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Review Article

Relationship between serum CRP, BNP, CyPA, IL-1β levels and prognosis of elderly patients with both diastolic heart failure and renal insufficiency

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Abstract: The relationship between serum CRP, BNP, CyPA, IL-1β levels and prognosis in elderly patients diagnosed with both diastolic heart failure (DHF) and renal insufficiency (RI) was explored. A total of 76 patients with heart failure (HF) alone, 77 patients with RI alone, and 95 patients with both DHF and RI in our hospital were enrolled as Groups A, B, and C, respectively. The patients with both HF and RI were classified according to NYHA heart function. According to the glomerular filtration rate (EGFR), they were assigned to mild, moderate, and severe groups, and the correlation of CRP, BNP, CypA, and IL-1β with their prognosis was analyzed. Group C showed significantly higher levels of CRP, BNP, CyPA and IL-1β than other two groups ($P < 0.05$), and Group B showed significantly higher levels than Group A ($P < 0.05$). The levels of CRP, BNP, CyPA, and IL-1β in the serum of patients with both HF and RI increased with the increase of NYHA grade and the severity of RI ($P < 0.05$). A total of 39 patients with readmission or death within 6 months after discharge were classified into an incident group, 56 patients without readmission or death were classified into the non-incident group. The incident group showed significantly higher serum levels of CRP, BNP, CyPA and IL-1β than the non-incident group ($P < 0.05$). The logistic regression analysis revealed that age, CRP, BNP, CyPA, and IL-1β were independent risk factors for events in patients with HF and RI. Serum CRP, BNP, CyPA, and IL-1β are highly expressed in patients with both HF and RI; which can be adopted as a short-term prognosis indicators for patients with both DHF and RI.

Keywords: CRP, BNP, CyPA, IL-1β, DHF with renal insufficiency

Introduction

Diastolic heart failure (DHF) is common cardiovascular disease, and is characterized by ventricular diastolic dysfunction, increased stiffness, and decreased compliance. It is the main factor of hospitalization and readmission of elderly patients. The occurrence of the disease seriously compromises the health and quality of life of the patients [1-3]. Renal dysfunction is common in patients with heart failure (HF) and is linked to high morbidity and mortality. The interaction between heart and renal dysfunction is the key factor to determine the development and prognosis of HF [4, 5]. At present, accurate predicting the prognosis of HF patients is an important topic among cardiovascular clinicians, and biomarkers are one of the focuses in this field [6].

C-reactive protein (CRP), produced by hepatocytes after inflammation, infection or tissue injury, is a marker of systemic inflammation and an acute phase reactive protein of the pentamerin protein family [7, 8]. In epicardial coronary artery disease, high CRP level is linked to adverse vascular reactions [9], and is also related to hospitalization of HF patients and increased left ventricular filling pressure [10]. Brain natriuretic peptide (BNP) is a cardiac hormone mainly secreted from the ventricles, which is widely used in clinical diagnosis of HF and cardiac insufficiency [11]. BNP can regulate the differentiation and proliferation of cardio-

myocytes in developing embryos [12]. BNP may also be involved in angiogenesis after skeletal muscle ischemia [13]. Cyclophilin A (CyPA) is a protein with peptidyl prolyl CIS trans isomerase (ppiase) activity [14]. CyPA can play a role in the signaling of endothelial stress, in which low concentrations can protect endothelial cells from apoptosis, while high concentrations can promote apoptosis [14]. Interleukin-1β (IL-1β), a classical inflammatory factor, can induce the synthesis and release of a series of secondary inflammatory mediators and IL-1β itself [15]. Studies have shown that IL-1β is associated with aerobic capacity in HF [16]. However, most literature mainly describes the expression of CRP, BNP, CyPA and IL-1β in HF patients. There is little research in the levels of CRP, BNP, CyPA and IL-1β in patients with HF and renal insufficiency (RI), and whether it has an impact on the prognosis of patients with HF and RI remains to be further studied.

In this paper, the expression of CRP, BNP, CyPA, and IL-1β in patients with HF and RI were measured to explore the relationship between the levels of serum CRP, BNP, CyPA and IL-1β and the prognosis of patients.

