Decongestion, kidney injury and prognosis in patients with acute heart failure

Horiuchi, Yu; Wettersten, Nicholas; van Veldhuisen, Dirk J.; Mueller, Christian; Filippatos, Gerasimos; Nowak, Richard; Hogan, Christopher; Kontos, Michael C.; Cannon, Chad M.; Mueeller, Gerhard A.

Published in:
International Journal of Cardiology

DOI:
10.1016/j.ijcard.2022.02.026

Publication date:
2022

International Journal of Cardiology 354 (2022) 29–37

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Decongestion, kidney injury and prognosis in patients with acute heart failure☆

Yu Horiuchi [a,b], Nicholas Wettersten [a,c], Dirk J. van Veldhuisen [d], Christian Mueller [e], Gerasimos Filippatos [f], Richard Nowak [g], Christopher Hogan [h], Michael C. Kontos [i], Chad M. Cannon [j], Gerhard A. Müeller [k], Robert Birkhahn [l], Pam Taub [a], Gary M. Vilke [m], Olga Barnett [n], Kenneth McDonald [o,p], Niall Mahon [o,q], Julio Nuñez [r,s], Carlo Briguori [t], Claudio Passino [u], Stephen Duff [v], Alan Maisel [a], Patrick T. Murray [v,*]

[a] Division of Cardiovascular Medicine, University of California San Diego, La Jolla, CA, USA
[b] Division of Cardiology, Mitsui Memorial Hospital, Tokyo, Japan
[c] Division of Cardiovascular Medicine, San Diego Veterans Affairs Medical Center, San Diego, CA, USA
[d] Department of Cardiology, University Medical Centre Groningen, University of Groningen, Groningen, the Netherlands
[e] Department of Cardiology, University Hospital Basel, University of Basel, Basel, Switzerland
[f] Department of Cardiology, Athens University Hospital Attikon, University of Athens, Athens, Greece
[g] Department of Emergency Medicine, Henry Ford Hospital System, Detroit, MI, USA
[h] Division of Emergency Medicine and Acute Care Surgical Services, VCU Medical Center, Virginia Commonwealth University, Richmond, VA, USA
[i] Division of Cardiology, VCU Medical Center, Virginia Commonwealth University, Richmond, VA, USA
[j] Department of Emergency Medicine, University of Kansas Medical Center, Kansas City, KS, USA
[k] Department of Nephrology and Rheumatology, University Medical Centre Göttingen, University of Göttingen, Göttingen, Germany
[l] Department of Emergency Medicine, New York Methodist Hospital, New York, NY, USA
[m] Department of Emergency Medicine, University of California San Diego, La Jolla, CA, USA
[n] Division of Cardiology, Danylo Halytsky Lviv National Medical University, Lviv, Ukraine
[o] Department of Cardiology, School of Medicine, University College Dublin, Dublin, Ireland
[p] Department of Cardiology, St Vincent's University Hospital, Dublin, Ireland
[q] Department of Cardiology, Mater Misericordiae University Hospital, Dublin, Ireland
[r] Department of Cardiology, Valencia University Hospital, INCLIVA, Valencia, Spain
[s] Centro de Investigación Biomédica en Red (CIBER) in Cardiovascular Diseases, Madrid, Spain
[t] Department of Cardiology, Mediterranea Cardiocentro, Naples, Italy
[u] Department of Cardiology and Cardiovascular Medicine, Fondazione Gabriele Monasterio, Pisa, Italy
[v] Department of Medicine, School of Medicine, University College Dublin, Dublin, Ireland

ARTICLE INFO

Keywords:
Acute heart failure
Acute renal tubular damage
Congestion
Prognosis

ABSTRACT

Background: In patients with acute heart failure (AHF), the development of worsening renal function with appropriate decongestion is thought to be a benign functional change and not associated with poor prognosis. We investigated whether the benefit of decongestion outweighs the risk of concurrent kidney tubular damage and leads to better outcomes.

Methods: We retrospectively analyzed data from the AKINESIS study, which enrolled AHF patients requiring intravenous diuretic therapy. Urine neutrophil gelatinase-associated lipocalin (uNGAL) and B-type natriuretic peptide (BNP) were serially measured during the hospitalization. Decongestion was defined as ≥30% BNP decrease at discharge compared to admission. Univariable and multivariable Cox models were assessed for one-year mortality.

Results: Among 736 patients, 53% had ≥30% BNP decrease at discharge. Levels of uNGAL and BNP at each collection time point had positive but weak correlations ($r \leq 0.133$). Patients without decongestion and with higher discharge uNGAL values had worse one-year mortality, while those with decongestion had better

☆ These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author at: University College Dublin Clinical Research Centre, UCD Catherine McAuley Education & Research Centre, Nelson Street, Dublin 7, Ireland.
E-mail address: patrick.murray@ucd.ie (P.T. Murray).

https://doi.org/10.1016/j.ijcard.2022.02.026
Received 20 August 2021; Received in revised form 11 February 2022; Accepted 16 February 2022
Available online 21 February 2022

outcomes regardless of uNGAL values (p for interaction 0.018). This interaction was also significant when the change in BNP was analyzed as a continuous variable ($p < 0.001$). Although higher peak and discharge uNGAL were associated with mortality in univariable analysis, only ≥30% BNP decrease was a significant predictor after multivariable adjustment.

Conclusions: Among AHF patients treated with diuretic therapy, decongestion was generally not associated with kidney tubular damage assessed by uNGAL. Kidney tubular damage with adequate decongestion does not impact outcomes; however, kidney injury without adequate decongestion is associated with a worse prognosis.

1. Introduction

Heart failure (HF) is a clinical syndrome of cardiac dysfunction often resulting in systemic organ dysfunction and compounded by concomitant comorbidities. Because of a close interaction between the heart and kidney, chronic kidney disease is one of the most common comorbidities in HF, and an acute deterioration in renal function is often observed in the setting of acutely decompensated HF [1–3]. This is termed worsening renal function (WRF), which is usually defined by an increase in creatinine or a decrease in estimate glomerular filtration rate (eGFR). Originally thought to be an adverse event, it is now well-described that the clinical significance of WRF depends on the context in which it occurs, with no known adverse consequences seen when WRF occurs with appropriate decongestion [4–8]. These findings suggest the benefit of decongestion may outweigh any potential harms of WRF.

