Adiponectin is valuable in the diagnosis of acute heart failure with renal insufficiency

ZHANG DAI[1*], YAN ZHANG[1*], HUIMING YE[2,3*], GUOQIANG ZHANG[1], HONGWEI JIN[1], ZIMING CHEN[4], YIHUI YAO[1], XUEBING TIAN[5], JIANFENG ZHOU[1], PEIHUA LI[1], XIANMING LIANG[1], HUABING XIE[5], SHENGXIANG GE[2] and ZHONGYING ZHANG[1,2,6]

[1]Department of Clinical Laboratory, Zhongshan Hospital Xiamen University, Xiamen, Fujian 361001; [2]State Key Laboratory of Molecular Vaccine and Molecular Diagnostics, School of Public Health, Xiamen University, Xiamen, Fujian 361002; [3]Department of Clinical Laboratory, Xiamen Maternal and Child Health Hospital, Teaching Hospital of Medical College Xiamen University, Xiamen, Fujian 361003; [4]Department of Reagent Research, Xiamen Innovax Biotech Co., Ltd., Xiamen, Fujian 361022; [5]Department of Clinical Laboratory, Xiamen Cardiovascular Hospital, Medical College Xiamen University; [6]Department of Clinical Laboratory, Zhongshan Teaching Hospital, Fujian Medical University, Xiamen, Fujian 361001, P.R. China

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Abstract. Acute heart failure (AHF) is a major public health issue due to its high incidence and poor prognosis; thus, efficient and timely diagnosis is critical for improving the prognosis and lowering the mortality rate. Amino-terminal pro-brain natriuretic peptide (NT-proBNP) is widely used in the diagnosis of AHF; however, its efficacy is controversial in diagnosing AHF with renal insufficiency. There were numerous studies reporting the association of adiponectin (ADPN) and heart diseases. Therefore, the present study aimed to investigate whether ADPN is helpful in identifying AHF with renal insufficiency. A total of 407 participants (218 AHF patients and 189 controls) were enrolled into the current study. The plasma levels of ADPN and NT-proBNP were measured using a sandwich enzyme-linked immunosorbent assay and an electrochemiluminescence immunoassay, respectively. In addition, these levels were compared among the various New York Health Association classes, as well as the ischemic and non-ischemic AHF cases. The correlation between the two biomarkers and the renal function was analyzed by Spearman's correlation, while the diagnostic efficiency of ADPN and NT-proBNP was evaluated in AHF patients with and without renal insufficiency. The results revealed that NT-proBNP exhibited a higher diagnostic efficiency as compared with ADPN in patients without renal insufficiency [area under the receiver operating characteristic curve (AUC), 0.905 vs. 0.775]. By contrast, the ADPN presented a better diagnostic value in comparison with NT-proBNP in AHF with renal insufficiency (AUC, 0.872 vs. 0.828). Therefore, a combination of these two biomarkers may provide an excellent efficacy in the diagnosis of AHF with renal insufficiency (AUC, 0.904; sensitivity, 71.2%; specificity, 98.3%). In conclusion, ADPN is a valuable biomarker for diagnosing AHF, particularly in patients with impaired renal function.

Introduction

Acute heart failure (AHF) is a major public health issue due to its high incidence and poor prognosis, while the number of hospitalizations for AHF continues to increase due to the aging population (1-4). Efficient and timely diagnosis is critical for improving the prognosis, as well as reducing the mortality rate, length of hospital stay and treatment costs (5,6). Compared with other detection methods for diagnosing AHF, plasma markers have certain advantages, including the simple and easy detection. Amino-terminal pro-brain natriuretic peptide (NT-proBNP) is one of the most commonly used markers in AHF diagnosis (7-9). However, renal dysfunction is a common comorbidity in AHF patients (10). In addition, patients with chronic kidney disease (CKD) present increased risks of accelerated atherosclerosis, nonfatal myocardial infarction, congestive heart failure (CHF), atrial and ventricular arrhythmias, and cardiac death (11). Although NT-proBNP is considered as a marker in AHF diagnosis, the diagnostic value of NT-proBNP in patients with renal insufficiency is still debated (12-15). Therefore, a more effective plasma marker is required for the diagnosis of AHF patients with renal insufficiency.

Correspondence to: Dr Zhongying Zhang, Department of Clinical Laboratory, Zhongshan Hospital Xiamen University, 201 Siming District South Lake Road, Xiamen, Fujian 361001, P.R. China
E-mail: zhongyingzhang_01@126.com

*Contributed equally

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A multimarker strategy may help diagnose and determine the prognosis of patients with AHF (16), particularly in patients with AHF and mild to moderate renal impairment, while multimarker approach based on a panel of serially evaluated biomarkers may provide the greatest prognostic improvement. A previous study demonstrated that seven circulating biomarkers, including NT-proBNP, high sensitivity cardiac troponin T, soluble ST2, growth differentiation factor 15, cystatin-C, galectin-3 and high-sensitivity C-reactive protein (CRP), measured at baseline and on days 2, 5, 14 and 60 in 1,161 patients provided an improved quick diagnosis (17).

