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Galectin-3, Acute Kidney Injury and Myocardial Damage in Patients With Acute Heart Failure

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ABSTRACT

Background: Galectin-3, a biomarker of inflammation and fibrosis, can be associated with renal and myocardial damage and dysfunction in patients with acute heart failure (AHF).

Methods and Results: We retrospectively analyzed 790 patients with AHF who were enrolled in the AKINESIS study. During hospitalization, patients with galectin-3 elevation ($>$ 25.9 ng/mL) on admission more commonly had acute kidney injury (assessed by KDIGO criteria), renal tubular damage (peak urine neutrophil gelatinase-associated lipocalin [uNGAL] $>$ 150 ng/dL) and myocardial injury ($\geq$ 20% increase in the peak high-sensitivity cardiac troponin I [hs-cTnI] values compared to admission). They less commonly had $\geq$ 30% reduction in B-type natriuretic peptide from admission to last measured value. In multivariable linear regression analysis, galectin-3 was negatively associated with estimated glomerular filtration rate and positively associated with uNGAL and hs-cTnI. Higher galectin-3 was associated with renal replacement therapy, inotrope use and mortality during hospitalization. In univariable Cox regression analysis, higher galectin-3 was associated with increased risk for the composite of death or rehospitalization due to HF and death alone at 1 year. After multivariable adjustment, higher galectin-3 levels were associated only with death.

Conclusions: In patients with AHF, higher galectin-3 values were associated with renal dysfunction, renal tubular damage and myocardial injury, and they predicted worse outcomes. (*J Cardiac Fail 2022;00:1−9*)

Key Words: acute heart failure, galectin-3, acute kidney injury, renal tubular damage, myocardial injury, prognosis.

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Renal dysfunction is 1 of the most common comorbidities for patients with heart failure (HF). An acute deterioration in kidney function is commonly observed in patients with acutely decompensated HF (AHF) and may portend poor prognoses.[1] Conversely, acute kidney injury (AKI) can induce cardiac dysfunction and damage through several pathways, such as volume overload, neurohormonal activation, inflammation, fibrosis, and oxidative stress.[2,3] This cross-talk between the heart and kidney is termed cardiorenal syndrome (CRS), and there is growing evidence that circulating cytokines involved in inflammation and fibrosis play a crucial role.[1,4] Galectin-3 (Gal-3) is a biomarker produced by macrophages after organ injury.[5] Mouse models have shown that following AKI, Gal-3 is produced in the kidney and promotes local inflammation and fibrosis and is released into the systemic circulation, inducing cardiac dysfunction and injury.[6,7] Therefore, the Gal-3 pathway may be associated with both renal and cardiac dysfunction or damage in patients with AHF. However, relationships between Gal-3 and CRS have not been fully investigated in patients with AHF.

The Acute Kidney Injury Neutrophil gelatinase-associated lipocalin (NGAL) Evaluation of Symptomatic Heart Failure Study (AKINESIS) was a prospective observational study of patients with AHF and included repeated sampling of biomarkers of renal glomerular function (creatinine), renal tubular injury (NGAL), inflammation and fibrosis (Gal-3), and myocardial congestion and damage (B-type natriuretic damage [BNP] and high-sensitivity cardiac troponin I [hs-cTnI]).[8] In this analysis, we aimed to investigate whether Gal-3 expression is associated with renal and myocardial dysfunction and portends worse outcomes in patients with AHF.

Methods

Study Population

This is a post hoc analysis of AKINESIS, which enrolled 927 patients with AHF at 16 sites in the United States and Europe from January 2011 through September 2013.[8] Each center's institutional review board approved the study. Patients must have received or planned treatment with intravenous diuretics. Patients with acute coronary syndrome were excluded. Among the 927 patients enrolled in the original AKINESIS study, 24, 93, 13, 3, and 4 lacked measurements of Gal-3, uNGAL, hs-cTnI, BNP, and estimated glomerular filtration rate (eGFR) on admission, respectively, leaving 790 patients in the current analysis.

Supplementary Table 1 shows the comparison of patients included in and excluded by the study. Male sex was more common in included patients than in excluded patients (63% vs 54%; $P = 0.046$). Other variables were not significantly different.

