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Original Article

Etiological distribution and risk factors of patients with cardiac insufficiency complicated with pulmonary infection

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Abstract: Objective: To explore the etiological distribution and influencing factors of patients with cardiac insufficiency complicated with pulmonary infection, and to analyze the diagnostic efficacy of procalcitonin (PCT), C-reactive protein (CRP), brain natriuretic peptide (BNP) and norepinephrine (NE) in the diagnosis of this disease. Methods: This study was a prospective study in which 164 patients with cardiac insufficiency were enrolled and divided into the infection group (43 patients) and the non-infected group (121 patients) according to whether they were complicated with pulmonary infection. Pathogen analysis and drug susceptibility test were performed on patients in the infected group. Serum PCT, CRP, BNP and NE levels were measured in the two groups, and the general data of the two groups were collected and compared. Multivariate Logistic regression analysis was further carried out for the indicators with statistical differences in univariate analysis, and ROC curve was employed to analyze the diagnostic efficacy of PCT, CRP, BNP and NE in diagnosing cardiac insufficiency complicated with pulmonary infection. Results: A total of 63 pathogenic bacteria were isolated from 43 patients, among which 43 were Gram-negative bacteria (68.25%), 18 were Gram-positive bacteria (28.57%), and 2 were fungi (3.17%). Among the Gram-negative bacteria, Pseudomonas aeruginosa and Klebsiella pneumoniae were highly resistant to cefuroxime, ampicillin and levofloxacin, while Staphylococcus aureus and Staphylococcus haemolyticus of Gram-positive bacteria were highly resistant to penicillin, erythromycin and gentamicin. Univariate analysis showed that there were significant differences between the two groups in age, length of hospital stay, cardiac function grading, smoking history, diabetes mellitus, invasive procedures, serum PCT, CRP, BNP and NE levels ($P<0.05$). Multivariate regression logistic regression analysis further demonstrated that; age ≥60 years old, long hospital stay, diabetes mellitus, invasive procedures and high levels of serum PCT, CRP, BNP and NE were independent risk factors for pulmonary infection in patients with cardiac insufficiency ($P<0.05$). ROC curve exhibited that PCT, CRP, BNP and NE had high clinical value in the diagnosis of cardiac insufficiency complicated with pulmonary infection (AUC>0.7, $P<0.001$). Conclusion: Gram-negative bacteria are the main cause of cardiac insufficiency complicated with pulmonary infection, and that drugs should be rationally used according to drug sensitivity results. Age ≥60 years, long hospital stay, diabetes, invasive procedures and high serum PCT, CRP, BNP and NE can increase the risk of infection in patients with cardiac insufficiency. Serum PCT, CRP, BNP and NE have high clinical value in the diagnosis of cardiac insufficiency complicated with pulmonary infection.

Keywords: Cardiac insufficiency, pulmonary infection, etiology, risk factors

Introduction

Cardiac insufficiency, also known as heart failure, refers to the abnormal systolic or diastolic function of the heart under the action of various factors, which in turn leads to the difficulty in ensuring the blood flow pumped by the heart to meet the needs of cells and tissues of the body, or to meet the metabolic needs only in the state of ventricular filling [1, 2]. Studies have found that patients with cardiac insufficiency commonly have pulmonary microcirculation disorders, which increases the risk of lung injury and causes lung infection. The aging population has driven the ongoing rise of the incidence of cardiac insufficiency, worsened by the fact that pulmonary infection also increases myocardial oxygen consumption and pulmonary circulation resistance, increasing cardiac afterload and aggravating the degree of heart failure

[3-5]. Owning to the untypical clinical manifestations of cardiac infection, it is often difficult to find the infection foci in a timely manner or make an accurate diagnosis, which inevitably leads to the untimely control and treatment of the disease, affecting the prognosis of patients. Therefore, early diagnosis of cardiac insufficiency with infection is of great clinical significance. However, in recent years, there are still some controversies about the etiology and influencing factors of cardiac insufficiency complicated with pulmonary infection. Therefore, the analysis of pathogen distribution and drug resistance in patients and the discussion of its main influencing factors are conducive to the clinical control and treatment of cardiac dysfunction complicated with pulmonary infection.