Methods

General information

A total of 95 patients with both DHF and RI were enrolled into Group C, including 52 males and 43 females, with a median age of (73.43± 9.87) years. At the same time, 76 patients with HF alone were enrolled into Group A, including 46 males and 30 females, with a median age of (71.12±10.76) years. A total of 77 patients with RI alone were enrolled into Group B, including 44 males and 33 females, with a median age of (71.45±10.13) years. Patients with DHF and RI were graded in accordance with NYHA [17], 36 in grade II, 38 in grade III, and 21 in grade IV. According to the estimated glomerular filtration rate (EGFR), 34 cases were assigned into mild group (GFR: 60 ~ < 90 ml/min), 43 cases in moderate group (GFR: 30 ~ < 60 ml/min) and 18 cases in severe group (GFR: < 30 ml/min). The study was carried out with the permission from the medical ethics committee of Affiliated Hospital of Nantong University, and was in accordance with the Helsinki Declaration. All patients were informed of the study and they signed the informed consent.

Inclusion criteria: Patients with complete clinical data, patients with good compliance, patients accompanied by family members at admission, patients with no history of mental illness, patients with good cognitive status, and those willing to actively participate in follow-up.

Exclusion criteria: Patients with advanced tumor diseases, patients suffering from acute myocardial infarction within the past month, patients with severe infection, pulmonary embolism, autoimmune diseases, sepsis or other chronic primary diseases.

Detection of serum indexes

In the morning after the patient was admitted to Affiliated Hospital of Nantong University, venous blood from the elbow (3 ml) was extracted with a vacuum blood sampling needle in a fasted state. The blood was centrifuged at 4000 R/min for 10 min. After that, the serum was carefully collected and placed in the freezer at 80°C for testing. The mk-3 automatic enzyme-linked analyzer purchased from Shanghai Yilian medical instrument development Co., Ltd. was used to quantify CRP, BNP, CyPA, and IL-1β in serum via double anti sandwich enzyme-linked immunosorbent assay (ELISA). The CRP, BNP, CyPA and IL-1β kits were all purchased from Shanghai gefan Biotechnology Co., Ltd. with product numbers of hc025, hb012, hc077 and hi003, respectively. Standards of different concentrations (50 μl) were added into the standard well, and 10 μl sample and 40 μl diluent were added into the sample well to be tested. In addition distilled water (50 μl) was added into the blank well (the same as other steps, but without enzyme standard reagent and sample), and enzyme standard reagent (50 μl) was added into the standard well and sample hole. The reaction well was sealed with sealing membrane, and washed after incubation in 37°C water bath for 1 hour. Substrate A and B (50 μl) were added into each well, mixed with the liquid in each well gently, and developed at 37°C for 15 minutes without light. Termination solution (50 μl) was added to each well, and within 15 minutes, the blank well was adopted as the reference value for zero adjustment, and the OD of each hole at 450 nm was measured. The CRP, BNP, CyPA, and IL-1β levels in serum were calculated.

Table 1. Comparison of clinical general data among the three groups

	Group A (n=76)	Group B (n=77)	Group C (n=95)	X^2/F	P
Gender				0.58	0.75
Male	46 (60.53)	44 (57.14)	52 (54.74)		
Female	30 (39.47)	33 (42.86)	43 (45.26)		
Average age (years)	71.12±10.76	71.45±10.13	73.43±9.87	1.31	0.27
Height				0.36	0.84
> 160 cm	59 (77.63)	62 (80.52)	73 (76.84)		
≤ 160 cm	17 (22.37)	15 (19.48)	22 (23.16)		
body mass index (kg/m^2)	23.67±3.87	23.72±3.61	24.71±4.01	2.04	0.13
Do you smoke?				0.38	0.83
Yes	28 (36.84)	31 (40.26)	34 (35.79)		
No	48 (63.16)	46 (59.74)	61 (64.21)		
Do you drink too much?				0.25	0.88
Yes	16 (21.05)	18 (23.38)	23 (24.21)		
No	60 (78.95)	59 (76.62)	72 (75.79)		
Past history					
Diabetes	23 (30.26)	22 (28.57)	29 (30.53)	0.10	0.95
Hypertension	18 (23.68)	19 (24.68)	21 (22.11)	0.16	0.92