Specimen Collection

Serum specimens for Gal-3, BNP and hs-cTnI measurements and urine specimens for NGAL and creatinine measurements were collected at 6 time points during hospitalization. The first specimen was collected on the day of enrolment within 2 hours of the first intravenous diuretic dose. The second specimen was collected 2−6 hours later. The 3rd, 4th and 5th specimens were collected on hospital days 1, 2 and 3, respectively. The last specimen was collected on the day of hospital discharge. Specimens were analyzed at the core laboratory with the ARCHITECT platform (Abbott Laboratories, Abbott Park, IL). Details of the assay performance are described elsewhere.[9] Serum creatinine was measured each day during hospitalization at each institution's respective laboratory facility.

Endpoints

We evaluated the relationships between Gal-3 on admission and biomarker-defined in-hospital endpoints. According to the Kidney Disease: Improving Global Outcomes criteria, AKI stages were defined as the following: stage 1, increase in serum creatinine by $\geq$ 0.3 mg/dL or 1.5−2 times, compared to the admission value; stage 2, increase in creatinine to 2−3 times compared to admission; and stage 3, increase in creatinine to $\geq$ 3 times compared to admission, increase in serum creatinine to $\geq$ 4.0 mg/dL or initiation of renal replacement therapy (RRT).[10,11] Acute renal tubular damage was defined as peak uNGAL value of $>$ 150 ng/dL.[12] Decongestion was defined by a $\geq$ 30% reduction in the last measured BNP compared to the admission BNP.[13] Myocardial injury was defined by a $\geq$ 20% increase in the peak value of hs-cTnI compared to the admission value.[14] We also evaluated other in-hospital clinical endpoints, such as inotrope use, mechanical ventilation, initiation of RRT, and mortality. One-year mortality and HF readmission were evaluated as a composite endpoint and also analyzed individually.

Statistical Analysis

Continuous variables were described as means with standard deviations or medians with 1st and 3rd quartiles if non-normally distributed.

Categorical variables were described as counts and percentages. The Student *t* test, Mann-Whitney test and ^{2} test were used for group comparison, as appropriate. Patients were classified by admission Gal-3 $>$ 25.9 ng/mL or $\leq$ 25.9 ng/mL, based on the previous reports.[15,16] Relationships between Gal-3 elevation and eGFR, uNGAL, BNP, and hs-cTnI were analyzed by using a multivariable linear regression model. These biomarkers were evaluated as area under the curves (AUC) of change during the first 3 days of hospital admission. To evaluate AUCs, individual changes in biomarkers were virtually visualized as a curve where the x-axis shows day of admission to day 3, and y-axis shows the value of the biomarker. Using this approach, the AUC between each sample measurement can be calculated and added together, resulting in an overall AUC score (unit of each biomarker $\times$ hour) that can be compared across treatment groups.[17–19] Baseline characteristics, such as demographics, medical histories, medications before admission, and admission laboratory data were tested in a univariable model, and factors with a *P*value $<$ 0.05 in univariable analysis were included in the multivariable linear regression model. Standardized beta-coefficients (β), 95% confidence intervals (CIs) and variance inflation factors (VIFs) of biomarkers were evaluated. Log-rank, Kaplan-Meier and Cox regression analyses were used for 1-year clinical outcomes. For HF readmission, the Fine-Gray model was used, and death was treated as a competing risk. Multivariable analysis included age, race, history of chronic obstructive pulmonary disease, systolic blood pressure, heart rate, sodium, hemoglobin, and blood urea nitrogen as well as biomarkers, based on prior studies.[20–23] Biomarkers were not normally distributed, and they were log-2 transformed in regression analysis so that associations represent the impact of a doubling in the biomarker. All statistical analyses were performed using R x64 4.1.0 for Windows.