Procalcitonin (PCT) and C-reactive protein (CRP) are clinically common, types of infectious markers, and are of great significance in the identification of infectious diseases such as bacterial or viral infections and sepsis [6-8]. Except the abnormal rise in infectious diseases, PCT and CRP levels also express abnormally in other diseases [9], such as cardiac insufficiency. Therefore, the clinical value of PCT and CRP in the diagnosis of cardiac insufficiency combined with pulmonary infection was one of the focuses of this study. Cardiac insufficiency can cause excessive activation of some neurohumoral factors in the body. Previous studies have found that Brain Natriuretic Peptide (BNP) and Norepinephrine (NE) levels are overexpressed in patients with cardiac insufficiency [10], and that they are important reference indicators for diagnosis of cardiac insufficiency [11]. It is also well established that BNP and NE levels also increase in severely infected patients, and their levels are closely related to the degree of infection [12], which suggests that BNP and NE may have certain clinical significance in the diagnosis of cardiac insufficiency complicated with pulmonary infection.

Based on previous findings, this study explored the etiological distribution and influencing factors of patients with cardiac insufficiency complicated with pulmonary infection, and the clinical significance of PCT, CRP, BNP and NE in the diagnosis of this disease, so as to provide relevant evidence for the clinical diagnosis and treatment of cardiac dysfunction complicated with pulmonary infection.

Materials and methods

General information

A total of 164 patients with cardiac insufficiency admitted to Tianjin Fifth Central Hospital from January 2016 to January 2018 were selected as the study subjects, and were divided into the infection group (43 cases) and the non-infection group (121 cases) according to whether they had pulmonary infection. The diagnostic criteria for the infection group referred to the relevant standards formulated by the Infectious Diseases Society of America in 2016 [13]. All patients were informed and consented to participating in the study. This study was approved by the Medical Ethics Committee of Tianjin Fifth Central Hospital. General information including age, gender, length of hospital stay, cardiac function grading, smoking history, diabetes history, use of prophylactic antibiotics, and invasive procedures were collected.

Inclusion and exclusion criteria

Inclusion criteria: (1) Patients met the diagnostic criteria for cardiac insufficiency formulated by the American College of Cardiology [14]; (2) Patients were aged between 20-85 years old; (3) Patients without immune diseases; (4) Patients without serious liver or kidney disease; (5) Patients that did not receive other treatment before admission.

Exclusion criteria: (1) Patients complicated with other serious diseases; (2) Patients with neurological or psychiatric diseases; (3) Patients who were participating in other research; (4) Patients who died or were discharged within 24 hours after admission; (5) Patients with poor compliance.

Methods

Pathogen identification and drug resistance analysis: Sputum specimens from the infected group were collected, inoculated into sterile culture bottles, and immediately submitted for examination. The cells were streaked on blood plate medium. Some special samples were inoculated into the broth medium before streaking into the blood plate medium. After incubation at 37°C for 24-72 h, the bacteria were initially identified based on Gram staining results and bacterial colony characteristics. Finally, the

strain identification was carried out by a fully automated microbiome (MicroScan WalkAway plus 96, Beckman Coulter, USA). The quality control bacteria were Staphylococcus aureus (ATCC25923), Staphylococcus epidermidis (ATCC12228), Klebsiella pneumoniae (ATCC70060), all purchased from the Chinese Center for Disease Control and Prevention. The Gram-positive bacteria susceptibility test was conducted by the GN2011 method, the gram-negative bacteria susceptibility test by the GP method, and the drug sensitivity test by the paper diffusion method.