The adipocyte-secreted protein adiponectin (ADPN) is a 247 amino acid peptide, predominantly secreted by adipocytes (18,19). Plasma ADPN is typically high in cats, which are overweight and functions by regulating the level of leptin (20). ADPN is considered as a useful biomarker in metabolic diseases, such as diabetes, high-fat-associated disease and dementia (21-23). In addition, it has been observed that ADPN exerts several protective functions in the peripheral tissues, including insulin sensitizing, anti-inflammatory and anti-oxidative effects, which may benefit various neurodegenerative diseases, such as Alzheimer's disease (24). The role of ADPN in heart diseases has been investigated in numerous studies. For instance, a cross-sectional study revealed that a low ADPN level was associated with diastolic dysfunction in women (25). Another study demonstrated that natriuretic peptides, which are promising candidates for the treatment of CHF, may have a beneficial effect on cardiomyocytes in patients through enhancing the ADPN production by human adipocytes *in vitro* and in patients with CHF (26). Furthermore, the circulating ADPN concentration increased in patients with chronic heart failure (HF), and thus it is regarded as a useful novel biomarker in CHF and AHF (27,28). A previous study suggested that when the ADPN level is used in conjunction with NT-proBNP in chronic HF, the prognostic value may be improved when compared with the use of each biomarker alone (29). Another study also identified ADPN as a robust biomarker and appropriate therapeutic targets in HF (30).

These aforementioned studies prompt the hypothesis that ADPN may be a useful biomarker in diagnosing AHF patients. However, there are a limited number of studies on whether the circulating level of ADPN was affected by glomerular filtration rate (GFR) and, thus, whether it has superiority in diagnosing AHF patients with renal insufficiency. The aim of the present study was to examine the value of ADPN in the diagnosis of these patients. In total, 407 participants were enrolled into the current study, including 218 participants diagnosed with AHF and 189 participants serving as the control group. ADPN was measured in the participants using an in-house sandwich enzyme-linked immunosorbent assay (ELISA) and NT-proBNP was measured by electrochemiluminescence immunoassay. The levels of circulating ADPN and NT-proBNP in the patients of AHF were also compared between different New York Health Association (NYHA) classes, as well as ischemic and non-ischemic AHF. The correlation between the renal function and the two biomarkers of all participants were compared by Spearman's correlation. Finally, the diagnostic efficiency of ADPN and NT-proBNP was evaluated in patients with and without renal insufficiency.

Patients and methods

Clinical cohort. The present study enrolled 407 patients with suspected cardiac-associated dyspnea who were admitted to the Emergency Department of the Xiamen Cardiovascular Hospital (Xiamen, China) between April 2015 and June 2015. Among them, 218 patients (53%) were diagnosed with AHF based on the 'European Society of Cardiology guidelines' (31) and classified according to the NYHA system, as follows: Class I, the patient suffers from heart disease, however, ordinary activities are not restricted by cardiac function; Class II, mild restrictions on the physical activity of patients with heart disease and no symptoms at rest, although patients may experience fatigue, dyspnea or angina following physical activity; Class III, severe restrictions on the physical activity of patients with heart disease with cardiac failure symptoms; and Class IV, patient is unable to participate in any physical activities. In light of the guidelines from the European Society of Cardiology guidelines, the following levels of NT-proBNP were used for excluding AHF patients: 450 pg/ml in patients aged <50 years; 900 pg/ml between the ages of 50 and 75 years; and 1,800 pg/ml in patients aged >75 years (31). Furthermore, cardiovascular magnetic resonance was conducted to determine whether ischemic AHF was present. The remaining 189 participants presented a normal cardiac function and served as the controls, including patients with bronchial asthma and other respiratory system diseases. Patients receiving dialysis within the three months prior to admission were excluded from the current study since ADPN and NT-proBNP levels are affected by dialysis. The study was approved by the Ethics Committee of Zhongshan Hospital, Xiamen University (Xiamen, China), and was conducted according to the Declaration of Helsinki (2008). Written informed consent was obtained from all participants.

Laboratory measurements. The levels of NT-proBNP and the renal function were detected immediately upon presentation to the Emergency Department. Plasma was collected in an EDTA-K3 anticoagulation tube and centrifuged at 1,006 x g at 4˚C for 15 min. NT-proBNP was detected using the Elecsy proBNP II electrochemiluminescence immunoassay (Roche Diagnostics, Basel, Switzerland) and the Cobas E601 analyzer (Roche Diagnostics). The residual plasma samples were preserved at -80˚C for ADPN level detection.

Subsequently, the plasma ADPN levels were detected using a sandwich ELISA kit (Xiamen Innovax Biotech Co., Ltd., Xiamen, China). The serum samples were diluted by 100 times during the ELISA procedure, while the total ADPN level was the sum of several polymers, including trimers, hexamers and high polymers.

Renal function tests, including creatinine and GFR, were performed with an auto-biochemistry analyzer (Cobas C701; Roche Diagnostics). The GFR was estimated using the Modification of Diet in Renal Disease equation as previously described (32). A GFR value of <60 ml/min/1.73 m^2 indicated renal insufficiency, while a GFR value of ≥60 ml/min/1.73 m^2 was considered to indicate normal renal function.

Statistical analysis. The SPSS version 19.0 statistical software package (IBM Corp., Armonk, NY, USA) was used to analyze

the data. The Skewness-Kurtosis test was used to determine the distribution of data, and the non-parametric Kruskal-Wallis test was performed if the data were not distributed normally and the values were reported as the median (25th quantile and 75th quantile). Enumeration data were compared using a χ^2 test. The Nemenyi post-hoc test was used to compare between multiple sets of data. Spearman's correlation co-efficient was calculated for the correlation of renal function with the ADPN and NT-proBNP levels. Receiver operating characteristic (ROC) curve analyses were performed and the area under the ROC curve (AUC) was calculated to evaluate the diagnostic accuracy of ADPN and NT-proBNP. Data were analyzed separately for participants with normal and impaired renal functions, and subsequently compared. The Z-test was also performed to determine the statistical difference of the ROC curve. A two-sided P-value of <0.05 was considered to indicate a statistically significant difference.