Table 1. Baseline Characteristics of Patients Grouped by More Than or Less Than and Equal to Admission Galectin-3 Levels of 25.9 ng/mL

	Gal-3 $>$ 25.9 ng/mL	Gal-3 $\leq$ 25.9 ng/mL	*P* value
Variables	n = 375	n = 415	
Age (years), mean (SD)	72 (13)	66 (14)	<0.001
Male sex, n (%)	223 (60)	278 (67)	0.034
White, n (%)	258 (69)	247 (60)	0.008
BMI (kg/m^2), mean (SD)	31.2 (8.8)	31.8 (8.8)	0.413
History of coronary artery disease, n (%)	190 (51)	173 (42)	0.014
History of myocardial infarction, n (%)	113 (30)	99 (23.9)	0.056
History of PCI, n (%)	92 (25)	83 (20.0)	0.148
History of CABG, n (%)	78 (21)	57 (14)	0.011
History of hypertension, n (%)	307 (82)	331 (80)	0.509
History of hyperlipidemia, n (%)	207 (55)	203 (49)	0.09
History of diabetes mellitus, n (%)	183 (49)	163 (39)	0.009
History of atrial fibrillation, n (%)	120 (32)	97 (23)	0.008
History of COPD, n (%)	99 (26)	104 (25)	0.727
Tobacco use, n (%)	41 (11)	87 (21)	<0.001
ACE-I, n (%)	161 (43)	186 (45)	0.644
ARB, n (%)	69 (18)	82 (20)	0.693
β-blocker, n (%)	275 (73)	284 (68)	0.152
Diuretics, n (%)	279 (74)	280 (68)	0.039
Shortness of breath, n (%)	267 (71)	272 (66)	0.103
Rales, n (%)	180 (48)	157 (38)	0.005
Edema, n (%)	295 (79)	293 (71)	0.012
Jugular vein distension, n (%)	107 (29)	101 (24)	0.209
Systolic BP (mmHg), mean (SD)	137 (30)	144 (29)	0.001
Heart rate (bpm), mean (SD)	85 (22)	90 (23)	0.004
Sodium (mEq/l), mean (SD)	138 (5)	139 (8)	0.069
Hemoglobin (g/dL), mean (SD)	11.4 (2.2)	11.9 (2.5)	0.001
eGFR (mL/min/1.73m^2), mean (SD)	49 (25)	73 (26)	<0.001
BNP (ng/L), median [IQR]	650 [245, 1265]	439 [202, 992]	<0.001
hs-cTnI (ng/L), median [IQR]	30.0 [14.0, 66.4]	23.1 [12.0, 51.3]	0.009
uNGAL (ng/dL), median [IQR]	16.4 [5.2, 50.4]	9.7 [3.8, 22.7]	<0.001
Urine creatinine (mg/dL), median [IQR]	16.4 [5.2, 50.4]	9.7 [3.8, 22.7]	<0.001
Loop diuretic dose within the first 3 days of hospitalization (mg/day), median [IQR]	67 [40, 113]	53 [27, 80]	0.001

ACE-I, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; BP, blood pressure; bpm, beats per minute; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; Gal-3, galectin 3; hs-cTnI, high sensitivity cardiac troponin I; IQR, interquartile range; PCI, percutaneous coronary intervention; SD, standard deviation; uNGAL, urine neutrophil gelatinase-associated lipocalin.

Results

Of the 790 patients included in the study, the mean age was 69 ± 14 years, 63% were male, 46% had coronary artery disease, and 44% had diabetes mellitus. The mean eGFR on admission was 61 ± 28 mL/min/1.73m^2. The completeness of biomarkers at each time point is shown in Supplementary Table 2. In brief, the completeness at the 1st−5th collection time points were 100%, 83%−89%, 80%–86%, 78%–88% and 76%–84%, respectively (Supplementary Table 2). Patients with admission Gal-3 > 25.9 ng/mL (375 patients, 47%) were older and more likely to be female and less likely to be white (Table 1). Coronary artery disease, coronary artery bypass grafting, diabetes mellitus, and atrial fibrillation were more prevalent, and tobacco use was less prevalent in patients with Gal-3 > 25.9 ng/mL. They were more likely have been treated previously with diuretics and had rales and edema at hospital admission. Systolic blood pressure, heart rate, hemoglobin, and eGFR were lower in patients with higher Gal-3. BNP, hs-cTnI, uNGAL, and urine creatinine were higher in patients with higher Gal-3. These patients received a higher total dosage of loop diuretics during the first 3 hospital days.