Detection of serum PCT, CRP, BNP and NE levels: In the early morning of the day after admission, 5 mL venous blood was extracted on an empty stomach and centrifuged at 3000 r/min for 5 min to separate the serum. Electrochemical luminescence method (Elecss-2010 electrochemiluminescence immunoassay analyzer, Roche) was employed to detect BNP levels, immunoturbidimetry (AU400 automatic biochemical analyzer, Olympus, Japan) was applied to detect CRP levels. While PCT levels were measured using enzyme-linked immunofluorescence (Spectra-Max Paradigm multiplate reader, Molecular Devices, USA), and NE levels were determined by enzyme-linked immunosorbent assay (Spectra-Max Paradigm multi-plate reader, Molecular Devices, USA). The kits were all purchased from Shanghai Beyotime Biotechnology Co., Ltd.

Statistical analysis

Statistical analysis was performed using SPSS 22.0, among which, the counting data was represented by number of cases and percentage, and the measurement data was expressed as the mean ± standard deviation ($\bar{x}$ ± sd). The measurement data were analyzed by the t test, and the comparison of counting data was performed by χ^2 test. Univariate analysis was employed to analyze the indicators with statistical difference. The clinical value of PCT, CRP, BNP and NE in the diagnosis of cardiac insufficiency complicated with pulmonary infection was analyzed by ROC curve. A statistically significant difference was assumed at P<0.05.

Results

Comparison of general information between the two groups

The results showed that there were significant differences between the two groups in length of hospital stay, age, cardiac function grading, smoking history, diabetes mellitus, and invasive procedures (P<0.05). See **Table 1**.

Distribution of pathogenic bacteria in the infected group

A total of 63 pathogenic bacteria were isolated from 43 patients, including 43 Gram-negative bacteria, accounting for 68.25%, 18 Gram-positive bacteria, accounting for 28.57%, and 2 fungi, accounting for 3.17%. See **Figure 1**.

Resistance of main Gram-positive and Gram-negative bacteria to antibiotics

The results indicated that Pseudomonas aeruginosa and Klebsiella pneumoniae in Gram-negative bacteria were highly resistant to cefuroxime, ampicillin and levofloxacin. While among Gram-positive bacteria, Staphylococcus aureus and Staphylococcus haemolyticus were highly resistant to penicillin, erythromycin and gentamicin. See **Tables 2**, **3**.

Comparison of serum PCT, CRP, BNP and NE levels between the two groups

The results demonstrated that the serum PCT, CRP, BNP and NE levels in the infected group were higher than those in the non-infected group (P<0.05). See **Figure 2**.

Multivariate logistic regression analysis

Multiple Logistic regression analysis exhibited that; age ≥60 years old, long hospital stay, diabetes, invasive procedures, and high serum PCT, CRP, BNP and NE levels were independent risk factors for patients with cardiac insufficiency complicated with pulmonary infection (P<0.05). See **Table 4**.

ROC curve results

The results suggested that PCT had a higher diagnostic value (AUC=0.894, P<0.001) when the cutoff value was 1.818 μg/L, CRP had a higher diagnostic value when the cutoff value was 18.292 mg/L (AUC=0.834, P<0.001), BNP had a high diagnostic value (AUC=0.762, P<0.001) when the cutoff value was 296.329 ng/L, and NE had a higher diagnosis value (AUC=0.749, P<0.001) when the cutoff value was 61.233 μg/L. See **Table 5** and **Figure 3**.

Table 1. Comparison of general data between the two groups

Influence factors	Infection group (n-43)	Non-infection group (n-121)	χ^2/t	P
Length of hospital stay (days)	18.23±2.21	13.47±1.98	13.129	<0.001
Age (years)				
≥60	25	44	6.173	0.013
<60	18	77		
Gender (cases)				
Male	23	67	0.046	0.831
Female	20	54		
Cardiac function grade (grade)				
II	6	30	6.840	0.033
III	14	53		
IV	23	38		
Smoking history (cases)				
Yes	27	35	15.474	<0.001
No	16	86		
Combined with diabetes (cases)				
Yes	25	18	30.964	<0.001
No	18	103		
Prophylactic use of antimicrobial agents				
Yes	24	51	2.387	0.122
No	19	70		
Invasive operation				
Yes	31	39	20.605	<0.001
No	12	82		