Observation indicators

(1) To observe the expression of serum CRP, BNP, CyPA, and IL-1β in the patients with different heart and renal function. (2) To compare the expression of serum CRP, BNP, CyPA, and IL-1β in patients with both HF and RI, RI alone, or HF alone. (3) A 6-month follow-up was carried out on the patients after discharge. The clinical data of patients with HF and RI were collected and compared. Among them, 39 patients with readmission or death were enrolled into an incident group, 56 patients without readmission or death were enrolled into the non-incident group. The risk factors of readmission or death were analyzed. (4) To observe the levels of CRP, BNP, CyPA and IL-1β in the prediction of adverse events in patients with HF and RI.

Statistical analysis

SPSS 20.0 was used for statistical analysis, and graphpad prism 7 was used to illustrate figures of the collected data. The count data was expressed as [n%], and chi square test was adopted for inter group comparison. The mean ± standard deviation ($\bar{x}$ ± SD) was used for measurement data, single factor analysis of variance was employed for multi-group comparison, and LSD-t was used for post test. Multivariate logistic regression analysis was carried out for analysis on the risk factors of patients with HF and RI. In addition, ROC was used to evaluate the level of CRP, BNP, CyPA and IL-1β in the prediction of adverse events in patients with HF and RI. $P < 0.05$ implies a significant difference.

Results

Comparison of clinical general data among the three groups of patients

As shown in **Table 1**, there was no significant difference in sex, average age, height, body mass index, smoking and drinking, and history among the three groups (all $P > 0.05$).

Comparison of serum CRP, BNP, CyPA and IL-1β levels among the three groups

The levels of CRP, BNP, CyPA and IL-1β in the serum of the three groups were detected, as shown in **Figure 1**. The levels of CRP, BNP, CyPA and IL-1β in Group C were significantly higher than those in the other two groups ($P < 0.05$), and the levels in Group B were significantly higher than those in Group A (all $P < 0.05$).

Serum levels of CRP, BNP, CyPA and IL-1β in patients with HF and RI

According to the NYHA classification of patients with HF and RI, it can be seen that the levels of

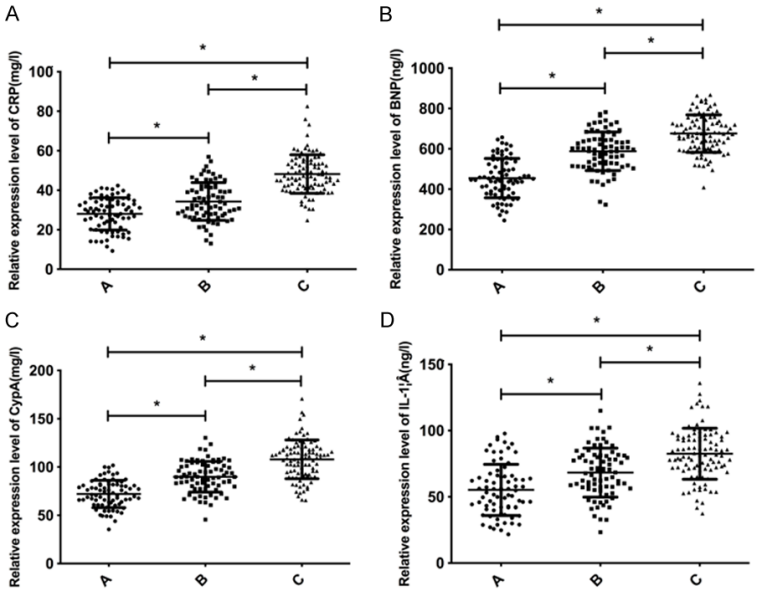

Figure 1. Comparison of serum CRP, BNP, CyPA and IL-1β levels among three groups. A. Group C showed significantly higher CRP level than the other two groups, and Group B showed significantly higher serum CRP level than Group A. B. Group C showed significantly higher BNP level than the other two groups, and Group B showed significantly higher BNP level than Group A. C. Group C showed significantly higher CyPA level than the other two groups, and Group B showed significantly higher CyPA level than Group A. D. Group C showed significantly higher IL-1β level than the other two groups, and Group B showed significantly higher IL-1β level than Group A. Note: * indicates in inter-group comparison, *P < 0.05.