Results

Clinical characteristics of the participants. A total of 407 participants were enrolled into the present study, including 262 males and 145 females, among them 218 participants were accurately diagnosed with AHF. The clinical characteristics of all participants are listed in Table I. In the AHF group, the plasma creatinine levels of the 218 participants were 0.87 (0.71, 1.13) mg/dl, while the estimated GFR was 86.26 (60.20, 106.98) ml/min/1.73 m^2. In the control group, the plasma creatinine levels of the 189 participants were 0.97 (0.80, 1.34) mg/dl and the estimated GFR was 75.04 (54.18, 95.08) ml/min/1.73 m^2. The reference values for creatinine and GFR were 0.60-1.09 mg/dl and 90-120 ml/min/1.73 m^2, respectively. Renal insufficiency was detected in 111 participants, among which 52 were diagnosed with AHF. Renal insufficiency was detected in 59 individuals within the control group. In addition, the plasma ADPN level was 11.05 (6.51, 16.28) μg/ml and the NT-proBNP was 2,158 (1,032, 4,930) pg/ml in the AHF group, whereas the ADPN level was 5.56 (3.43, 7.39) μg/ml and the NT-proBNP was 220 (56, 690) pg/ml in the control group.

ADPN levels are significantly associated with the NYHA class, and may assist in distinguishing non-ischemic from ischemic AHF. The results revealed that ADPN and NT-proBNP levels were significantly higher in participants with an advanced NYHA class (Table II; Fig. 1A and B). Statistically significant differences were detected in the ADPN levels between the control group and the NYHA class I (P=0.04); however, there was no significant difference in the NT-proBNP level between these groups (P=0.26). In terms of the plasma ADPN level, significant differences were detected between class I and II (P=0.12), class II and III (P=0.00), and class III and IV (P=0.04). Regarding the plasma NT-proBNP levels, marked differences were observed between class I and II (P=0.02) and class III and IV (P=0.02).

Participants with AHF were further divided into the ischemic and non-ischemic HF groups based on the disease pathogenesis of AHF. The non-ischemic group included cases of valvular heart disease, hypertension, dilated cardiomyopathy, hypertrophic cardiomyopathy and hypertensive heart disease. The ischemic group included coronary artery disease and atherosclerosis heart disease cases. As shown in Table III and Fig. 1C and D, the ADPN levels in the ischemic group were significantly reduced when compared with those in the non-ischemic group (P=0.02). However, there was no statistically significant difference detected in the NT-proBNP levels between the two groups (P=0.81). The combination of these two indicators may help clinicians to establish a timely and accurate diagnosis of AHF, and to subsequently select the appropriate treatment.

Circulating ADPN levels are affected by renal function to a lesser extent as compared with NT-proBNP levels. The GFR value of the participants was determined to examine the renal function (renal insufficiency: GFR≥60). The levels of NT-proBNP (pg/ml) in both the AHF and control (normal cardiac function) patients were significantly higher in individuals with renal insufficiency as compared with those with normal renal function [AHF renal insufficiency 4,697.0 (1,878.5, 10,744.5) vs. normal renal function 1,892.0 (892.5, 3,870.0) and Control renal insufficiency 656.0 (316.8, 2,172.5) vs. normal renal function 104.0 (37.0, 331.0), respectively; both P<0.01; Fig. 2A and B]. Similarly, the levels of ADPN (μg/ml) in AHF patients were also significantly affected by the renal function, since the ADPN level in AHF patients with renal insufficiency was significantly higher compared with those with normal renal function [AHF renal insufficiency 12.9 (8.6, 16.5) vs. normal renal function 10.6 (6.2, 15.7); P=0.04; Fig. 2C]. By contrast, in control patients (normal cardiac function), there was no evident difference in the ADPN level between the normal and abnormal renal function groups [renal insufficiency 5.8 (3.7, 7.5) vs. normal renal function 5.3 (3.3, 7.2); P=0.62; Fig. 2D).

The correlation between AHF serum biomarkers (NT-proBNP and ADPN) and renal function were then further investigated. In the present study, the levels of creatinine and GFR were considered to reflect the renal function. As shown in Fig. 3A and B, the NT-proBNP levels were significantly correlated with the renal function. The NT-proBNP levels were positively correlated with creatinine and negatively correlated with GFR in both the AHF and control groups. The correlation coefficients in the control and AHF groups were 0.386 (P<0.01) and 0.343 (P<0.01) for creatinine, respectively, and -0.488 (P<0.01) and -0.412 (P<0.01) for GFR, respectively. By contrast, as shown in Fig. 3C and D, ADPN was not significantly correlated with creatinine and GFR. In the control and AHF groups, the correlation coefficients for creatinine were observed to be 0.124 (P=0.12) and 0.073 (P=0.29), respectively, while for GFR, the coefficients were 0.008 (P=0.21) and -0.177 (P=0.16), respectively. These findings indicated that the ADPN level was affected to a lesser extent by impaired renal function as compared with the NT-proBNP level, which may be helpful in diagnosing AHF patients with impaired renal function.

