Variations and Clinical Implications of Serum Gal-3 and IL-6 in Heart Failure Individuals Complicated with Renal Impairment

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ABSTRACT

Objective: To investigate the variations and clinical implications of serum Gal-3 and IL-6 values in individuals with heart failure (HF) complicated with renal impairment.

Study Design: Analytical study.

Place and Duration of the Study: Department of Nephrology, The Affiliated Hospital of Hebei University, Baoding, Hebei, China, from May 2022 to 2023.

Methodology: A total of 80 HF individuals who were treated in the Department of Nephrology, The Affiliated Hospital of Hebei University, Baoding, Hebei, China, from May 2022 to 2023, were classified into the normal renal function band (n = 40) and the renal impairment band (n = 40) according to glomerular filtration rate (eGFR). The serum galactose-3 (Gal-3) and interleukin-6 (IL-6) values and their correlation with renal impairment were compared between the two bands, along with an analysis of the sensitivity and specificity of Gal-3 and IL-6 using receiver operating characteristic (ROC) curves.

Results: There were higher Gal-3 and IL-6 values in the renal impairment band, in contrast to the normal renal function band ($p < 0.05$). Spearman's correlation analysis indicated a significant association between Gal-3 and IL-6 values in HF individuals and renal impairment ($p < 0.05$). The AUC values of Gal-3 and IL-6 in predicting renal impairment in HF individuals were <0.914 and <0.717, respectively; the specificity of Gal-3 and IL-6 in predicting renal impairment was 70.00% and 62.50%, respectively, the sensitivity was 97.50% and 80.00%, respectively.

Conclusion: HF individuals complicated with renal impairment have increased serum Gal-3 and IL-6 values, both of which are significantly associated with renal impairment.

Key Words: *Heart failure, Renal impairment, Galactose lectin-3, Interleukin-6 protein*.

How to cite this article: Li J, Li H, Zhang Y, Fan X, Wang Q, Li Z. Variations and Clinical Implications of Serum Gal-3 and IL-6 in Heart Failure Individuals Complicated with Renal Impairment. *J Coll Physicians Surg Pak* 2025; **35(03)**:297-301.

INTRODUCTION

Heart failure (HF), by definition, means the terminal stage of various heart diseases, which comes with a high incidence and is characterised by recurrent episodes and poor prognosis, severely affecting the physical health and life safety of individuals.[1] Studies have shown that HF not only leads to weakened cardiac function but also impairs the renal function,[2] while renal impairment will aggravate the deterioration of the cardiac function and seriously impact the prognosis. Accordingly, early detection and intervention are crucial for improving the prognosis of HF individuals and inhibiting the progression of the disease. Galactose-3 (Gal-3), an important member of the lectin family, has been shown to significantly contribute to the metastasis,[3] adhesions, apoptosis, and other pathological processes of tumour cells. Additionally, some studies have indicated that the Gal-3 values in HF individuals are increased,[4] in comparison with normal individuals, with the increase directly proportional to the prognosis. Relevant studies have indicated a strong association between the inflammatory response and the progression of HF and renal impairment, while the inflammatory factor interleukin-6 (IL-6) is considered a pathogenic factor of deterioration of cardiac and renal function, which can induce the occurrence and development of CHF,[5] but there are limited research reports on this. This study aimed to explore the changes and clinical significance of serum Gal-3 and IL-6 levels in patients with HF and renal damage, providing clinical guidance for early diagnosis and evaluation of patients with HF and renal damage.

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Received: July 05, 2024; Revised: January 16, 2025; Accepted: February 14, 2025
DOI: https://doi.org/10.29271/jcpsp.2025.03.297

METHODOLOGY

From May 2022 to 2023, all 80 heart failure patients who met the inclusion and exclusion criteria at the Department of Nephrology, The Affiliated Hospital of Hebei University, Baoding, Hebei, China, were included in the study. Patients were classified into the normal renal function band (n = 40) [Egfr ≥60Ml / (min. 1.73m^2)] and the renal impairment band (n = 40) [Egfr ≤60Ml / (min. 1.73m^2)],[6] according to glomerular filtration rate. Demographic information, including gender, age, BMI, smoking history, history of myocardial infarction, LVEF, and serum Gal-3 and IL-6 values, was collected from all individuals. The patient data statistics were conducted through the hospital medical record system. Ethical approval was obtained from the Institutional Ethics Committee of the Affiliated Hospital of Hebei University, Baoding, Hebei, China (No: HDFYLL-KY-2023-018; dated: 15 February 2023), and all participants provided written informed consent.