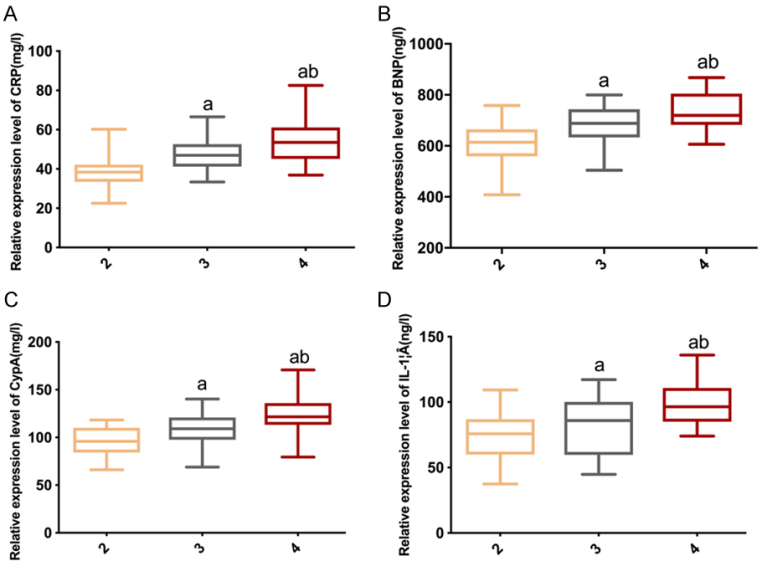

Figure 2. Serum levels of CRP, BNP, CyPA, and IL-1β in patients with HF and RI. A. The serum CRP level rose with the elevation of NYHA grade, and there was a difference between the grades. B. The BNP level increased with the increase of NYHA grade, and there was a difference between the grades. C. The CyPA level increased with the increase of NYHA grade, and there was a difference between the grades. D. The serum IL-1β level increased with the increase of NYHA grade, and there was a difference between the grades. Note: 2: grade II, 3: grade III, 4: grade IV. a is compared with grade II, $^{a}P < 0.05$; b is compared with grade III, $^{b}P < 0.05$.

serum CRP, BNP, CyPA and IL-1β in patients gradually increased with the increase of NYHA classification, and the difference between the classifications being significant (P < 0.05), as shown in **Figure 2**.

Serum levels of CRP, BNP, CyPA and IL-1β in patients with HF and RI

According to the renal function group of patients with HF and RI, it can be seen that the levels of serum CRP, BNP, CyPA and IL-1β in patients gradually increased as the severity of RI, and the difference between the severity groups is significant (P < 0.05), as shown in **Figure 3**.

Comparison of expression levels of events and non-events

According to the end incident grouping, it can be seen from **Figure 4** that the serum CRP, BNP, CyPA, and IL-1β levels in the incident group were higher than those in the non-incident group, with a significant difference (P < 0.05).

Analysis of prognostic factors

Univariate analysis was used. There were differences in age, CRP, BNP, CyPA and IL-1β levels between the incident and the non-incident groups (P < 0.05) (**Table 2**). The indexes with differences in single factor analysis were included in the assignment (**Table 3**). The results of risk factor Logistic regression analysis showed that, as shown in **Table 4**, age (HR: 4.267, 95% CI: 1.239-14.693), CRP (HR: 5.806, 95% CI: 1.798-18.747), BNP (HR: 10.468, 95% CI: 2.927-37.440), CyPA (HR: 5.192, 95% CI: 1.504-17.926), IL-1β (HR: 4.349, 95% CI:

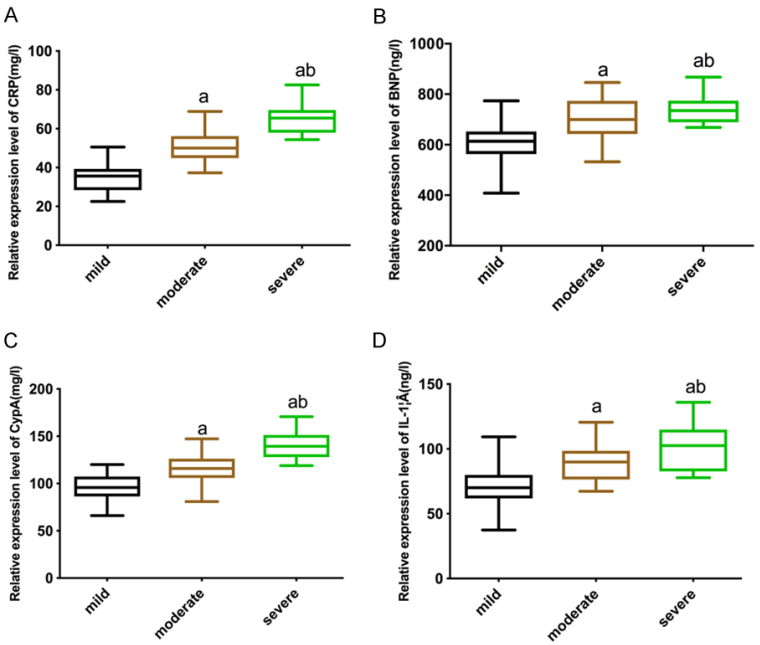

Figure 3. Serum levels of CRP, BNP, CyPA and IL-1β in patients with HF and RI. A. The serum CRP level of patients increased with the severity of RI, and there was a difference between the severity groups. B. The level of BNP in serum increased with the severity of RI, and there were differences among the severity groups. C. The level of CyPA in the serum of the patients increased with the severity of RI, and there were differences among the severity groups. D. The serum IL-1β level increased with the severity of RI, and there were differences among the severity groups. Note: a indicates low severity, $^{a}P < 0.05$; b indicates low severity, $^{b}P < 0.05$.

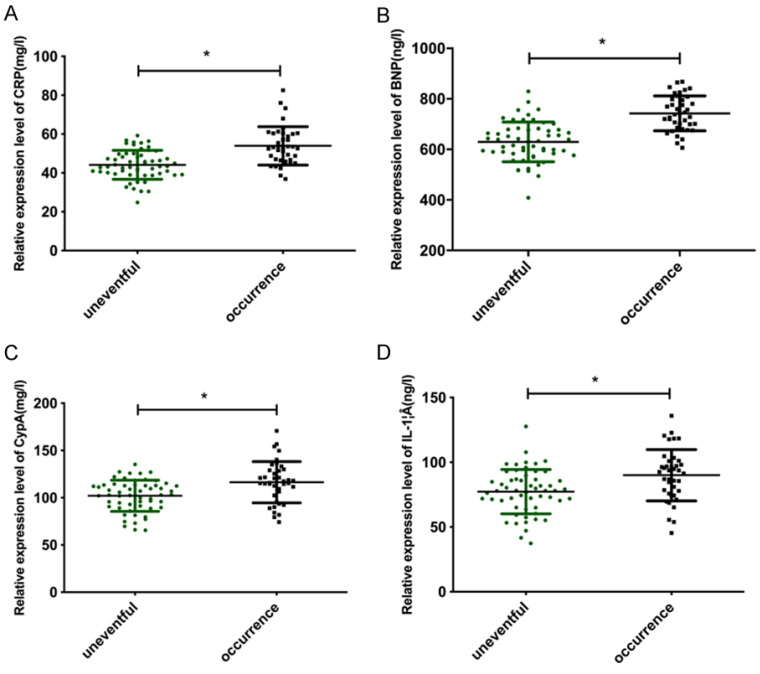

Figure 4. The expression level of serum factors were compared.. A. The serum CRP level in the incident group was significantly higher than that in the non-incident group. B. The serum BNP level in the incident group was significantly higher than that in the non-incident group. C. The level of CyPA in the incident group was significantly higher than that in the non-incident group. D. The serum level of IL-1β in the incident group was significantly higher than that in the non-incident group. Note: * indicates in inter-group comparison groups, *P < 0.05.