However, creatinine is a marker of the glomerular filtration function, and several studies have reported a dissociation between WRF and elevations in biomarkers that evaluate kidney damage at the level of the tubule [9–12]. Therefore, the presence of kidney tubular injury could be overlooked when assessed only by creatinine or eGFR, and the direct relationships between decongestion and kidney tubular damage and their prognostic implications for clinical outcomes have not been well assessed. It remains uncertain whether the development of kidney tubular damage offsets the benefits of decongestion. Conversely, tubular damage with refractory congestion may identify a higher risk cohort suffering from a more severe form of cardio-renal syndrome.

The Acute Kidney Injury Neutrophil gelatinase-associated lipocalin (NGAL) Evaluation of Symptomatic heart faIlure Study (AKINESIS) was a prospective observational study of acute HF (AHF) patients who required intravenous diuretic therapy [13]. We have recently demonstrated the clinical implications of WRF can be risk stratified by changes in B-type natriuretic peptide (BNP), which is a well-established biomarker of congestion [8,14]. BNP has been shown to decrease rapidly, corresponding to decongestive therapy and decreasing cardiac pressures, and its decrease is a strong predictor of better outcomes in AHF [8,15–17]. In this sub-analysis, we evaluated whether the prognostic implications of congestion status, as assessed by change in BNP, interact with an elevation in urine NGAL (uNGAL), a kidney tubular damage biomarker. NGAL is from the lipocalin family of proteins and is released from kidney tubular cells following injuries under stress conditions such as contrast-induced nephropathy, cardiac surgery, and critical illness [18–20]. We investigated 1) the relationship between decongestion and kidney tubular damage during the treatment for AHF, 2) the prognostic value of uNGAL for in-hospital and one-year mortality and one-year HF readmission, and 3) whether prognostication with uNGAL can be further discriminated by BNP decrease.

2. Methods

2.1. Study population

We retrospectively analyzed the AKINESIS study, which was a prospective, international, multicenter cohort study of AHF patients, enrolling 927 patients at 16 sites in the United States and Europe from January 2011 through September 2013 [13]. The study was approved by institutional review boards at each site and all patients gave written consent. Patients were enrolled if they had findings consistent with HF and had received or planned intravenous diuretic therapy. Exclusion criteria were (1) acute coronary syndrome, (2) dialysis-dependence or planned initiation during the hospitalization, (3) major organ transplantation, (4) enrolment in a drug treatment study within the past 30 days or prior enrolment in this study, and (5) pregnant or vulnerable population determined by an institutional review board. In the current analysis, we excluded 70 patients discharged from the emergency department, 43 patients without serial BNP measurements, and 78 patients without uNGAL measurement during hospitalization, leaving 736 patients for analysis.

2.2. Biomarker assessment

Specimens for uNGAL and BNP measurement were collected at six-time points of hospitalization; on admission; 4 h later; hospital days 1, 2, and 3 and day of discharge or anticipated discharge. Serum creatinine was measured each day during hospitalization. Details of sample analysis have been previously published [8,21]. Levels of uNGAL were indexed to urine creatinine to account for urine dilution. Decongestion was defined as a ≥ 30% BNP decrease at the last available value (either at discharge or the last measured) compared to the admission value based on prior literatures and our previous report showing discrimination for prognosis in WRF at this cut-off [8,17,22,23]. As a sensitivity analysis, change in BNP was also analyzed as a continuous variable as the ratio of discharge to admission values.

2.3. Outcomes

The clinical outcomes were in-hospital and one-year mortality and one-year HF readmission. The one-year outcomes were determined by phone follow-up or medical record review. Follow up was available in >98% of participants.

2.4. Statistical analysis

Continuous variables were described as means with standard deviations (SD), and categorical variables were described as counts and percentages. Non-normally distributed data were described as medians and interquartile ranges (IQR). Patient characteristics were compared by tertiles of discharge uNGAL values with ANOVA, Kruskal-Wallis and Chi-square tests as appropriate. Patient characteristics by ≥30% or < 30% BNP decrease were also assessed by *t*-test, Mann–Whitney and Chi-square tests as appropriate. Levels of uNGAL and eGFR, and the incidence of WRF were also compared in patients with ≥30% and < 30% BNP decrease. WRF was defined by the criteria initially used in AKINESIS; sustained increase (more than two consecutive days) in creatinine of 0.5 mg/dl or ≥ 50% above first value or initiation of acute renal-replacement therapy, within the first 5 days of hospitalization. Correlations between uNGAL and BNP were evaluated by Spearman's rank correlation coefficient. For the assessment of the clinical events, levels of uNGAL were examined by admission and peak values for in-hospital mortality, and admission, peak and discharge values for one-year mortality and HF readmission. When a patient lacked a measurement at discharge, the last measured value was substituted. Because of the relatively small number of in-hospital deaths (24 patients, 3%), only

bivariable logistic regression analysis with uNGAL and BNP decrease was performed. Kaplan-Meier, log-rank and Cox regression analysis were used for one-year mortality and HF readmission. uNGAL was examined both as tertiles and as a continuous variable using restricted cubic splines with 3 knots for an interaction with BNP change during hospitalization. An interaction analysis was also performed with eGFR values instead of uNGAL. The change (delta) between the lowest values during hospitalization and admission values, and delta between discharge and admission values were evaluated. In multivariable Cox regression analysis, decreased BNP and uNGAL were adjusted for age, Black race, history of chronic obstructive pulmonary disease, oedema, systolic blood pressure, heart rate, sodium, hemoglobin, blood urea nitrogen (BUN) and high sensitivity cardiac troponin I based on prior studies [24–27]. Multicollinearity was assessed by variance inflation factor (VIF). We also evaluated net reclassification improvement (NRI) and integrated discrimination improvement (IDI) when uNGAL values were added to the model composed of other factors in the multivariable analysis.Levels of uNGAL, cardiac troponin and relative change in BNP were log-2 transformed. All statistical analyses were performed using R version 4.0.3.