During hospitalization, patients with Gal-3 > 25.9 ng/mL on admission less commonly had a decrease in BNP ≥ 30% and more commonly had an increase in hs-cTnI ≥ 20% and peak uNGAL values > 150 ng/dL (Fig. 1A). The incidences of AKI stage 1, 2 and 3 were 23% (181 patients), 2% (15 patients) and 3% (26 patient), respectively, in all patients. Patients with Gal-3 > 25.9 ng/mL more commonly had AKI (Fig. 1B). RRT and inotrope use were more common, and in-hospital mortality was higher in those with Gal-3 > 25.9 ng/mL (Fig. 1C).

When relationships between the AUCs of Gal-3 and other biomarkers were evaluated by multiple linear regression models, Gal-3 was significantly and negatively associated with eGFR and positively associated with uNGAL and hs-cTnI (Fig. 2). There was no significant association between Gal-3 and BNP. VIFs of biomarkers in each model were ≤ 1.27 for eGFR, ≤ 1.64 for uNGAL, ≤ 1.66 for BNP, and ≤ 1.74 for hs-cTnI.

The composite endpoint was observed in 261 patients (33%); 140 patients died (18%), and 154 patients (19%) were readmitted due to HF within 1 year. Patients with admission Gal-3 > 25.9 ng/mL had higher incidences of the composite endpoint and mortality than those with Gal-3 ≤ 25.9 ng/mL, whereas the incidence of HF readmission was not different between the groups (Fig. 3). Higher Gal-3 was associated with an increased risk for the