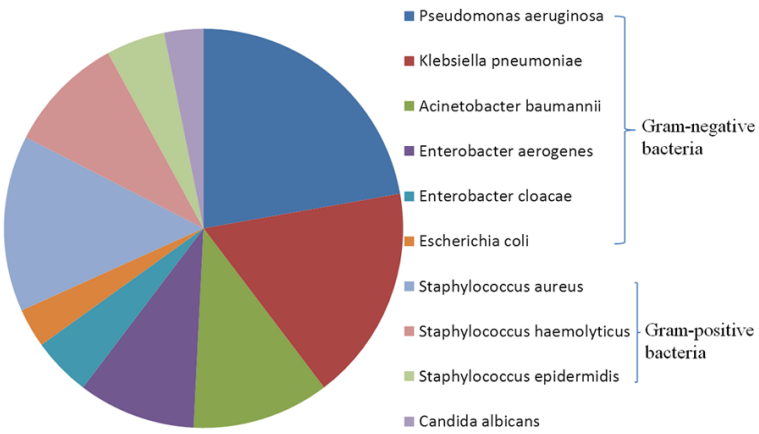

Figure 1. Distribution of pathogenic bacteria in the infected group.

Discussion

The results of this survey showed that the pathogens with cardiac insufficiency and pulmonary infection were mainly Gram-negative bacteria, of which Pseudomonas aeruginosa (22.22%) and Klebsiella pneumoniae (17.46%) accounted for the highest proportion. The respiratory tract is the most susceptible site of infection for this type of pathogen. The possible reason is that patients with cardiac insufficiency are unable to ensure the vitality of tissues and organs due to the blood flow pumped by the viscera, resulting in abnormal function of tissues and organs, weakened alveolar elasticity, decreased bronchial ciliary motility, difficulty in removing the pulmonary secretion from the body, and declined immune function of the body, eventually increasing the risk of infection of this type of pathogen [15]. Studies indicated that among Gram-positive bacteria, Staphylococcus aureus and Staphylococcus hemolyticus also had a high infection rate (14.29% and 9.52% respectively), which might be associated with invasive procedures, long-term use of antibacterial drugs and other factors [16]. The resistance test results in

Table 2. Drug resistance results of major Gram-negative bacteria

Antibacterial agents	Pseudomonas aeruginosa (n=14)	Klebsiella pneumoniae (n=11)
	Strains/Drug resistance rate	Strains/Drug resistance rate
Cefuroxime	12/85.71	7/63.64
Ampicillin	13/92.86	9/81.82
Levofloxacin	12/85.71	6/54.55
Ceftriaxone	6/42.86	3/27.27
Cefotaxime	4/28.57	3/27.27
Ceftazidime	3/21.43	1/9.09
Ciprofloxacin	1/7.14	1/9.09
Meropenem	1/7.14	1/9.09
Imipenem	1/7.14	1/9.09

Table 3. Drug resistance results of major Gram-positive bacteria

Antibacterial agents	Staphylococcus aureus (n=9)	Hemolytic staphylococcus (n=6)
	Strains/Drug resistance rate	Strains/Drug resistance rate
Penicillin	8/88.89	6/100
Erythromycin	9/100	5/83.33
Gentamicin	8/88.89	5/83.33
Clindamycin	5/55.56	2/33.33
Rifampicin	4/44.44	2/33.33
Tetracycline	5/55.56	3/50.00
Moxifloxacin	2/22.22	1/16.67
Vancomycin	1/11.11	1/16.67
Levofloxacin	1/11.11	
Teicoplanin	1/11.11	

our current study displayed that Pseudomonas aeruginosa and Klebsiella pneumoniae in Gram-negative bacteria were more resistant to cefuroxime, ampicillin and levofloxacin, while Staphylococcus aureus and Haemolytic staphylococcus in Gram-positive bacteria were more resistant to penicillin, erythromycin and gentamycin. It indicates that there are some differences in the secondary infection caused by different pathogenic bacteria and the drug resistance of pathogenic bacteria, which is of certain clinical value in guiding rational drug use.