3. Results

3.1. Patient characteristics by discharge uNGAL values

Among 736 patients, the mean age was 69 ± 14 years, 64% were male, 47% had coronary artery disease, 44% had diabetes, and 26% reported a history of chronic kidney disease (CKD). The median creatinine was 1.20 mg/dl (IQR 0.94–1.60 mg/dl), median eGFR was 57 ml/min/1.73m^2 (IQR 40–78 ml/min/1.73m^2), and median BNP was 569 ng/L (IQR 233–1108 ng/L) on admission. Median length of hospital stay was 6 days (IQR 4–10 days). Admission values of uNGAL were missing in 9 patients. The discharge sample was collected at the day of discharge in 56%, within 3 days before discharge in 24% and more the three days in 20% of patients. Median admission, peak and discharge levels of uNGAL were 27.2 μg/g (IQR 13.1–68.0 μg/g), 48.5 μg/g (IQR 22.5–128.1 μg/g) and 29.0 μg/g (IQR 13.3–76.1 μg/g), respectively. Patients with higher levels of discharge uNGAL were older, more likely to be Caucasian and female, more frequently had a history of CKD, and had higher admission BUN and creatinine (Table 1). They were less often treated with angiotensin converting enzyme inhibitors or angiotensin receptor blockers and had lower levels of admission hemoglobin and eGFR. Patients with higher discharge uNGAL more often received renal replacement therapy during hospitalization, while use of inotropes and mechanical ventilation were not associated with discharge uNGAL levels.

3.2. Patient characteristics by BNP decrease

At discharge, 388 patients (53%) had achieved a ≥ 30% decline in BNP compared to admission. Patients with ≥30% BNP decrease were younger, less likely to be Caucasian and less often have a history of CKD (Supplemental Table 1). They had higher SBP, sodium and eGFR, and lower BUN and creatinine on admission.There was a greater weight loss in patients with a ≥ 30% BNP decrease compared to those with a < 30% BNP decrease (−1.4 kg [IQR −3.7 to 0 kg] versus −0.9 kg [IQR −2.5 to 0.8 kg], p = 0.025) with greater average daily urine output (2064 ± 1121 ml/day versus 1840 ± 989 ml/day, p = 0.031) within the first 3 days of hospitalization. The average dose of loop diuretics within the first 3 days of admission was not different between those with or without ≥30% BNP decrease (intravenous furosemide equivalent 58 mg/day [IQR 40–105 mg/day] versus 60 mg/day [IQR 38–93 mg/day], p = 0.569). Among 417 patients (57%) with data of hematocrit at admission and discharge, an elevation of discharge levels compared to admission was observed in 36% in a ≥ 30% BNP decrease and 32% in a < 30% BNP decrease (p = 0.380).

Table 1
Baseline characteristics of patients by tertile of uNGAL at hospital discharge.

	Tertile 1 ≤17.6 μg/g n = 245	Tertile 2 17.7 μg/g to 50.8 μg/g n = 246	Tertile 3 ≥50.9 μg/g n = 245	p-value
Age (years), mean (SD)	64 (13)	71 (13)	71 (14)	<0.001
Caucasian, n (%)	145 (59)	164 (67)	167 (68)	0.084
Male sex, n (%)	205 (84)	155 (63)	112 (46)	<0.001
History of CAD, n (%)	112 (46)	128 (52)	104 (42)	0.096
History of hypertension, n (%)	191 (78)	203 (83)	198 (81)	0.437
History of hyperlipidemia, n (%)	126 (51)	125 (51)	124 (51)	0.982
History of diabetes mellitus, n (%)	96 (39)	115 (47)	114 (47)	0.158
History of COPD, n (%)	59 (24)	76 (31)	54 (22)	0.063
History of CKD, n (%)	48 (20)	59 (24)	83 (34)	0.001
Tobacco use, n (%)	46 (19)	39 (16)	27 (11)	0.054
ACE-I or ARB, n (%)	83 (34)	91 (37)	62 (25)	0.016
β-blocker, n (%)	181 (74)	173 (70)	174 (71)	0.651
Diuretics, n (%)	171 (70)	180 (73)	169 (69)	0.557
Oedema, n (%)	179 (73)	183 (74)	191 (78)	0.431
JVD present, n (%)	59 (24)	71 (29)	67 (27)	0.474
Rales present, n (%)	97 (40)	107 (44)	116 (47)	0.223
Systolic BP (mmHg), mean (SD)	140 (31)	141 (28)	140 (31)	0.797
Heart rate (bpm), mean (SD)	89 (23)	88 (23)	85 (21)	0.121
Sodium (mEq/l), mean (SD)	138 (10)	139 (5)	138 (5)	0.461
Hemoglobin (g/dl), mean (SD)	12.5 (2.5)	11.6 (2.5)	11.0 (2.1)	<0.001
BUN (mg/dl), median [IQR]	21.0 [15.0, 28.8]	24.0 [17.0, 36.0]	30.7 [20.7, 46.0]	<0.001
Creatinine (mg/dl), median [IQR]	1.13 [0.94, 1.41]	1.17 [0.90, 1.50]	1.38 [1.00, 2.04]	<0.001
eGFR (ml/min/1.73 m2), mean (SD)	69 (29)	62 (27)	50 (25)	<0.001
BNP (ng/L), median [IQR]	498 [211, 1004]	628 [265, 1138]	629 [231, 1188]	0.07
hscTnI (ng/l) (median [IQR])	25.3 [12.5, 54.8]	27.8 [13.9, 64.4]	24.3 [12.2, 57.2]	0.502
uNGAL (ug/g) (median [IQR])	11.5 [7.0, 19.6]	27.4 [16.9, 45.3]	83.8 [41.5, 258.0]	<0.001
Renal replacement therapy, n (%)	2 (1)	2 (1)	11 (5)	0.004
Inotrope use, n (%)	19 (8)	23 (9)	25 (10)	0.633
Mechanical ventilation, n (%)	24 (10)	16 (7)	19 (8)	0.399

ACE-I, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; BNP, B-type natriuretic peptide; BP, blood pressure; BUN, blood urea nitrogen; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; hscTnI, high sensitivity cardiac troponin I; IQR, interquartile range; JVD, jugular venous distention; SD, standard deviation; uNGAL, urine neutrophil gelatinase-associated lipocalin.