Diagnostic value of ADPN and NT-proBNP for AHF in normal renal function and impaired renal function patients. To determine whether the plasma levels of ADPN and NT-proBNP had diagnostic values in AHF, the ROC curve analysis was applied to examine their diagnostic

Table I. Clinical characteristics of 407 participants.

Characteristics	AHF	Control	P-value
No. of cases (n)	218	189	0.80
Diabetes mellitus (n)	123	109	0.31
Smoking (n)	58	42	
Age (years)[a]	63 (51, 74)	63 (55, 71)	0.14
Weight (kg)[a]	62 (53, 72)	63 (57, 76)	0.21
Height (m)[a]	1.65 (1.61, 1.73)	1.67 (1.63, 1.74)	0.18
BMI (kg/m^2)[a]	23.34 (21.39, 26.76)	22.78 (20.97, 25.47)	0.27
NT-proBNP (pg/ml)[a]	2,158 (1,032, 4,930)	220 (56, 690)	<0.001
ADPN (μg/ml)[a]	11.05 (6.51, 16.28)	5.56 (3.43, 7.39)	<0.001
Renal function[a]			
CREA (mg/dl)	0.87 (0.71, 1.13)	0.97 (0.80, 1.34)	
GFR (ml/min/1.73 m^2)	86.26 (60.2, 106.98)	75.04 (54.18, 95.08)	
Renal insufficiency	52	59	
Normal renal function	166	130	
Systolic pressure (mmHg)[a]	124 (108, 143)	129 (114, 147)	
Pathogenesis (n)			
Non-ischemic	138	-	
Ischemic	80	-	
NYHA class (n)			
I	9	-	
II	61	-	
III	91	-	
IV	57	-	

[a]Values are reported as the median (25th quantile, 75th quantile). No significant difference between the two groups was detected for diabetes, smoking and obesity by the χ^2 test. BMI, body mass index; NT-proBNP, amino-terminal pro-brain natriuretic peptide; ADPN, adiponectin; CREA, creatinine; GFR, glomerular filtration rate; NYHA, New York Health Association.

Table II. Levels of ADPN and NT-proBNP in the control group and in heart failure patients with different NYHA cardiac function classifications.

Group	NT-proBNP (pg/ml)	ADPN (μg/ml)
Control (n=189)	219.5 (55.5, 690.0)	5.6 (3.4, 7.4)
NYHA class		
I (n=9)	152.0 (119.0, 664.0)	8.2 (5.6, 8.6)
II (n=61)	1,367.0 (759.0, 3706.0)	10.0 (5.7, 11.2)
III (n=91)	2,158.0 (1,105.5, 4,152.0)	11.5 (6.0, 16.6)
IV (n=57)	3,986.0 (1,798.0, 9,233.0)	14.8 (10.1, 22.8)

Values are presented as the median (25th quantile, 75th quantile). NT-proBNP, amino-terminal pro-brain natriuretic peptide; ADPN, adiponectin; NYHA, New York Health Association.

Table III. Levels of ADPN and NT-proBNP in the serum of normal, ischemic and non-ischemic groups.

Group	ADPN μg/ml	NT-proBNP pg/ml
Normal (n=189)	5.6 (3.4, 7.4)	219.5 (55.5, 690.0)
Ischemic (n=80)	9.8 (6.0, 13.2)	2,376.0 (935.5, 5,896.5)
No-ischemic (n=138)	11.2 (6.9, 18.7)	1,898.0 (1,116.5, 3,697.0)

Values are presented as the median (25th quantile, 75th quantile). NT-proBNP, amino-terminal pro-brain natriuretic peptide; ADPN, adiponectin.

efficiency. As shown in Table IV and Fig. 4A, among the patients with a normal renal function (n=296), NT-proBNP presented a significantly better diagnostic efficiency for AHF (AUC=0.905; 95% CI=0.866-0.936) in comparison with that of ADPN (AUC=0.775; 95% CI=0.723-0.821; P<0.001). The optimal cutoff value for NT-proBNP was 296.0 pg/ml, while the sensitivity and specificity were 92.1 and 72.3%, respectively. ADPN achieved an optimal diagnostic efficiency at the threshold of 10.6 μg/ml, while the sensitivity and specificity were 43.9 and 94.9%, respectively. Compared with NT-proBNP alone, the combination of the two biomarkers did not exhibit a higher diagnostic efficiency (AUC=0.920; 95% CI, 0.883-0.948; P=0.12).

Table IV. Diagnostic value of ADPN, NT-proBNP and their combination in acute heart failure patients with impaired or normal renal function.