1.269-14.902) were independent risk factors for the occurrence of events in patients suffering from HF and RI (**Table 4**).

CRP, BNP, CyPA, IL-1β levels predict adverse events in patients with HF and renal function

The ROC curve suggested that the AUC, specificity, sensitivity, and best cut-off of serum CRP were 0.737 (0.636-0.839), 75.00%, 66.67%, and 49.14 mg/l, respectively. The AUC, specificity, sensitivity, and best cut off value of BNP were 0.767 (0.672-0.863), 69.64%, 74.36%, and 684.00 ng/l, respectively. The AUC, specificity, sensitivity, and best cut off value of CyPA were 0.688 (0.576-0.799), 78.57%, 61.54%, and 113.70 mg/l, respectively. The AUC, specificity, sensitivity, and best cut off value of IL-1β were 0.691 (0.578-0.804), 75.00%, 64.10%, and 86.74 ng/l, respectively. As shown in **Figure 5**.

Discussion

With the aging of the population and the increasing prevalence of HF, the proportion of patients over 75 years old has increased to about 12% [18, 19]. HF often occurs in combination with RI, which very easily generates a vicious circle and aggravates the patient's condition. As a result, the patient's heart and kidney

Table 2. Single factor analysis [n (%)]

	Occurrence group (n=39)	No incident group occurred (n=56)	X^2	P
Gender			0.07	0.78
Male	22 (56.41)	30 (53.57)		
Female	17 (43.59)	26 (46.43)		
Age			8.28	0.00
> 70	29 (74.36)	25 (44.64)		
≤ 70	10 (25.64)	31 (55.36)		
Height			0.26	0.61
> 160 cm	31 (79.49)	42 (75.00)		
≤ 160 cm	8 (20.51)	14 (25.00)		
Do you smoke?			0.73	0.39
Yes	12 (30.77)	22 (39.29)		
No	27 (69.23)	34 (60.71)		
Do you drink too much?			1.55	0.21
Yes	12 (30.77)	11 (19.64)		
No	27 (69.23)	45 (80.36)		
CRP			16.39	< 0.05
High level	29 (74.36)	18 (32.14)		
Low level	10 (25.64)	38 (67.86)		
BNP			19.94	< 0.05
High level	30 (76.92)	17 (30.36)		
Low level	9 (23.08)	39 (69.64)		
CypA			7.82	< 0.05
High level	26 (66.67)	21 (37.50)		
Low level	13 (33.33)	35 (62.50)		
IL-1β			5.66	0.02
High level	25 (64.10)	22 (39.29)		
Low level	14 (35.90)	34 (60.71)		

functions will gradually decline, and then the body will have a series of metabolic disorders, which seriously threatens the life and health of the patient [20, 21]. At the same time, it has been mentioned that elderly patients with HF accompanied by diabetes or RI are at increased risk of hospitalization due to hyperkalemia or acute RI [22]. At present, many biomarkers have been widely used in clinical research.