3.3. Association of BNP, uNGAL and eGFR

During the hospitalization, levels of uNGAL and BNP at each collection time point had positive but weak correlations ($r \leq 0.133$, Supplemental Table 2), but this correlation was no longer significant by time of discharge. When the correlation of uNGAL with BNP was examined by individuals who achieved and did not achieve a ≥ 30% BNP decrease, there was a significant correlation between uNGAL and BNP levels in those with a < 30% BNP decrease but there was no correlation between uNGAL and BNP levels in those with a ≥ 30% BNP decrease (Supplemental Table 2). Levels of admission, peak and discharge uNGAL were not different between patients with a ≥ 30% BNP decrease and a < 30% BNP decrease (admission values, 28.0 μg/g [IQR 13.6–67.0 μg/g] in ≥30% BNP decrease versus 25.7 μg/g [IQR 12.8–70.0 μg/g] in <30% BNP decrease, p = 0.527; peak values 48.8 μg/

g [IQR 22.6–122.2 μg/g] versus 47.8 μg/g [IQR 21.9–129.5 μg/g], p = 0.799; and discharge values 38.3 μg/g [IQR 14.9–99.3 μg/g] versus 38.6 μg/g [IQR 14.0–108.7 μg/g], p = 0.882). eGFR was higher in patients with ≥30% BNP decrease compared to those with <30% BNP decrease at all time points (admission, 64 ± 29 ml/min/1.73 m2 versus 58 ± 27 ml/min/1.73 m2, p = 0.002; the lowest eGFR during hospitalization 53 ± 25 ml/min/1.73 m2 versus 49 ± 25 ml/min/1.73 m2, p = 0.03; hospital discharge, 61 ± 31 ml/min/1.73 m2 versus 56 ± 27 ml/min/1.73 m2, p = 0.039, for ≥30% BNP decrease versus <30% BNP decrease, respectively). WRF occurred in 62 patients and its incidence was not different between the groups (9% in ≥30% BNP decrease versus 8% in <30% BNP decrease, p = 0.629).

3.4. In-hospital mortality

In-hospital mortality was 3% (24 patients). Regardless of the uNGAL tertile, patients with a ≥ 30% BNP decrease had lower in-hospital mortality than patients with a < 30% BNP decrease. For patients with a < 30% BNP decrease, a stepwise increase in mortality was seen with higher tertiles of uNGAL with the highest in-hospital mortality observed in patients with BNP < 30% and the highest uNGAL (Fig. 1A and B). In logistic regression analysis, higher levels of peak uNGAL were significantly associated with in-hospital mortality in univariable and bivariable models with BNP decrease (Table 2A).

3.5. One-year outcomes

During the one-year follow-up, 130 patients (18%) died and 146 (19%) patients were re-hospitalized due to HF. Overall, irrespective of when uNGAL was measured (admission, peak or discharge), patients with a < 30% BNP decrease had a higher one-year mortality than those with a ≥ 30% BNP decrease for each tertile of uNGAL (Fig. 2A, B and C). With respect to specific time points of uNGAL measurements, higher tertiles of admission and peak uNGAL were associated with higher mortality in patients with both a ≥ 30% and < 30% BNP decrease (p for interaction = 0.758 and 0.389, Fig. 2A and B). However, higher tertiles of discharge uNGAL predicted poor prognosis only in patients with <30% BNP decrease but not in ≥30% decrease (p for interaction = 0.025, Fig. 2C). This finding was also observed when discharge uNGAL was analyzed using restricted cubic spline analysis (Fig. 2D, p for interaction = 0.018). This interaction was not affected whether change in BNP was analyzed as a continuous variable (p < 0.001). These findings were not observed with admission and peak uNGAL (p for interaction ≥0.273). In univariable Cox analysis, peak and discharge uNGAL were associated with one-year mortality (Table 2B). However, in multivariable analysis, uNGAL was no longer significantly associated with one-year mortality; in contrast a ≥ 30% BNP decrease remained

Table 2A
Logistic regression analysis for in-hospital mortality.

Univariable analysis	OR	95% CI	p-value
Admission uNGAL	1.19	0.99–1.43	0.078
Peak uNGAL	1.27	1.06–1.53	0.013
BNP decrease	0.08	0.02–0.33	< 0.001

Bivariable analysis	Adjusted OR	95% CI	p-value
Admission uNGAL	1.2	0.99–1.46	0.065
BNP decrease	0.07	0.02–0.32	< 0.001
Peak uNGAL	1.31	1.07–1.6	0.009
BNP decrease	0.07	0.02–0.32	< 0.001

significantly associated with lower one-year mortality. No significant multicollinearity was observed in the multivariable models (VIF ≤ 1.17 for model with admission uNGAL, ≤ 1.18 for peak uNGAL, ≤ 1.20 for discharge uNGAL, Supplemental Table 3). Neither admission, peak nor discharge uNGAL improved risk reclassification assessed by NRI and IDI (Supplemental Table 4). When an interaction of eGFR changes and BNP decrease for one-year mortality was assessed in the Cox models, no significant interaction was observed (p for interaction ≥0.641 with ≥30% BNP decrease and ≥ 0.640 with ratio of BNP change). Regarding one-year HF readmission, neither BNP decrease nor uNGAL values was associated with its incidence in the Kapan Meier analysis (Supplemental Fig. 1). No significant interaction was observed with BNP decrease and uNGAL values for HF readmission in Cox analysis (p for interaction ≥0.624 with ≥30% BNP decrease and ≥ 0.222 with ratio of BNP change). When these analysis were performed with eGFR instead of uNGAL values, no significant interaction was observed for one-year HF readmission (p for interaction ≥0.498 with ≥30% BNP decrease and ≥ 0.232 with ratio of BNP change). In univariable and multivariable Cox analysis, uNGAL and BNP decrease were not associated with HF readmission (Table 2C). No significant multicollinearity was observed in the multivariable models (VIF ≤ 1.30 for model with admission uNGAL, ≤ 1.31 for peak uNGAL and ≤ 1.32 for discharge uNGAL, Supplemental Table 3). Admission, peak or discharge uNGAL did not improve reclassification of risk for HF readmission assessed by NRI and IDI (Supplemental Table 4).