All individuals conformed to the diagnostic standard of HF according to the guidelines for the Diagnosis and Treatment of Chronic Heart Failure established by the Chinese Society of Cardiology in 2007.[7] Individuals were categorised as NYHA Class II to IV at admission; individuals with lower limb oedema or dyspnoea symptoms; and individuals with LVEF <45%.

Exclusion criteria included individuals with infection or other inflammatory diseases, serious hepatic and renal dysfunction, malignant tumours, congenital heart disease, or severe mental illness.

After admission, 3 mL of venous blood was drawn from each patient following fasting and subsequently preserved in dry tubes. After centrifugation at 3000 r/min for 10 minutes using an Eppendorf Ebende 5425R high-speed refrigerated centrifuge (Cat. No: 5406000097), the supernatant was preserved at -80°C in a refrigerator. Afterwards, the Gal-3 and IL-6 protein values in the two bands were measured by the enzyme-linked immunosorbent assay (ELISA). The Galectin-3 kit (Cat. No: F00945) manufactured by the Shanghai Xitang Biotechnology Co., Ltd. and IL-6 Elisa kit (Cat. No: SEKH-0013) manufactured by the Beijing Solar Bio Science and Technology Co., Ltd. were used. All operation procedures were performed in strict accordance with the kit instructions, along with an analysis of the correlation between renal impairment and serum Gal-3 and IL-6 values. An analysis was conducted on the sensitivity and specificity of serum Gal-3 and IL-6 in detecting renal impairment.

In order to assess the method for renal impairment,[6] the glomerular filtration rates (GFR) of the participants were determined with eGFR calculation software, applying the CKD-EPI equation, which was developed by the American renal epidemiology collaboration in 2009.

The data were statistically analysed using the SPSS version 26.0 software. Measurement data were analysed using the Kolmogorov-Smirnov test, and the results showed a normal distribution and were expressed as ($\bar{x}\pm s$). Differences between the two cohorts were compared using the independent sample t-test. Nominal data were presented as n (%), and χ^2 test was employed to compare the two cohorts. The association between Gal-3 and IL-6 values, and renal impairment were analysed through Pearson's correlation. The sensitivity and specificity of serum Gal-3 and IL-6 values were assessed using the ROC curve. A p-value of <0.05 was considered as statistically significant.

RESULTS

The two bands did not show discernible discrepancies in gender, age, BMI, smoking history, myocardial infarction history, and LVEF (p >0.05, Table I).

In the renal impairment band, Gal-3 values were notably elevated, while IL-6 values were markedly lower compared with those in the normal renal function band (p <0.05, Table II).

There was a positive association between Gal-3 and IL-6 values and renal impairment in HF individuals (all p <0.05), as illustrated by the Spearman's correlation analysis Table III.

The AUC values of Gal-3 and IL-6 for predicting renal impairment in HF individuals were <0.914 and <0.717, respectively, and the specificity of Gal-3 and IL-6 for predicting renal impairment was 70.00% and 62.50%, respectively, and the sensitivity was 97.50% and 80.00%, respectively, as manifested by the ROC curve analysis (Table IV, Figure 1).

DISCUSSION

The clinical manifestations of HF include weakened systolic and diastolic function accompanied by fatigue, dyspnoea, and fluid retention, which are serious and terminal stages of various cardiovascular diseases. With an ageing society and the development of social structure in recent years, this disease has seen an increasing incidence year by year, severely affecting the physical health and life safety of individuals.[8,9]