	ADPN		NT-proBNP		Combination	
Parameter	Normal renal function	Renal insufficiency	Normal renal function	Renal insufficiency	Normal renal function[a]	Renal insufficiency[b]
Diagnosis efficiency	77.5%	87.2%	90.5%	82.8%	92.0%	90.0%
CI	72.3-82.1%	79.5-89.3%	86.6-93.6%	74.5-89.3%	88.3-94.8%	83.3-95.3%
Cut-off	10.6 μg/ml	10.6 μg/ml	296.0 pg/ml	1,129.0 pg/ml	35.0%	75.0%
Sensitivity	43.9%	65.4%	93.1%	90.4%	95.0%	71.2%
Specificity	94.9%	91.5%	72.3%	67.8%	75.9%	98.3%
PPV	91.8%	87.2%	79.6%	71.2%	92.9%	93.8%
NPV	61.9%	75.0%	81.8%	88.9%	82.1%	61.1%

[a]Logistic combination = 0.159 x YAPN + 2.712 x Ylg NT-proBNP-8.533; [b]Logistic combination = 0.327 × YAPN + 1.657 × Ylg NT-proBNP - 8.30. ADPN, adiponectin; NT-proBNP, amino-terminal pro-brain natriuretic peptide; PPV Combination = 0.327 x Y_{APN} + 1.657 x $Y_{l\ g\ NT\text{-}proBNP}$-8.30. NT-proBNP, amino-terminal pro-brain natriuretic peptide; ADPN, Adipocyte-secreted protein Adiponectin.

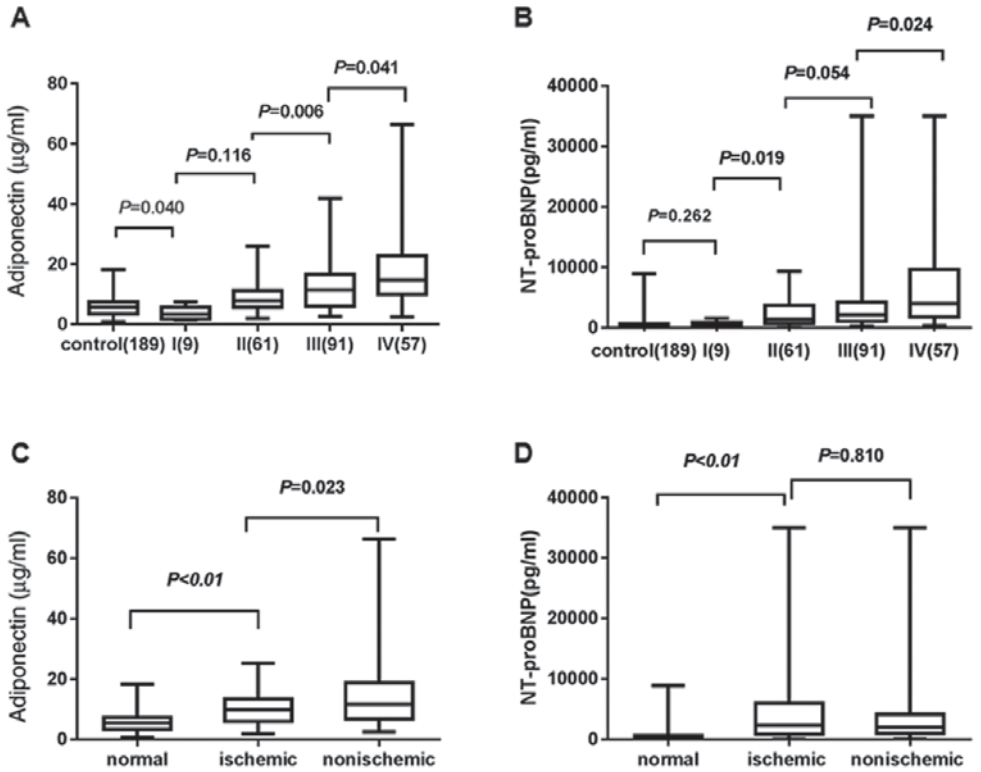

Figure 1. Comparative levels of plasma NT-proBNP and ADPN in different NYHA classes, as well as in ischemic and non-ischemic HF. Plasma (A) ADPN and (B) NT-proBNP levels in the control group and AHF patients divided according to the NYHA class. Plasma (C) ADPN and (D) NT-proBNP levels in patients with normal, ischemic and non-ischemic HF. Differences between normal and ischemic HF was statistically significant for ADPN (P<0.01) and NT-proBNP (P<0.01), while the difference between ischemic and non-ischemic HF was statistically significant only for ADPN but not NT-proBNP (P=0.02 vs. P=0.81, respectively). AHF, acute heart failure; NT-proBNP, amino-terminal pro-brain natriuretic peptide; ADPN, adiponectin; NYHA, New York Health Association.

As shown in Table IV and Fig. 4B, among patients with an abnormal renal function (n=111), ADPN presented a better diagnostic efficiency (AUROC=0.872; 95% CI, 0.795-0.928) in comparison with that of NT-proBNP (AUROC=0.828, 95%CI: 0.745-0.893), although the difference was not statistically significant (P=0.34). The optimal cutoff value for NT-proBNP in the renal insufficiency patients was 1,129.0 pg/ml, with sensitivity and specificity of 90.4 and 67.8%, respectively. The optimal threshold for ADPN was also 10.6 μg/ml, and the sensitivity and specificity were 65.4 and 91.5%, respectively. Compared with NT-proBNP alone, combination of the two biomarkers significantly increased the diagnostic efficiency (AUC=0.90; 95% CI, 0.833-0.951; P=0.02). Compared with ADPN alone, combination of the

Table V. Comparative diagnostic efficiencies of ADPN and NT-proBNP in participants in different age groups.