4. Discussion

In hospitalized AHF patients treated with intravenous diuretic therapy, we found decongestion defined as a ≥ 30% BNP decrease was not associated with an elevation in uNGAL. A decrease in BNP, but not uNGAL, was an independent predictor of one-year mortality. Intriguingly, higher levels of discharge uNGAL predicted poor prognosis only in

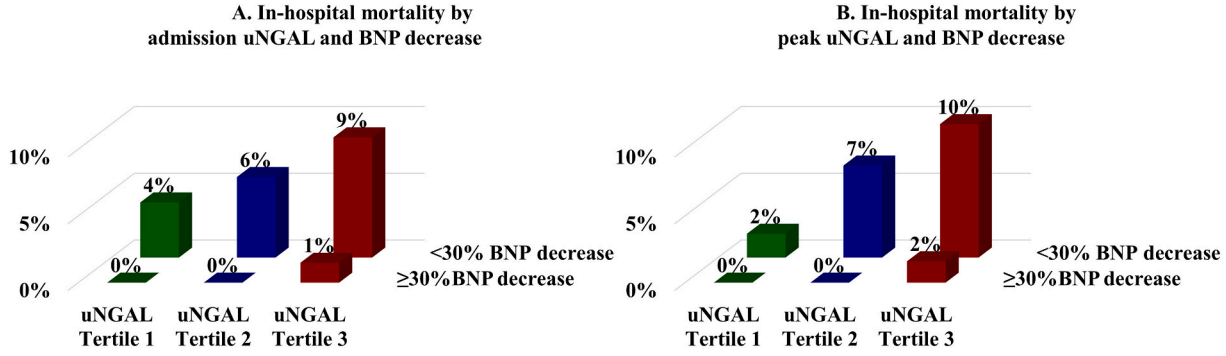


Fig. 1. In-hospital mortality by uNGAL and BNP decrease.
Patients with a ≥ 30% BNP decrease had lower in-hospital mortality in every strata of admission (Fig. 1A) and peak (1B) levels of uNGAL. Tertiles of uNGAL were ≤ 16.5 μg/g, 16.6 μg/g to 48.0 μg/g, and ≥ 48.1 μg/g for admission and ≤ 29.5 μg/g, 29.6 μg/g to 85.0 μg/g, and ≥ 85.1 μg/g for peak values.
BNP, B-type natriuretic peptide; uNGAL, urine neutrophil gelatinase-associated lipocalin.