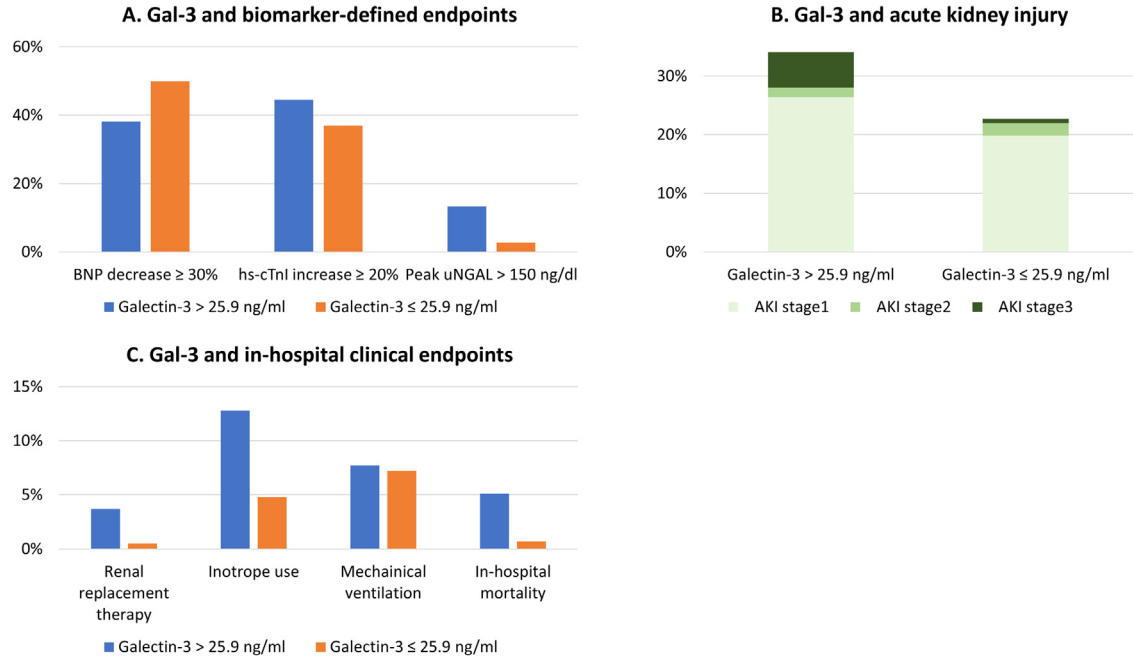

Fig. 1. Levels of galectin-3 and adverse events. A, Galectin-3 and biomarker defined endpoints. Patients with admission values of Gal-3 > 25.9 ng/mL less commonly had BNP ≥ 30% decrease and more commonly had hs-cTnI ≥ 20% increase and peak uNGAL > 150 ng/dL than those with Gal-3 ≤ 25.9 ng/mL ($P < 0.05$ for all). B, Galectin-3 and acute kidney injury. The incidence of AKI was higher in patients with Gal-3 > 25.9 ng/mL than those with Gal-3 ≤ 25.9 ng/mL ($P < 0.05$). C, Galectin-3 and in-hospital clinical endpoints. Renal-replacement therapy, inotrope use and in-hospital death were more frequently observed in patients with Gal-3 > 25.9 ng/mL ($P < 0.05$). AKI, acute kidney injury; BNP, B-type natriuretic peptide; Gal-3, galectin 3; hs-cTnI, high-sensitivity cardiac troponin I; uNGAL, urine neutrophil gelatinase-associated lipocalin.