	ADPN		NT-proBNP		Combination	
Parameter	>75 years	50-75 years	<50 years	>75 years	50-75 years	<50 years
AUC (%)	78.9	75.9	79.7	90.6	90.8	91.3
Cut-off	10.6	10.6	10.6	1,497.0	335.0	221.5
Sensitivity (%)	67.9	44.1	52.6	78.6	94.6	92.1
Specificity (%)	87.5	95.1	100	93.7	78.8	72.7
PPV (%)	71.4	78.4	95.8	73.9	80.7	85.3
NPV (%)	56.5	70.3	58.3	71.4	94.0	84.2

ADPN, adiponectin; NT-proBNP, amino-terminal pro-brain natriuretic peptide; AUC, area under the curve.

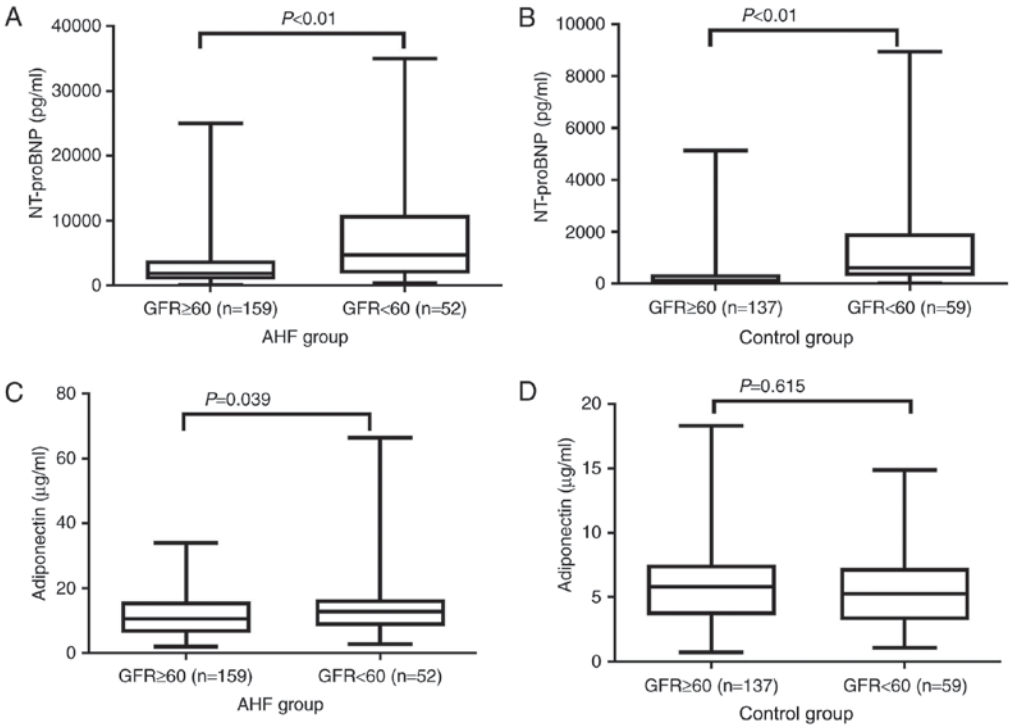

Figure 2. Comparative levels of ADPN or NT-proBNP in the AHF patients and controls, with (GFR≥60) and without (GFR<60) renal function insufficiency. NT-proBNP levels in the (A) AHF patients and (B) controls with normal or abnormal renal function are shown. ADPN levels in (C) AFH patients and (D) controls with normal or abnormal renal function are displayed. AHF, acute heart failure; NT-proBNP, amino-terminal pro-brain natriuretic peptide; ADPN, adiponectin; GFR, glomerular filtration rate.

two biomarkers also significantly increased the diagnostic efficiency (P=0.04). Combined analysis of the two biomarkers demonstrated a higher area under the curve (AUC=0.90) and specificity (98.3%), but with lower sensitivity (70.8%), in diagnosing AHF in patients.

Diagnostic efficiency of ADPN in AHF is less affected by age than NT-proBNP. As shown in Table V, the optimal diagnostic cutoff values of NT-proBNP and ADPN in different age groups were analyzed. Patients with a normal renal function (n=218) were divided into three groups according to their age, namely the groups of ≥75, 50-75 and ≤50 years. The plasma NT-proBNP levels were affected by the age of patients. The present study revealed that the optimal cut-off values of NT-proBNP in diagnosing AHF were 221.5, 335.0 and 1,497.0 pg/ml in these groups, respectively.

The AUC in individuals aged >75 years was 78.9% when ADPN was 10.6 μg/ml, and the sensitivity and specificity were 67.9 and 87.5%, respectively (Table V). The positive and negative predictive rates were 71.4 and 56.5%, respectively. Within the group aged 50-75 years, the AUC was 75.9%, the sensitivity and specificity were 44.1 and 95.1%, respectively and the positive and negative predictive rates were 78.4 and 70.3%, respectively. In the group aged <50 years, the sensitivity and specificity were 52.6 and 100.0%, respectively and the positive and negative predictive rates were 95.8 and 58.3% respectively. These results suggest that as a diagnostic marker ADPN was insensitive to age, however it had a lower diagnosis efficiency compared with NT-proBNP.