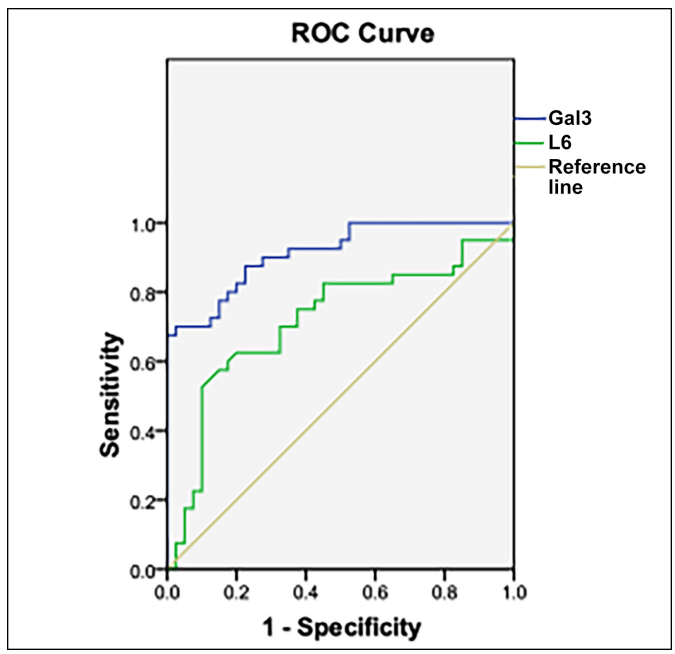

Figure 1: ROC curve of serum Gal-3 and IL-6 levels.

Table I: Comparison of general data between the two groups.

Index	Renal impairment group	Normal renal group	χ^2/t	p-value*
Gender (M/F)	24/16	26/14	0.213	0.644$^{\triangle}$
Age ($\bar{x}\pm s$, years)	63.12 ± 5.25	62.54 ± 5.18	0.497	0.620*
BMI ($\bar{x}\pm s$, kg/m^2)	24.26 ± 2.13	24.19 ± 2.09	0.148	0.882*
NYHA grade				
Grade II	14	13	0.267	0.875$^{\triangle}$
Grade III	22	24		
Grade IV	4	3		
Left ventricular ejection fraction ($\bar{x}\pm s$, %)	37.75 ± 3.74	39.07 ± 3.92	1.541	0.127*

Note: Independent sample t-test, $^{\triangle}\chi^2$ test, p <0.05.

Table II: Comparison of serum Gal-3 and IL-6 levels between the two groups.

Group	Case	Gal-3 (μg/L)	IL-6 (ng/L)
Renal impairment	40	11.77 ± 2.39*	114.14 ± 34.27
Normal renal	40	7.95 ± 1.48	98.52 ± 28.32
t		8.594	2.222
p-value*		<0.001	0.029

Note: Independent sample t-test, p <0.05.

Table III: Correlation of renal impairment with Gal-3 and IL-6 levels.

Item	Gal-3		IL-6	
	r	p-value*	r	p-value*
Renal impairment	0.697	<0.001	0.244	<0.029

Note: Pearson's correlation analysis, p <0.05.

Table IV: ROC curve analysis of serum Gal-3, and IL-6 levels in HF patients complicated with renal impairment.

Marker	AUC	p-value*	95% CI	Specificity	Sensitivity
Gal-3(μg/L)	0.914	<0.001	0.855~0.973	70.00%	97.50%
IL-6	0.717	<0.001	0.600~0.834	62.50%	80.00%

Meanwhile, HF is usually accompanied by complications such as renal impairment, which is among the top three complications of HF and comes with an incidence accounting for about 29.7% of the total number of individuals, thus significantly affecting the prognosis of individuals.[10] Studies have indicated that once HF is complicated by renal damage,[11,12] it is more likely to develop adverse events such as cardiovascular disease, along with a poorer prognosis. Gal-3, as a powerful inflammatory factor, plays roles in the immune response, cell growth, and apoptosis processes, reflecting the development of the disease to a certain extent.[13,14] At the same time, it has also been shown that IL-6 is produced by cells such as monocytes,[15,16] macrophages, cardiomyocytes, and fibroblasts and is a peptide substance with a variety of biological functions that can reduce myocardial contractility, increase the expression of pro-fibrotic factors, and promote tissue fibrosis. Current studies have reported that IL-6 can function as a predictor for the risk of cardiovascular events and is of significant importance in reflecting the severity of HF. This study aims to investigate the variations and clinical implications of serum Gal-3 and IL-6 values in HF individuals complicated with renal impairment.