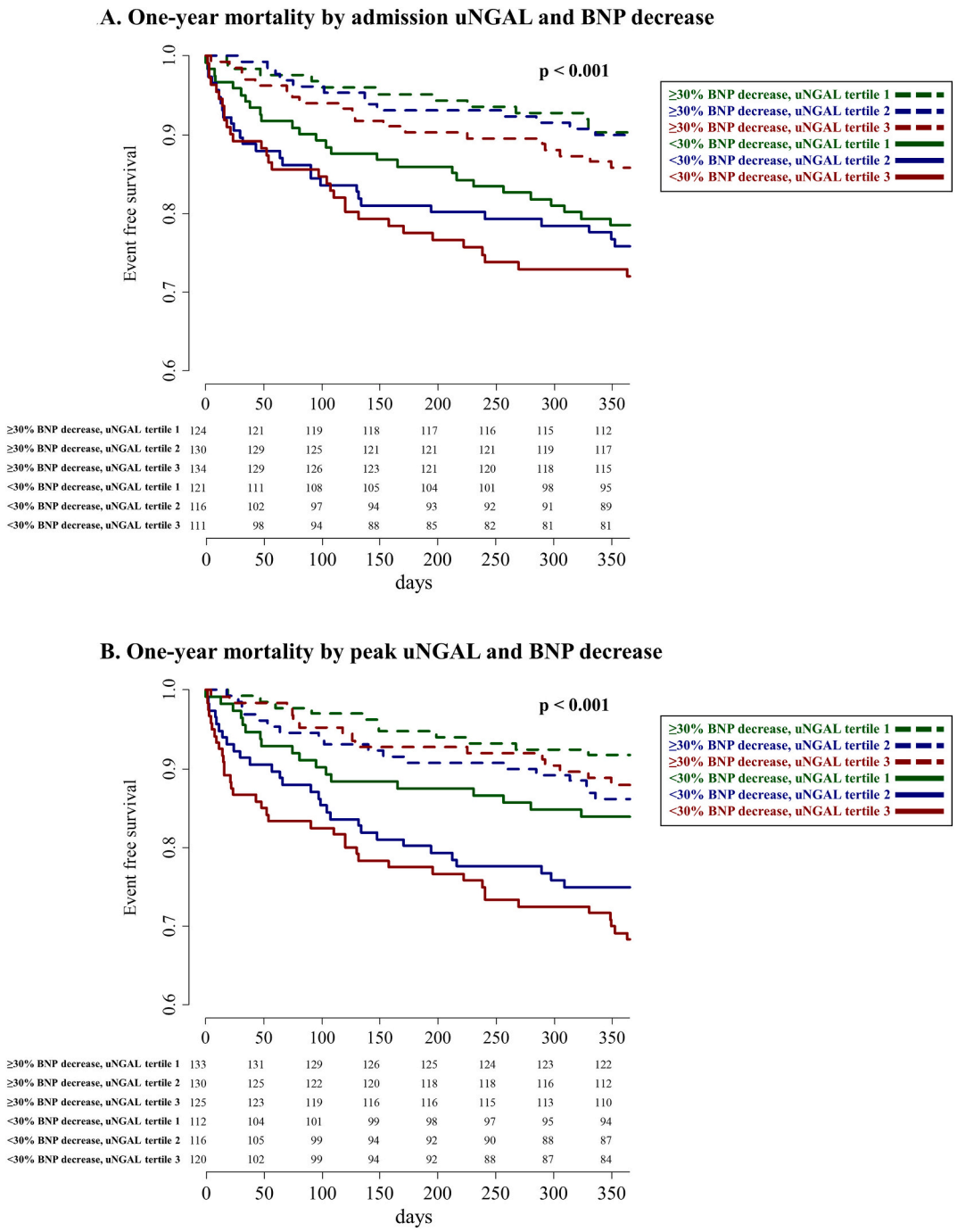


Fig. 2. One-year mortality by uNGAL and BNP decrease. A. One-year mortality by admission uNGAL and BNP decrease. B. One-year mortality by peak uNGAL and BNP decrease. C. One-year mortality by discharge uNGAL and BNP decrease. D. Hazard ratios of uNGAL for one-year mortality in patients with and without BNP decrease.

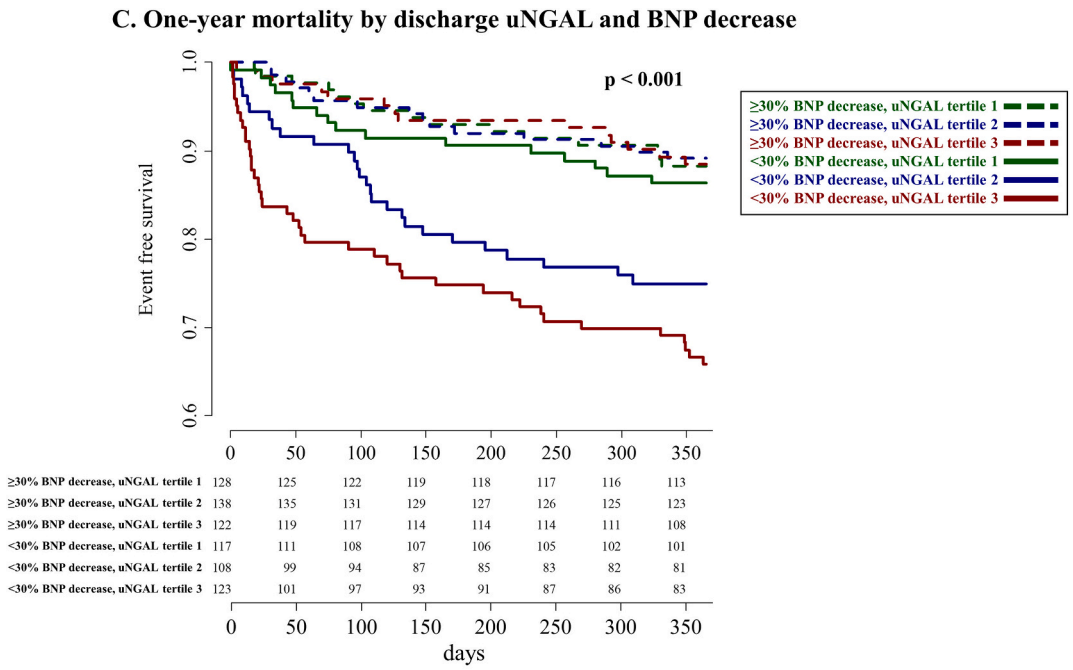
Higher tertiles of admission and peak uNGAL were associated with higher mortality in patients with both ≥30% and < 30% BNP decrease at discharge or the last value (p for interaction = 0.758 and 0.389, Fig. 2A and B). For discharge uNGAL, a ≥ 30% BNP decrease was associated with lower one-year mortality regardless of uNGAL levels, while higher levels of discharge uNGAL predicated poor prognosis in patients with <30% BNP decrease (p for interaction = 0.025, Fig. 2C). This finding was also observed when discharge uNGAL was analyzed using restricted cubic spline analysis (Fig. 2D, p for interaction = 0.018).

Tertiles of uNGAL were ≤ 16.5 μg/g, 16.6 μg/g to 48.0 μg/g, and ≥ 48.1 μg/g for admission, ≤29.5 μg/g, 29.6 μg/g to 85.0 μg/g, and ≥ 85.1 μg/g for peak, and ≤ 17.6 μg/g, 17.7 μg/g to 51.1 μg/g, and ≥ 51.2 μg/g for discharge.

BNP, B-type natriuretic peptide; HR, hazard ratio; uNGAL, urine neutrophil gelatinase-associated lipocalin.

patients with a < 30% BNP decrease and patients with a ≥ 30% BNP decrease had lower one-year mortality regardless of the levels of uNGAL. This finding remained significant when the change in BNP was considered as a continuous variable. These findings reinforce the importance of achieving adequate decongestion in AHF regardless of kidney tubular damage, but also caution about the presence of kidney tubular damage with residual congestion at hospital discharge.