At present, no consensus has been achieved concerning the influencing factors of cardiac insufficiency complicated with pulmonary infection. Studies abroad suggest that advanced age, underlying disease, and prolonged bed rest may increase the risk of infection [17, 18]. In this study, univariate analysis was conducted by incorporating factors such as age, gender, length of hospital stay, cardiac function classification, history of smoking, history of diabetes, use of preventive antibiotics, and invasive procedures. What's more, multiple Logistic regression analysis was further conducted on the indexes with statistical differences, and the results showed that; age ≥60 years, long hospital stay, diabetes mellitus and invasive procedures were independent risk factors for cardiac insufficiency complicated with pulmonary infection, which also accorded with the results of the above studies [17, 18]. The body function of elderly patients tends to decline, the bronchial mucosa system is gradually shrinking, the cilia activity is weakened, and the body's immune function is reduced, which leads to the accumulation of lung secretions, providing conditions for the growth and reproduction of microorganisms, and promoting the occurrence of infection. Diabetes mellitus is also an independent risk factor for increased infection, which may be due to the abnormal metabolic function of such patients, weakened body resistance, plus the high blood glucose

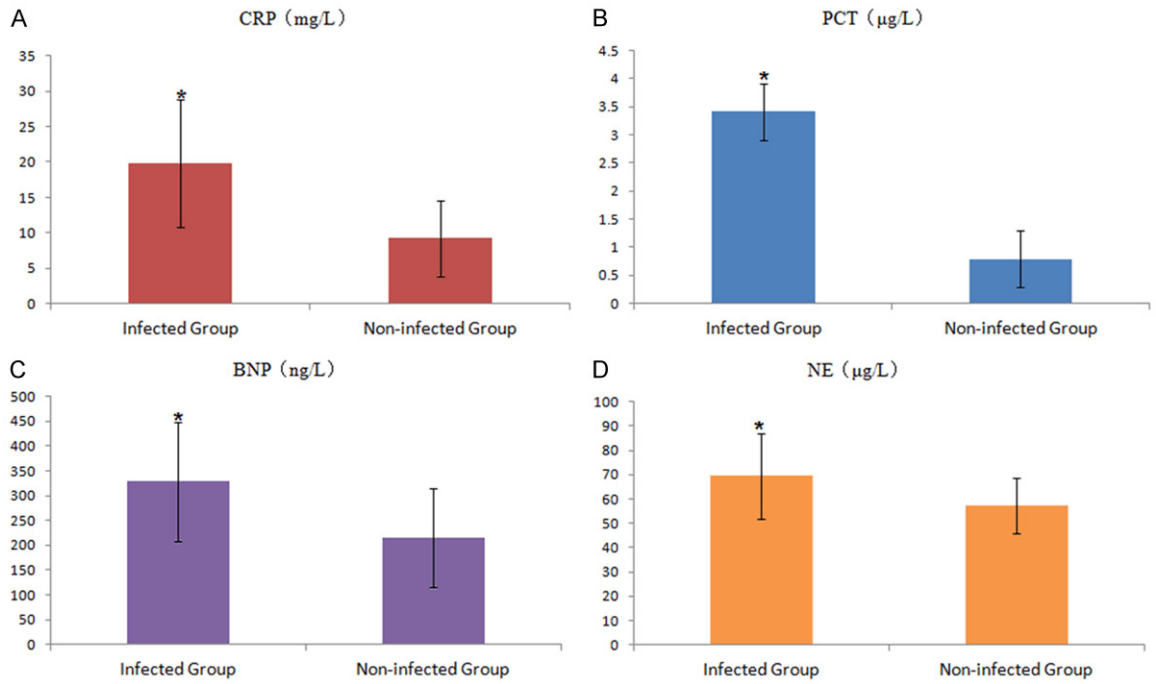

Figure 2. Comparison of serum PCT, CRP, BNP and NE levels in the two groups. A: Serum PCT level; B: Serum CRP level; C: Serum BNP level; D: Serum NE level. *P<0.05, compared with non-infected group. PCT: Procalcitonin; CRP: C-reactive protein; BNP: Brain natriuretic peptide; NE: Norepinephrine.