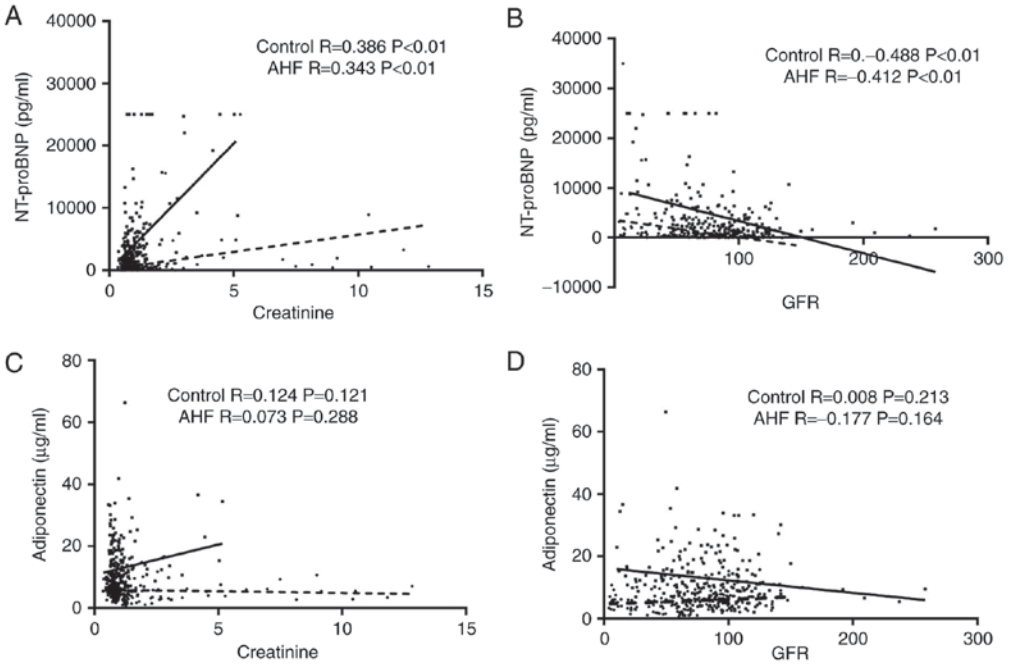

Figure 3. Comparative correlation of ADPN or NT-proBNP with renal function in the control and AHF groups. Renal function was examined according to the creatinine level and GFR. Correlation between NT-proBNP and (A) creatinine or (B) GFR in the control and AHF groups. The correlation coefficients were 0.386 (P<0.01) and 0.343 (P<0.01) for creatinine, respectively, and -0.488 (P<0.01) and -0.412 (P<0.01) for GFR, respectively. The correlation of ADPN with (C) creatinine or (D) GFR in the control and AHF groups is also displayed. The correlation coefficients were 0.124 (P=0.12) and 0.073 (P=0.29) for creatinine, respectively, and 0.008 (P=0.21) and -0.177 (P=0.16) for GFR, respectively. AHF, acute heart failure; NT-proBNP, amino-terminal pro-brain natriuretic peptide; ADPN, adiponectin; GFR, glomerular filtration rate.

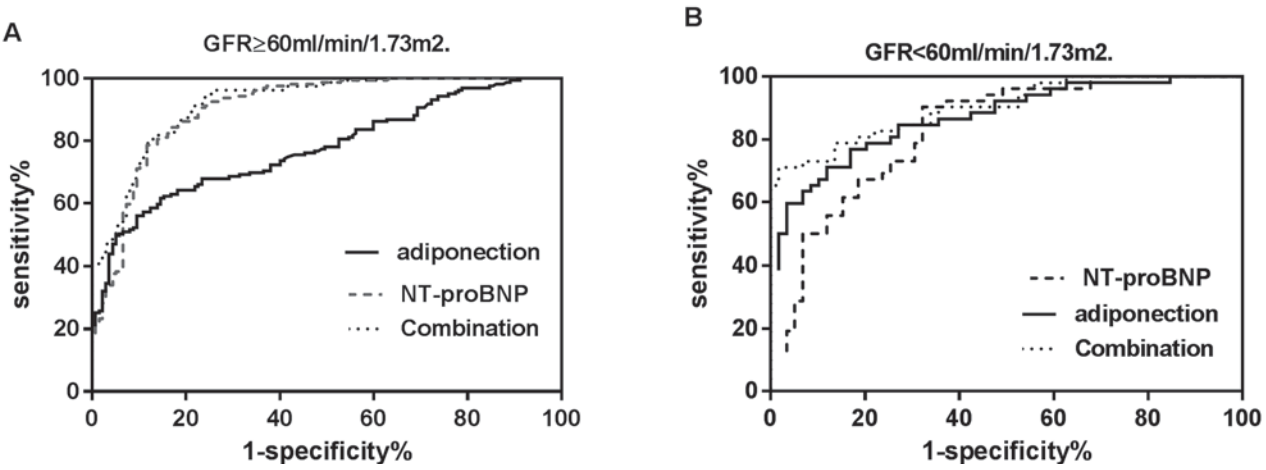

Figure 4. Receiver operating characteristic curve of adiponectin, NT-proBNP and their combination in acute heart failure patients with (A) normal renal function and (B) renal insufficiency. NT-proBNP, amino-terminal pro-brain natriuretic peptide.

Discussion

AHF is the most common cause of unplanned hospital admissions, and is associated with high mortality rates (2,33), with the cost of managing AHF being a global burden (34). Efficient and timely diagnosis is critical for reducing the mortality rates (35). NT-proBNP has long been used as a routine and rapid diagnostic method for patients with AHF (7-9); however, the use of NT-proBNP in diagnosing AHF in patients with renal insufficiency is controversial, since its level is markedly affected by the renal function (13-15,35). A significant proportion of patients exhibit functional impairment of both the heart and kidneys (36,37). Thus, diagnosing AHF patients with renal insufficiency rapidly and correctly is challenging in clinical practice.