Numerous different pathophysiologic processes may contribute to



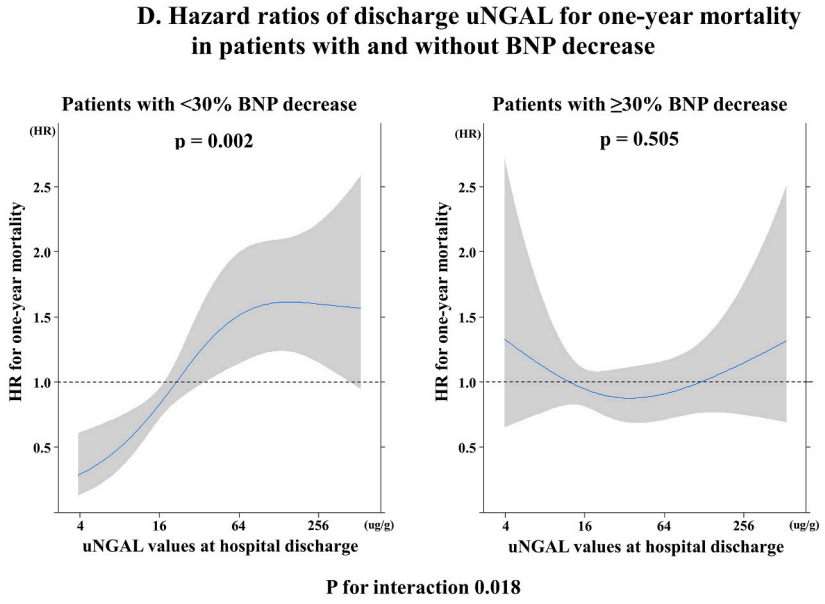


Fig. 2. (*continued*).

kidney injury and dysfunction in AHF [1]. One of the most important hemodynamic contributors is systemic congestion with elevated venous pressure leading to renal congestion. Diuretics and vasodilators may also contribute to drastic changes in volume status during AHF treatment, leading to neurohormonal activation with impaired sodium and water handling in the kidney. The effects of these deleterious processes are primarily recognized by changes in creatinine, a measure of glomerular filtration, and creatinine's change is thought to be induced by kidney tubular damage [2]. However, kidney dysfunction and injury can be assessed both at the level of the glomerulus with changes in filtration, i.e. changes in creatinine, and at the level of the tubule with novel biomarkers of injury [28]. While creatinine frequently rises in AHF, multiple studies have offered evidence suggesting WRF during decongestion therapy in AHF generally lacks kidney injury [9,11,13,21]. Among AHF patients treated with aggressive diuretic therapy in the ROSE-AHF trial, changes in serum creatinine and cystatin C were not correlated with changes in tubular injury biomarkers, such as uNGAL, *N*-acetyl-β-d-glycosaminidase, or kidney injury molecule-1 [9]. Our findings from AKINESIS showed serum and uNGAL were not predictive of subsequent WRF in hospitalized AHF patients [11,13,21]. While these studies in general show a lack of kidney tubular damage with WRF in AHF, whether decongestive therapy and kidney tubular damage are related and whether decongestion or kidney tubular damage have prognostic implications independent of changes in creatinine has not been fully evaluated.

In the current analysis, we explored the relationship between kidney tubular damage and decongestion assessed by a decrease in BNP. A decrease in BNP was not accompanied by an increase in kidney tubular damage, whereas higher levels of uNGAL were associated with higher BNP levels at each collection time point except discharge. These positive correlations could be due to kidney tubular damage from persistent kidney congestion or underlying acute or chronic kidney damage

Table 2B
Cox regression analysis for one-year mortality.

Univariable analysis	HR	95% CI	p-value
Admission uNGAL	1.06	0.98–1.16	0.148
Peak uNGAL	1.10	1.01–1.20	0.021
Discharge uNGAL	1.14	1.05–1.23	0.002
BNP decrease	0.42	0.29–0.60	< 0.001

Multivariable analysis	Adjusted HR	95% CI	p-value
Admission uNGAL	1.02	0.93–1.12	0.632
BNP decrease	0.55	0.37–0.82	0.003
Peak uNGAL	1.05	0.96–1.15	0.305
BNP decrease	0.56	0.38–0.82	0.003
Discharge uNGAL	1.07	0.97–1.18	0.164
BNP decrease	0.55	0.37–0.80	0.002

Table 2C
Cox regression analysis for one-year HF rehospitalization.

Univariable analysis	HR	95% CI	p-value
Admission uNGAL	1.00	0.92–1.09	0.977
Peak uNGAL	0.98	0.90–1.06	0.592
Discharge uNGAL	0.98	0.90–1.07	0.633
BNP decrease	1.00	0.72–1.38	0.976

Multivariable analysis	Adjusted HR	95% CI	p-value
Admission uNGAL	1.00	0.91–1.08	0.837
BNP decrease	1.10	0.77–1.55	0.607
Peak uNGAL	0.96	0.88–1.05	0.399
BNP decrease	1.12	0.79–1.58	0.530
Discharge uNGAL	0.96	0.88–1.06	0.422
BNP decrease	1.12	0.79–1.59	0.529

Levels of uNGAL were log-2 transformed. In multivariable Cox regression analysis, BNP decrease and uNGAL were adjusted for age, African American Race, history of chronic obstructive pulmonary disease, oedema, systolic blood pressure, heart rate, sodium, hemoglobin, blood urea nitrogen and high sensitivity cardiac troponin I.
BNP, B-type natriuretic peptide; uNGAL, urine neutrophil gelatinase-associated lipocalin.

limiting diuretic responsiveness and thus the ability to effectively decongest a patient [29]. Any combination of these phenomena might explain the positive correlations between uNGAL and BNP found in patients with a $< 30\%$ BNP decrease but not those with a $\geq 30\%$ BNP decrease. These findings suggest that kidney tubular injury without effective decongestion identifies a high-risk population of patients with cardio-renal syndrome that cannot be ignored.