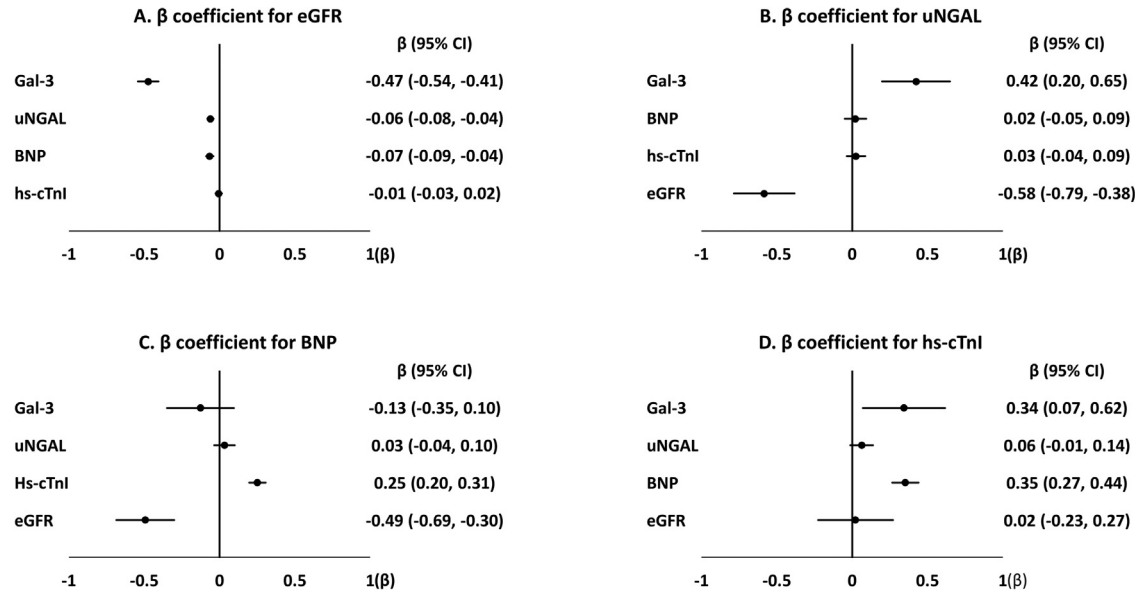

Fig. 2. Relationship between galectin-3 and other biomarkers. Standardized beta-coefficient (β) of biomarkers for eGFR, uNGAL, BNP, and hs-cTnI in multivariable linear regression models are shown. AUCs of the first 3 days of hospitalization were used for biomarkers (eGFR, uNGAL, BNP, hs-cTnI, and urine creatinine). For eGFR, factors included in the model were age, gender, race, heart rate, systolic blood pressure, history of CAD, PCI, CABG, and dyslipidemia, smoking, ACE inhibitors, hemoglobin, edema, rales, furosemide dose during the first 3 days of hospitalization, Gal-3, uNGAL, BNP, and hs-cTnI. For uNGAL, factors included in the model were age, gender, history of PCI, hemoglobin, edema, furosemide dose during the first 3 days, Gal-3, BNP, hs-cTnI, eGFR, and urine creatinine. For BNP, factors included in the model were age, gender, systolic blood pressure, body mass index, history of CAD, CABG, COPD, and diabetes mellitus, beta-blocker, hemoglobin, rales, jugular vein distention, Gal-3, uNGAL, hs-cTnI, eGFR, and urine creatinine. For hs-cTnI, factors included in the model were age, gender, heart rate, body mass index, history of CAD and COPD, diuretics use on admission, rales, hemoglobin, furosemide dose during the first 3 days, Gal-3, uNGAL, BNP, and eGFR. In multivariable linear regression analysis for eGFR, VIFs of Gal3, uNGAL, BNP and hs-cTnI were 1.23, 1.17, 1.24, and 1.27, respectively. For uNGAL, VIFs of Gal3, BNP, hs-cTnI and eGFR were 1.51, 1.26, 1.21, and 1.64, respectively. For BNP, VIFs of Gal3, uNGAL, hs-cTnI, and eGFR were 1.61, 1.56, 1.12, and 1.66, respectively. For hs-cTnI, VIFs of Gal3, uNGAL, BNP, and eGFR were 1.55, 1.20, 1.29, and 1.74, respectively. ACE-I, angiotensin-converting-enzyme inhibitor; BNP, B-type natriuretic peptide; CABG, coronary artery bypass grafting; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; Gal-3, galectin 3; hs-cTnI, high sensitivity cardiac troponin I; PCI, percutaneous coronary intervention; uNGAL, urine neutrophil gelatinase-associated lipocalin; VIF, variance inflation factor.

composite endpoint (hazard ratio [HR] of log2 Gal-3 1.36, 95% CI 1.16–1.60; $P < 0.001$) and mortality (HR 1.87, 95% CI 1.55–2.25; $P < 0.001$) in univariable analysis and for mortality in multivariable analysis (adjusted HR 1.61, 95% CI 1.27– 2.04; $P < 0.001$) Table 2. Gal-3 was not associated with HF rehospitalization (HR 0.97, 95% CI 0.77–1.23; $P = 0.803$).

Discussion

In this analysis of patients with AHF, we investigated a relationship between Gal-3 and cardiorenal biomarkers and adverse events. We found that patients with higher Gal-3 levels more commonly had lower eGFRs and renal tubular injuries, congestion and myocardial damage. Gal-3 values were significantly related to renal glomerular dysfunction, tubular injury and myocardial damage, independent of possible confounding factors. Further, Gal-3 elevation was associated with in-hospital adverse events, including RRT, inotrope use and mortality. Gal-3 elevation also predicated worse 1-year outcomes, especially mortality.

Gal-3 has been reported to be associated with fibrosis of the kidney, and elevated Gal-3 values predicted rapid decline of renal glomerular function and progressive renal impairment.[24] In the current analysis, higher Gal-3 values may reflect progressive glomerular dysfunction; patients with higher Gal-3 values had worse renal function on admission and were more likely to have AKI after hospitalization. Moreover, Gal-3 elevation was also associated with renal tubular damage, defined by an elevation in uNGAL, a known biomarker of acute renal tubular damage. In patients with AHF, a decrease in GFR with treatment after hospitalization is not generally associated with actual renal tubular injury and can be a functional and hemodynamic change in renal function.[25] Therefore, the association of Gal-3 with both renal functional deterioration and tubular injury is of significant importance. Values of Gal-3 and uNGAL