Clinical trials and basic studies show that CRP may be the atherogenic factor of atherosclerosis [23]. CRP can regulate vascular endothelial growth factor (VEGF), activate hypoxia inducible factor-1α (HIF-1α) through CD64/PI3K/Akt and MAPK/ERK signaling pathways, and promote adipose derived stem cell-induced angiogenesis [7]. Related studies showed that CRP level in patients with RI is significantly increased, and significantly higher than that in healthy people [24, 25], and animal experiments showed that CRP expression in dogs with advanced HF was significantly up-regulated [26]. BNP is a kind of natriuretic peptide produced and released from the ventricles due to the increase of wall tension and overall tension [27]. It combines with A-type natriuretic peptide receptor found on endothelial cells and vascular smooth muscle, giving rise to the generation of cyclic guanosine (CGMP) and activation of downstream signal cascades, resulting in vasodilation of veins and arteries, increasing cardiac output and improving systemic symptoms [28]. Simioniuc [29] studied the data of patients with HF and RI by retrospective analysis. It was found that the level of NT Pro BNP increased by more than 25% in patients with the disease. CyPA is a key mediator of platelet-dependent thrombosis and thrombotic inflammation, and organ dysfunction after shock [30]. The inhibition of CyPA in cells can lead to the impairment of blood homeostasis [31]. Moreover, in clinical studies, the level of plasma CyPA in patients with HF was significantly increased [32]. Early studies have found that IL-1β can inhibit β adrenergic response and cardiac contractility, and affect contraction and intracellular Ca^{2+} dynamics [33]. At the same time, the results of Caki et al [34] showed that the IL-1β level was significantly up-regulated in ischemic acute renal failure. The results revealed that Group C showed significantly higher levels of CRP, BNP, CyPA and IL-1β than the other two groups, and Group B showed significantly higher levels of them than Group A ($P < 0.05$). It is suggested that the up-regulation of CRP, BNP, CyPA, and IL-1β is linked to the occurrence of

Table 3. Assignment table

Factor	Assignment
Age	> 70 age: 1, ≤ 70 age: 2
CRP	High expression (> 45.46 mg/L): 1, Low expression (≤ 45.46 mg/L): 2
BNP	High expression (> 689.34 ng/L): 1, Low expression (≤ 689.34 ng/L): 2
CypA	High expression (> 103.12 mg/L): 1, Low expression (≤ 103.12 mg/L): 2
IL-1β	High expression (> 81.56 ng/L): 1, Low expression (≤ 81.56 ng/L): 2

Table 4. Multi factor analysis

	β	SD	X^2	P	HR (95% CI)
Age	1.451	0.631	5.291	0.021	4.267 (1.239-14.693)
CRP	1.759	0.598	8.649	0.003	5.806 (1.798-18.747)
BNP	2.348	0.650	13.043	0.000	10.468 (2.927-37.440)
CypA	1.647	0.632	6.786	0.009	5.192 (1.504-17.926)
IL-1β	1.470	0.628	5.473	0.019	4.349 (1.269-14.902)

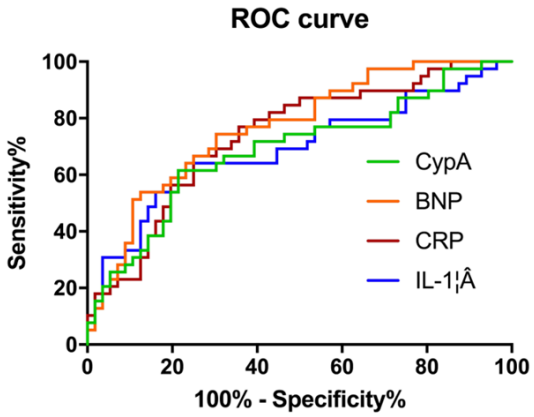

Figure 5. CRP, BNP, CyPA, IL-1β levels predicted adverse events in patients with HF and renal function. ROC curve indicated that the AUC, specificity, sensitivity, and best cut-off value of serum CRP level in predicting readmission or death of patients with HF and renal function were 0.737 (0.636-0.839), 75.00%, 66.67%, and 49.14 mg/l, respectively. The AUC, specificity, sensitivity, and best cut off value of BNP were 0.767 (0.672-0.863), 69.64%, 74.36%, and 684.00 ng/l, respectively. The AUC, specificity, sensitivity, and best cut off value of CyPA were 0.688 (0.576-0.799), 78.57%, 61.54%, and 113.70 mg/l, respectively. The AUC, specificity, sensitivity, and best cut off of IL-1β were 0.691 (0.578-0.804), 75.00%, 64.10%, and 86.74 ng/l, respectively.

the disease, and it is highly expressed in the serum of patients with cardiorenal failure and RI, suggesting that the detection of serum CRP, BNP, CyPA, and IL-1β levels is of great guiding significance for the evaluation of patients' condition.