ADPN is a 247 amino acid peptide that is predominantly secreted by adipocytes (18) and is recognized as a useful biomarker in numerous diseases, including fat-associated and heart diseases (19,29,30,38). As an adipokine, ADPN has anti-inflammatory and cardioprotective effects (39). The present study results demonstrated that plasma ADPN levels increased with the increase of the NYHA class of patients (Fig. 1A), which was consistent with the findings of previous studies (28-30). In addition, previous results indicated that ADPN may have an anti-inflammatory and

anti-atherosclerotic role (40,41). Another study revealed that regular aerobic exercise decreased the potential risk of coronary heart disease by improving the plasma levels of interleukin-6, ADPN, leptin and CRP (42). Furthermore, a cohort study performing long-term follow-up of the glucose tolerance in patients with acute myocardial infarction indicated that elevated levels of ADPN predicted the outcome following acute myocardial infarction (43), while low ADPN levels may, indicate coronary artery disease (25,44). In the present study, the levels of ADPN were found to be lower in ischemic heart disease as compared with those in non-ischemic AHF (Fig. 1C and Table III), which was consistent with the aforementioned results. It was also observed that the level of ADPN in NYHA cardiac function I participants was higher compared with that of the control group, the difference was statistically significant between the two groups (P=0.04); by contrast, NT-proBNP did not exhibit a marked difference between these two groups.

In the present study, the NT-proBNP levels were observed to be significantly correlated with the renal function and age of participants (Tables IV and V), and the cut-off value for diagnosing AHF evidently varied in the presence of renal insufficiency, which made it difficult for physicians to determine whether the nephropathy was associated with HF. In addition, the cut-off value of ADPN was not altered in the presence of renal insufficiency, which facilitated the diagnosis. The use of ADPN as a marker of AHF exhibited superiority since it was not affected by the age and renal function of the patients (Tables IV and V). The ADPN receptor 2 is mainly distributed in the liver, and only a small amount will be filtered out through the kidneys, indicating that ADPN is less susceptible to the GFR in comparison with NT-proBNP (45,46). In the current study, compared with NT-proBNP, the same cut-off value of ADPN could be utilized to diagnose patients with AHF. Furthermore, the combination of ADPN and NT-proBNP achieved a significantly higher diagnostic value compared with NT-proBNP alone in patients with renal sufficiency. Thus, ADPN may serve as a novel biomarker in the diagnosis of AHF in patients with abnormal renal function.

Through the ROC curve analysis of the diagnostic value of ADPN and NT-proBNP, the results of the present study indicated that ADPN was not associated with the renal function and age. While the sensitivity of NT-proBNP was higher compared with that of ADPN, the specificity of NT-proBNP was lower than that of ADPN. ADPN and NT-proBNP were used to obtain a logistic regression equation, and the predictor of the equation was used to diagnose AHF. The efficiency of the combination of ADPN and NT-proBNP was better in diagnosing AHF patients with renal insufficiency. Although the influence of dialysis on the diagnostic efficiency of these markers was not discussed in the present study, there was no doubt in assessing the diagnostic efficiency of ADPN for AHF patients with renal insufficiency based on the aforementioned results.

Several studies have revealed the association of serum ADPN levels with the degree of renal failure. For instance, the association of ADPN with CKD was demonstrated recently in a case-control study conducted by Lim *et al* (47) in 450 CKD cases and 920 controls involving Chinese and Indian adults aged 40-80 years. The authors observed that a higher level of serum ADPN was positively associated with CKD independently of traditional risk factors in the examined Asian population (48). In other studies, higher ADPN levels were reported in end-stage renal disease (49,50), whereas the role of ADPN in mildly impaired renal function was inconsistent, with a previous study demonstrating lower levels of ADPN were associated with CKD (51), while others reporting that higher levels were associated with CKD or no significant association was observed as discussed by Lim *et al* (47).

The present study has certain limitations. Firstly, only two markers were measured for diagnosing AHF. In addition, the sample size of the study and the number of participants with renal insufficiency were small. Furthermore, patients with severe renal impairment were not represented adequately in the current study. Thus, a large-scale trial comparing several different markers of AHF is required in order to further evaluate the diagnostic accuracy of ADPN and NT-proBNP in patients with renal insufficiency. Finally, patients with hemodialysis need to be enrolled in order to further evaluate the diagnostic accuracy of each biomarker.

In conclusion, NT-proBNP demonstrated a higher diagnostic efficiency compared with ADPN in AHF patients without renal insufficiency, while ADPN presented a better diagnostic value. Therefore, a combination of these two biomarkers may provide improved efficacy in the diagnosis of AHF with renal insufficiency. In addition, the present study observed that ADPN was less affected by the renal function and age of patients, and can be used for diagnosing AHF, particularly in patients with impaired renal function.

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Availability of data and materials

The datasets used during the present study are available from the corresponding author upon reasonable request.

Authors' contributions

ZD, YZ, HY and ZZ conceived and designed the study. ZD, YZ, HY, GZ, HJ, ZC, YY, ZC, XT, JZ, XL, HX, PL and SG performed the experiments. ZD and ZZ wrote the paper. All authors read and approved the manuscript.

Ethics approval and consent to participate

All experimental protocols were approved by the Ethics Committee of Zhongshan Hospital, Xiamen University (Xiamen, China) and written informed consent was obtained from all patients.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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