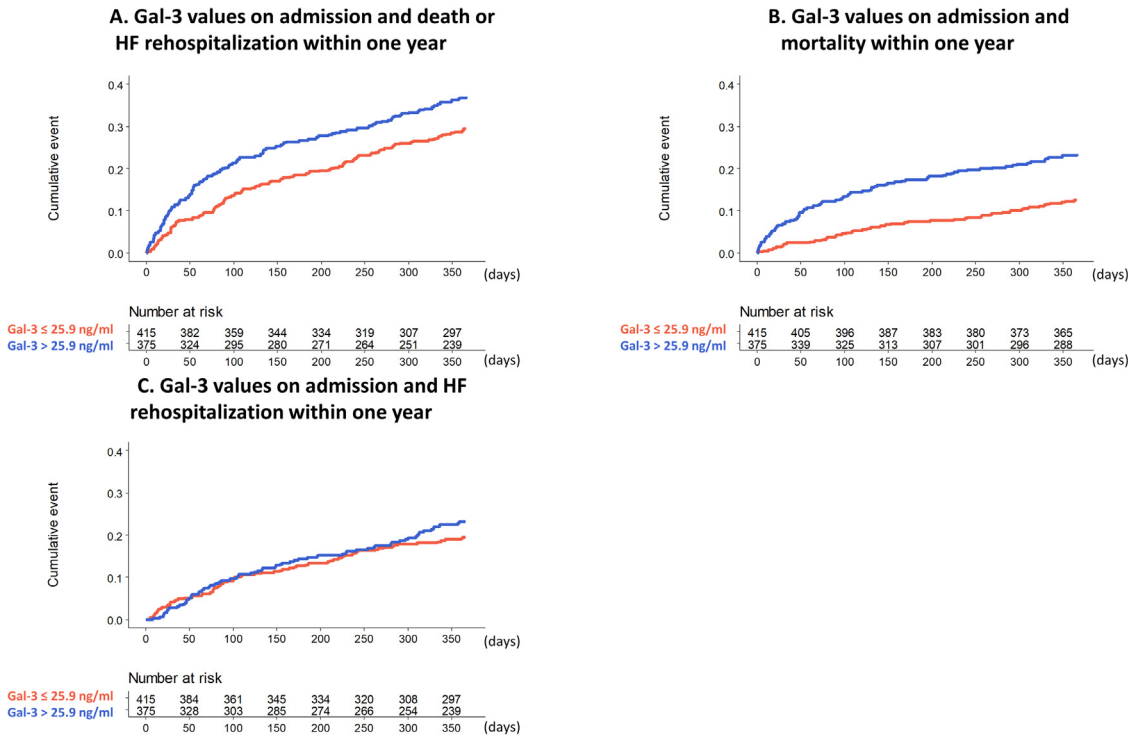

Fig. 3. Galectin-3 and clinical outcomes. Patients with Gal-3 > 25.9 ng/mL on admission had higher incidence of the composite of death or readmission due to heart failure and mortality within 1 year ($P = 0.01$ for the composite endpoint; $P < 0.01$ for mortality; $P = 0.875$ for HF rehospitalization).

Table 2. Hazard Ratios for Clinical Events at 1 Year

		Univariable			Multivariable	
	HR	95% CI	*P* value	Adjusted HR	95% CI	*P* value
Death or HF rehospitalization						
log_2Gal-3	1.36	1.16−1.60	< 0.001	1.09	0.89−1.32	0.397
Death						
log_2Gal-3	1.87	1.55−2.25	< 0.001	1.61	1.27−2.04	< 0.001
HF rehospitalization						
log_2Gal-3	0.97	0.77-1.23	0.803	0.80	0.58−1.10	0.160

Multivariable Cox regression analysis included age, race, history of chronic obstructive pulmonary disease, systolic blood pressure, heart rate, sodium, hemoglobin, BUN, BNP, hscTnI and uNGAL. Values of Gal3, BNP, hs-cTnI and uNGAL were log-2 transformed.

BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CI, confidence interval; Gal-3, galectin 3; hs-cTnI, high sensitivity cardiac troponin I; HR, hazard ratio; uNGAL, urine neutrophil gelatinase-associated lipocalin.

may be affected by changes in GFR because these biomarkers are cleared by the kidney, but these relationships remained significant after adjustment for GFR and other possible confounders.[24,26] In the event of AKI, macrophage infiltration with increased Gal-3 expression is observed in the renal tubular cells, and that is associated with renal inflammation and fibrosis.[7] Gal-3 may play an important role in renal dysfunction and injury, and its assessment may help to predict kidney-related adverse events in patients with AHF.