The results of Du et al [35] showed that NYHA cardiac function grade was positively correlated with BNP level, and BNP concentration increased with the development of chronic congestive HF. Some studies have shown that the level of NT proBNP and BNP in patients with EGFR < 15 ml/min/1.73 m^2 is much higher than that in those with EGFR > 60 ml/min/1.73 m^2 [36]. At the same time, it has been proposed that CyPA has a certain correlation with renal function impairment of progressive peripheral arterial occlusive disease, and has a significant negative correlation with EGFR [37]. In addition, it has been found that interferon inducers can reduce the severity of chronic HF by reducing the IL-1β level [38]. This study revealed that the CRP, BNP, CyPA, and IL-1β levels in patients' serum increased with the increase of NYHA classification ($P < 0.05$), and the levels of CRP, BNP, CyPA, and IL-1β in patients' serum increased with the increase of the severity of RI, and the difference between the groups in severity was significant ($P < 0.05$). It is suggested that the CRP, BNP, CyPA, and IL-1β levels are significantly correlated with the severity of HF combined with RI, and increase with the aggravation of the disease. Some literature has predicted the death of patients with acute HF and evaluated the cardiovascular death within 3 months. The results show that the BNP level of the survivors is significantly lower than those that died ($P < 0.05$) [39]. Ibrahim et al [40] found that older average age and higher relative level of BNP were the risk factors for the 2-year survival of patients with chronic HF and RI. Serum high sensitive C-reactive protein (hs CRP) is an independent risk factor for death in patients with HF [41]. Su et al [42] suggested that high CyPA level and low melatonin level were independent risk factors for hypertension induced left ventricular hypertrophy. IL-1β is an independent prediction factor of all-cause mortality in patients with idiopathic dilated cardiomyopathy

[43]. The results revealed that the CRP, BNP, CyPA and IL-1β levels in the incident group were significantly higher than those in the non-incident group ($P < 0.05$). According to the results of logistic regression analysis of risk factors, age, high expression of CRP, BNP, CyPA and IL-1β were independent risk factors for the occurrence of events in patients with HF and RI. High CRP level and other inflammatory markers have been verified to have significant prognostic and therapeutic relevance, and related studies have proposed that the combination of soluble ST2 and CRP is an effective tool for identifying patients with HF at risk of death [44]. A study from Stolfo et al [45] shows that compared with acute decompensated HF patients with renal function deterioration without BNP reduction, patients with BNP reduction ≥ 40% have lower mortality, emergency heart transplantation and readmission rates. It is suggested that the change of BNP level can predict the prognosis of patients with renal function deterioration. Kim et al [46] showed that the measurement of soluble ST2 level at discharge was helpful to predict the short-term prognosis of patients with acute decompensated HF and RI. Because the prognosis of patients with HF and RI is poor, it is very important to find suitable markers. ROC curve results suggested that serum CRP, BNP, CyPA and IL-1β levels could be used to predict the prognosis of readmission or death of patients with HF and RI after discharge. At the same time, it has been proposed that HMGB1 level can be used as a biomarker of prognosis in patients with multiple injuries [47]. BNP levels at admission can be used to assess mortality after discharge in patients with HF [48]. However, there is still some controversy about whether the detection of serum levels can be used as a prognostic indicator after admission, so more clinical studies are needed to confirm it.

The relationship between the expression level of CRP, BNP, CyPA, IL-1β and the prognosis of patients with HF and RI was discussed. However, there are still some limitations. Serum CRP, BNP, CyPA, and IL-1β levels were not detected after treatment. In the future, we can deepen the research in this direction, and further explore whether serum CRP, BNP, CyPA, and IL-1β can be used as the efficacy prediction and evaluation indexes for HF patients with RI.

Serum CRP, BNP, CyPA and IL-1β are highly expressed in patients with HF and RI, which can be used as a short-term prognosis indicator for patients with both DHF and RI.

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Disclosure of conflict of interest

None.

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