomarker for the activation of the p53 pathway. GDF-15 co-localizes with p53 in human atherosclerotic plaque macrophages, which supports this theory [32,33]. p53 is a link between aging and age-related diseases like atherosclerosis and HF [34]. In particular, elevated GDF-15 levels in community-dwelling individuals and patients with CV disease are being linked to aging, diabetes, atherosclerosis, and heart failure [35].

Our study findings also revealed significantly higher serum levels of hsTnI among ischemic heart failure patients compared to the non-IHD group. The fact that high sensitivity troponin "hsTn" assays are specific for myocardial infarction but not for the source of myocardial injury is a significant aspect. A variety of different disorders, including acute and chronic HF, can induce myocardial injury, either persistently or abruptly [36, 37]. Multiple pathophysiological processes exist, with minor changes, in both acute and chronic HF. Acute MI is the most common cause of elevated troponin levels in both acute and chronic HF. Ischemia for a long time causes myocardial necrosis, cell membrane breakdown, and the release of structural and cytosol troponins [38]. The interpretation of increased cTnT and I levels in patients with IHD might be difficult. Asymptomatic stenoses of one or more large or small coronary arteries may exist in patients with HF. As a result, the increase in biochemical biomarkers of myocyte injury seen in patients with chronic HF and coronary stenoses could be

due to ischemia of the myocardium supplied by the stenosed artery [39].

The concentration of plasma immunoreactive BNP is a sensitive biochemical marker of HF [40]. A rise in BNP accurately detects ventricular dysfunction in patients with heart failure symptoms. However, in individuals who do not have overt symptoms of HF, BNP levels are not specific for ventricular dysfunction, suggesting that other cardiac processes such as myocardial ischemia may also generate BNP increases [41]. Notably, in the present research, there were higher plasma BNP levels among patients with ischemic HF than non-IHD patients with HF, but did not reach a level of significant difference, which could be explained by a relatively small sample size.

In the present study, for the first time to our knowledge, we found significant positive correlations between serum GDF15 with both plasma BNP and serum hsTnI among heart failure patients with ischemic heart disease.

We used ROC curves to visually highlight the significance of the examined biomarkers in distinguishing HF patients with IHD from those with other etiologies. The current study first revealed that serum GDF15 at a cutoff of ≤ 717 pg/mL have highest specificity (85.51% vs. 50.72% for BNP and 59.42% for hscTnI). Additionally, hsTnI at a cutoff of > 45.2 pg/mL have the highest sensitivity (70.59% vs. 68.63% for BNP and 33.33% for GDF15) and AUC (0.611 vs. 0.551 for BNP and 0.511 for GDF15) in discriminating heart failure with IHD from heart failure due to etiologies other than BNP plasma levels at a cutoff of > 264 pg/mL, with non-significant differences between the three markers regarding their AUC. These findings suggest that assays of various biomarkers of cardiovascular stress provide information beyond what standard cardiovascular risk factors may provide. Given that HF syndrome involves a variety of interplay ranging from cardiac remodeling to altered renal function and neurohormonal activation pathways, a multi-marker approach in the context of several other biomarkers that target different pathophysiological pathways may yield significant results in risk stratification and HF management. This is because a multi-biomarker method like this has the potential to specify the care of HF patients [42].

CONCLUSION

Serum GDF15 and hsTnI levels are significantly elevated in HF patients with IHD and correlated in a positive manner. Serum GDF15 has the highest specificity and hsTnI has the highest sensitivity in discriminating heart failure with IHD from heart failure due to etiologies other than BNP plasma levels, so a multi-marker approach is of great importance in the diagnosis, evaluation, and risk stratification of heart failure patients in addition to clinical and echocardiographic assessments.

Study's Limitations:

Relatively small sample size was the main study limitation. Additionally, lack of multicentre approach was another study limitation.

Acknowledgment:

Not applicable.

Ethics Approval and Consent to Participate:

The study was approved by the local Ethics Committee of Medical Research of the Faculties of Medicine, Aswan and South Valley Universities, but the reference number is not applicable. The study was conducted in accordance with the Declaration of Helsinki. Informed written consent was obtained from every participant.

Consent for Publication:

Not applicable.

Source of Funds:

Not applicable.

Availability of Data and Materials:

The datasets used and analyzed in this study are available upon reasonable request.

Declaration of Interest:

The authors declare no competing interest.

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