We also showed that Gal-3 was independently associated with an elevation in hs-cTnI. Hs-cTn elevation is commonly observed in patients with AHF and is associated with worse prognoses.[23] Proposed mechanisms for troponin elevation and myocardial injury in AHF include myocardial stretch from volume overload, subendocardial ischemia with left ventricular hypertrophy, elevated intracardiac pressures, and arrhythmia. Although systemic inflammation and fibrosis are also thought to induce myocardial damage, that has not been fully elucidated in a large-scale clinical cohort.[27] In the current study, Gal-3 was independently associated with hs-cTnI after adjustment for possible confounders. The confounding factors in the multivariable model included older age, heart rate and hemoglobin, suggesting that the association between hs-cTnI and

Gal-3 was independent of known causes of acute myocardial injury.[28] Moreover, this association can also be independent of hemodynamic deterioration due to AHF and CRS because the model included diuretic dosage and eGFR and BNP levels. Furthermore, several studies have shown that AKI may induce remote cardiac damage through the Gal-3 pathway.[7,29–31] In a mouse model with AKI, increased expression of Gal-3 in renal tubular cells led to an increase in circulating Gal-3 levels, promoting Gal-3 expression in the heart and resulting in myocardial fibrosis and dysfunction.[7] Our study cannot show as direct a link as this animal model shows, but our findings are in line with the concept that Gal-3 reflects or even induces adverse outcomes when AKI occurs in AHF.

Additionally, multiple studies have shown that Gal-3 levels are prognostic for cardiovascular outcomes in patients with HF.[15,32,33] In the current analysis, patients with elevated Gal-3 more commonly had in-hospital adverse events, such as receiving RRT and inotrope and death. Also, Gal-3 values predicted 1-year mortality, independent of BNP, hscTnI, uNGAL, and other confounding factors. Our results suggest that Gal-3 may help to identify patients at increased risk for adverse cardiorenal events during initial hospital admission and at high risk for mortality after hospitalization, independent of known predictors of poor prognosis in patients with AHF.

Limitations

This is a post hoc analysis of a prospective cohort study. Although we showed associations between biomarkers of kidney injury, inflammation and fibrosis, and myocardial damage, causal relationships could not be determined in this observational study. Identified or unidentified confounders may have influenced the results of multivariable analyses. We considered factors that could affect the value of biomarkers in multivariable liner regression analysis, but changes in blood pressure and acid/base balance were lacking and, thus, were not included in the model. Unfortunately, data concerning echocardiography was lacking in 41% of the patients, so they were not included in the current analysis. The missing values of biomarkers, especially at the later time point, could have affected the results. Causes of HF and years from diagnosis were not recorded either. Kidney injury was evaluated only by uNGAL, and other biomarkers were not measured. Other common biomarkers of inflammation, such as C-reactive protein and interleukin-6, were not measured either.

Conclusions

In patients with AHF, higher Gal-3 values were associated with renal dysfunction, renal tubular damage and myocardial injury. An increased expression of Gal-3 predicted worse in-hospital and 1-year clinical outcomes. The assessment of Gal-3 on admission may help to identify patients who are at high risk for kidney-related adverse events, myocardial injury during hospitalization and poor prognoses.

Lay Summary

Among patients hospitalized for acute heart failure (AHF), those with galectin-3 elevation on admission more commonly had renal dysfunction, renal tubular damage and myocardial injury during hospitalization. Higher galectin-3 levels were associated with renal-replacement therapy, inotrope use and in-hospital mortality. Galectin-3 elevation was also associated with increased risk for the composite of death or HF rehospitalization and death alone at 1 year. In patients with AHF, the assessment of galectin-3 may help to identify patients who are at high risk for kidney-related adverse events, myocardial injuries and poor prognoses.

Conflicts of Interest

CM has previously received grant funding and other support from Abbott Laboratories and Alere and research support and speaker/consulting honoraria from several diagnostic companies, including Roche, Singulex and Sphingotec. GF has served as a trial committee member for trials sponsored by Bayer, Novartis, Servier, and Medtronic. CMC's institution has received research support from Abbott Laboratories and Alere. RB has received grant funding from Alere. AM has previously received grant funding from Abbott Laboratories and Alere. PTM has received research funding from Abbott Laboratories and Alere. PTM's institution receives funding from Abbott Laboratories. All other authors declare no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2022.09.017.

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