Table 4. Results of multivariate logistic regression analysis

Related factors	B	SE	Wald/χ^2	P	OR	95% CI
Ages	1.386	0.223	9.351	0.002	2.214	1.108, 4.227
Length of hospital stay	3.114	0.356	14.328	<0.001	3.498	1.336, 4.316
Combined with diabetes	0.876	0.332	8.759	0.003	2.578	1.479, 5.683
Invasive operation	0.941	0.375	7.942	0.013	2.554	1.163, 5.734
PCT (μg/L)	1.213	0.187	13.221	<0.001	1.784	1.245, 3.398
CRP (mg/L)	0.765	0.316	12.986	<0.001	2.112	1.098, 4.987
BNP (ng/L)	0.983	0.387	11.872	<0.001	1.345	1.054, 3.426
NE (μg/L)	1.332	0.286	13.143	<0.001	1.175	1.017, 2.982

Note: PCT: Procalcitonin; CRP: C-reactive protein; BNP: Brain natriuretic peptide; NE: Norepinephrine.

Table 5. ROC curve results

Indicators	Cutoff value	AUC	95% CI	Sensitivity	Specific degrees	P
PCT (μg/L)	1.817	0.894	0.831, 0.957	0.744	0.901	<0.001
CRP (mg/L)	18.292	0.834	0.762, 0.906	0.605	0.917	<0.001
BNP (ng/L)	296.329	0.762	0.677, 0.846	0.628	0.785	<0.001
NE (μg/L)	61.233	0.749	0.656, 0.841	0.767	0.603	<0.001

Note: PCT: Procalcitonin; CRP: C-reactive protein; BNP: Brain natriuretic peptide; NE: Norepinephrine.

level which provides nutrients for the reproduction of pathogens. For patients who have been hospitalized for a long time, their bed time has accordingly increased, and frequent exposure to invasive examinations or medical equipment not only increases the time of exposure to various pathogenic microorganisms, but also increases the risk of cross-infection.

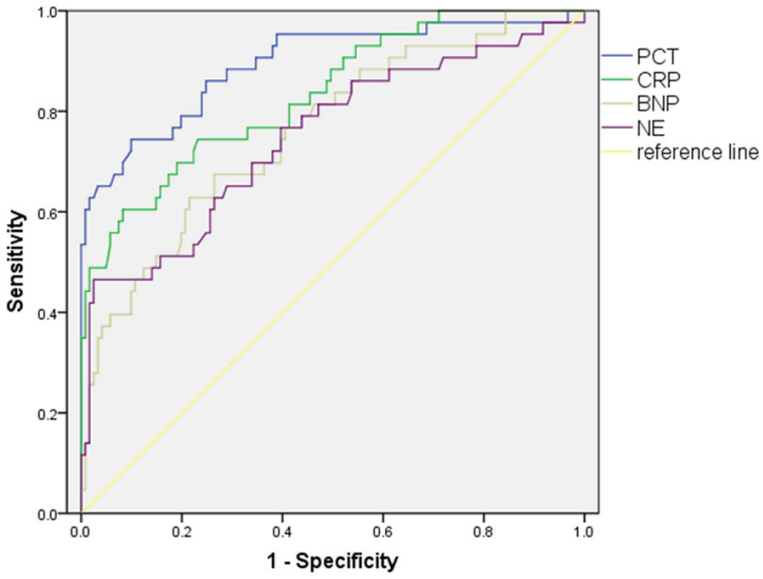

Figure 3. ROC curve results. PCT: Procalcitonin; CRP: C-reactive protein; BNP: Brain natriuretic peptide; NE: Norepinephrine.