In contrast to those with normal renal function, in the renal impairment band, this study observed higher values of Gal-3 and IL-6 ($p < 0.05$), indicating elevated expression of Gal-3 and IL-6 in individuals with renal dysfunction. The reason is that Gal-3 can aggravate the fibrosis of myocardial interstitium and peripheral blood vessels by stimulating fibroblast activation and participating in the synthesis, maturation, and externalisation of cells. However, elevated expression of Gal-3 values increases the probability of dialysis-related amyloidosis and aggravates renal impairment.[17] It has been found that when HF individuals develop renal dysfunction, the activation of the inflammatory system stimulates cells to generate a significant amount of pro-inflammatory cytokines IL-6, resulting in severe cell damage, and the value gradually increases with the development of the disease. Moreover, it has been shown that inflammatory factor IL-6 can induce GFR changes by reducing sodium excretion, increasing fluid retention, and raising renal vein pressure leading to dilatation of intravascular volume, indicating that diseases such as renal impairment is closely related to the expression of IL-6 values. However, there have been no previous relevant conclusions, indicating the novelty of this study.[18] Guan *et al*. discovered that the expression of serum Gal-3 and IL-6 values in HF individuals can effectively reflect their renal function and contribute significantly to investigating the progression of renal disease,[14,19] which is consistent with the above conclusions.

Meanwhile, the Spearman's correlation analysis showed that Gal-3 and IL-6 values were positively correlated with renal impairment in HF individuals, suggesting that serum Gal-3 and IL-6 values are associated with renal impairment. The reason is that Gal-3, as a multifunctional soluble lectin protein, can regulate a variety of biological processes through the interaction of sugar recognition domains. Gal-3 plays pivotal role in facilitating cell proliferation and differentiation, effectively modulate cell cycle, adhesion, and anti-apoptotic abilities and contributes to collective inflammatory responses with elevated expression. The production of neuroendocrine and IL-6 and other pro-inflammatory cytokines from heart failure inhibits myocardial contractility, leads to ventricular remodelling due to myocardial fibrosis, and increases the production of pro-inflammatory cytokines, forming a vicious cycle and exacerbating the process of renal cell fibrosis. These findings suggest that IL-6 can be regulated by inflammation-related pathways and reflects the pathological status of the kidney, which is highly consistent with the above conclusions. Multiple studies, both national and international, have shown that Gal-3 values are an independent predictor of renal impairment and poor prognosis in HF individual.[5,20] Furthermore, elevated Gal-3 levels can effectively reflect the risk of adverse cardiovascular and cerebrovascular events in individuals. Meanwhile, numerous studies have reported that IL-6 can reduce myocardial contractility and mediate this negative inotropic effect by activating nitric oxide synthase (NOS) to generate nitric oxide (NO).[21-23] Additionally, elevated IL-6 values can exacerbate the development of renal impairment, leading to poor prognosis and increased risk of death. This study also documented that the AUC, diagnostic cut-off values and corresponding specificity and sensitivity of Gal-3 and IL-6 in predicting renal impairment were 70.0, 62.5, 97.5, and 80.0%, respectively, indicating that Gal-3 and IL-6 can serve as excellent diagnostic indicators for renal impairment in HF individuals. Furthermore, clinical studies have suggested that elevated Gal-3 values can expedite renal fibrosis, decrease glomerular filtration rate in individuals, and further aggravate renal diseases. Multiple research results have shown that serum IL-6 levels in patients with heart failure are significantly elevated, and the increase in IL-6 levels becomes more significant with the improvement of NYHA grading,[24,25] which was positively correlated with the severity of chronic heart failure. Independently associated with GFR, IL-6 values can be considered an independent diagnostic factor in individuals with renal disease after adjusting for other related factors. The results of this study align closely with the above conclusions, indicating that Gal-3 and IL-6 values can serve as excellent diagnostic indicators for HF complicated with renal impairment.

This study had some limitations. Specifically, there was no long-term follow-up, and the sample size was small. Further validation of the present study's results is necessary for future research that addresses these issues.

CONCLUSION

Elevated serum Gal-3 and IL-6 values can be considered key indices for HF complicated with renal impairment, which are correlated with renal impairment to a certain extent. Measurement of the two serum indices can provide some clinical value for the early diagnosis of HF complicated with renal impairment.

FUNDING:
This study is supported by the Science and Technology Projects in Baoding, China (No. 2341ZF143).

ETHICAL APPROVAL:
Approval for the study was obtained from the Ethics Committee of the Affiliated Hospital of Hebei University, Baoding, Hebei, China (Approval Code: HDFYLL-KY-2023-018; dated: 15 February 2023). The study was conducted in accordance with the Declaration of Helsinki.

PATIENTS' CONSENT:
Informed consent was obtained from the patients.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
JL, ZL: Designed of the study and prepared the manuscript.
HL, YZ: Collected and analysed the clinical data.
XF, QW: Contributed to acquisition, analysis, interpretation of data, and drafting of the manuscript.
All authors approved the final version of the manuscript to be published.

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