PCT is the premise of calcitonin and is normally secreted by thyroid C cells with extremely low levels [19]. However, in the case of infection, liver macrophages and monocytes, stimulated by endotoxin and various inflammatory factors, secrete a large amount of PCT, leading to a significant increase in serum PCT level. Its abnormalities can be detected at 2 h and peak at 12-24 h after infection, and the change in the level is closely related to the severity of infection [20]. Data showed that the rise in PCT level was mainly caused by bacterial infection or endotoxin and inflammatory factors released by bacteria, while its increase was not associated with viral infection or other factors in the body, so this indicator was considered to have high clinical value in the diagnosis of pulmonary bacterial infection [21]. Our findings showed that, compared with patients with simple cardiac insufficiency, PCT level of patients complicated with pulmonary infection increased significantly, and the ROC curve presented a higher diagnostic value (AUC=0.894) at a cut-off value of 1.818 μg/L, which also suggested that PCT could be used as one of the indicators to diagnose cardiac insufficiency with pulmonary infection.

CRP is a kind of acute phase inflammatory response protein, which has the characteristics of early onset and rapid rise, and can sensitively reflect the inflammation and stress state of the body. When an infectious disease occurs, CRP levels rise in varying degrees. Studies have shown that CRP, as a sensitive indicator to detect the body's inflammatory response, can rise significantly several hours after the body has been infected, and its level is not affected by radiation or chemotherapy drugs or hormone drugs [22]. Previous studies have confirmed that CRP level in patients with bacterial pneumonia increases significantly and also increases alongside with the severity of the disease [23]. The results of present study showed that CRP level was significantly elevated in patients with cardiac insufficiency complicated with pulmonary infection, and had a high diagnostic value (AUC=0.834) when the cut-off value was 18.292 mg/L.

The renin-angiotensin-aldosterone system has important clinical significance in cardiovascular diseases, which can regulate the homeostasis, tissue perfusion and arterial pressure of extracellular volume. NE is a type of indicator in the renin-angiotensin-aldosterone system, whose overexpression in patients with cardiac insufficiency is closely related to the degree of cardiac insufficiency, and can cause further deterioration of cardiac function and Myocardial injury [24]. BNP is a kind of peptide secreted by left ventricular cardiomyocytes, which is considered to be one of the major markers for the diagnosis of cardiac insufficiency [25]. BNP has diuretic, natriuretic and vasodilator effects and exerts an extensive inhibitory effect on the renin-angiotensin-aldosterone system. When there is excessive ventricular overload or myocardial ischemia, it will promote the secretion of BNP, thereby enhancing its biological activity. Cardiac insufficiency or pulmonary infection can increase ventricular load, leading to BNP to be released into the blood in a pulsed manner [26]. However, in patients with functional insufficiency complicated with pulmonary infection, ventricular injury will be further aggravated, and BNP level will rise significantly [23]. This

study demonstrated that compared with patients with cardiac insufficiency, NE and BNP levels were markedly increased in patients with co-infection, and both NE and BNP had high clinical value in the diagnosis of cardiac insufficiency complicated with pulmonary infection (AUC=0.749, 0.762).

In conclusion, Gram-negative bacteria are the main cause of cardiac insufficiency complicated with pulmonary infection, and rational drug use should be made according to drug sensitivity results. Age ≥60 years, long hospital stay, diabetes, invasive procedures and high serum PCT, CRP, BNP and NE levels can increase the risk of infection in patients with cardiac insufficiency. In addition, serum PCT, CRP, BNP and NE have high clinical value in the diagnosis of cardiac insufficiency complicated with pulmonary infection. However, this study also has some shortcomings, such as the narrowed sample size and the failure in dynamically observing the changes of various indicators, which need to be confirmed by follow-up research.

Disclosure of conflict of interest

None.

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