Prior studies have reported variable prognostic implications of kidney tubular damage biomarkers in AHF. Several studies have reported an elevated uNGAL at presentation predicts mortality, HF hospitalization and other cardiovascular events [30,31]. However, in AKINESIS, which is one of the largest cohorts of AHF patients specifically designed to assess the clinical implication of NGAL, we reported that neither admission nor peak uNGAL predicted a composite outcome of death, renal replacement therapy, HF readmission or an urgent HF related outpatient visit within 30 and 60 days from study enrolment [32]. Similarly, in our current analysis, admission, peak and discharge levels of uNGAL were not associated with one-year mortality after confounding factors were considered. Although higher peak uNGAL values were associated with in-hospital mortality, this needs to be interpreted cautiously, considering the limited number of in-hospital deaths, allowing only bivariable analysis with BNP change to be performed. Intriguingly, two recent studies have reported that elevated kidney injury biomarkers are actually associated with a better prognosis. The ROSE-AHF trial reported an increase in all three kidney injury biomarkers after diuretic treatment was paradoxically associated with improved 180-day survival [9]. In addition, patients with both elevated kidney injury biomarkers and serum cystatin C had the lowest mortality. Similar results were reported in an analysis of CARRESS-HF trial that randomized AHF patients with pre-existing WRF to intensive volume removal with pharmacological therapy or ultrafiltration [10]. Although intensive volume removal induced further WRF and increases in renal tubular injury biomarkers, these changes were also associated with a higher incidence of hemoconcentration and a better recovery of creatinine at 60 days. These findings suggest the benefits of decongestion outweigh the risks not only of WRF, but also kidney tubular damage in patients hospitalized with AHF.

Building on these studies, we showed even in patients who had more severe kidney injury assessed by uNGAL at hospital discharge, their prognosis was better when accompanied by adequate decongestion assessed by a decrease in BNP. Inversely, higher levels of discharge uNGAL were associated with higher one-year morality only in patients without an adequate BNP decrease. These findings reinforce the importance of achieving decongestion during hospitalization and suggest kidney tubular damage may be tolerable in these circumstances. However, in the setting of inadequate decongestion, persistent kidney tubular damage portends a worse prognosis. In this case, the inability to adequately decongest may be a result of significant kidney tubular damage leading to diuretic resistance. These results are in agreement with our prior findings that WRF was not associated with poor prognosis in AHF when patients achieve an appropriate decrease in BNP but when there is an inadequate BNP decrease, WRF predicts a higher mortality [8]. Therefore, clinicians may primarily focus on diuretic therapy to accomplish decongestion even in the setting of concurrent kidney tubular damage and WRF, but special attention should be given to patients with residual congestion and kidney damage and/or dysfunction who have significantly worse outcomes. Further research is needed to determine best treatments to optimize congestion status and reduce mortality in these higher risk patients.

In the current analysis, neither BNP decrease nor uNGAL values predicted HF readmission within one-year follow up. HF readmission is frequently difficult to predict because it is influenced not only by status at discharge, but also by disease severity, post-discharge dietary choices, fluid intake, adherence to oral medications, and social factors [33,34]. In addition, the recurrence of congestion after discharge is a more important predictor of renal dysfunction and HF hospitalization than the degree of congestion at discharge. These complexities in HF hospitalization may explain why BNP decrease and uNGAL were not associated with HF readmission in this study.

4.1. Limitations

This is a post-hoc analysis of a prospective cohort study. Identified or unidentified confounders may have influenced the result. Multivariable analysis was not performed for in-hospital mortality because of the limited number of events. Last measured value of uNGAL was collected at more than 3 days before hospital discharge in 20%, which may not reflect treatment in this subset of patients after the final collection of the specimen. While decongestion was evaluated by BNP decrease, other methods such as physical examination, echocardiographic findings or direct hemodynamic assessment with heart catheterization may also be considered. Unfortunately, this data was not available in the AKINESIS. However, greater weight loss and urine output in the BNP decrease group suggest greater volume depletion in these patients. While the incidence of hemoconcentration was numerically higher in those with BNP decrease, this was not statistically significant possibly due to the limited number of hemoglobin measurements at hospital discharge. Kidney injury was only evaluated by uNGAL and other biomarkers were not measured. While uNGAL may be useful for risk stratification

especially in patients without adequate decongestion, its routine use in AHF is not currently recommended.

5. Conclusions

Among AHF patients treated with diuretic therapy, decongestion was not associated with kidney tubular damage as assessed by uNGAL. The presence of kidney tubular damage at hospital discharge was not associated with increased mortality at one year when accompanied by adequate decongestion. However, with residual congestion, AHF patients with the kidney tubular damage have a worse one-year survival. These findings emphasize the importance of achieving decongestion in AHF even if this approach is associated with kidney tubular damage, but also recognizing that AHF patients with residual congestion and kidney tubular damage are a high-risk population with higher one year mortality.

Declaration of Competing Interest

The Acute Kidney Injury NGAL Evaluation of Symptomatic heart faIlure Study (AKINESIS) was funded by Abbott Laboratories (Chicago, Illinois) and Alere, Inc. (San Diego, California). The sponsors assisted in the design of the study, data management, and study oversight. The sponsors did not participate in the analysis presented in this manuscript or preparation, review or approval of the manuscript.

Y.H., N.W., D.J.vV., R.N., C.H., M.C.K., G.A.M., P.T., G.M.V., O.B., K. M., N.M., J.N., C.B. and C.P. declare no conflicts of interest. C.M. has previously received grant funding and other support from Abbott Laboratories and Alere, Inc., and research support and speaker/consulting honoraria from several diagnostic companies by Roche, Singulex, and Sphingotec. G.F. has served as a trial committee member for trials sponsored by Bayer, Novartis, Servier and Medtronic. C.M.C.'s institution has received research support from Abbott Laboratories and Alere, Inc. R.B. has received grant funding from Alere, Inc. A.M. has previously received grant funding from Abbott Laboratories and Alere, Inc. P.T.M. has received research funding from Abbott Laboratories and Alere, Inc. P.T.M.'s institution receives funding from Abbott Laboratories.

Acknowledgements

Dr. Nicholas Wettersten and this work was supported (or supported in part) by Career Development Award Number IK2 CX002105 from the United States (U.S.) Department of Veterans Affairs Clinical Sciences R&D (CSRD) Service.

The contents do not represent the view of the U.S. Department of Veterans Affairs or the United States Government.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2022.02.026.

References

[1] C. Ronco, P. McCullough, S.D. Anker, I. Anand, N. Aspromonte, S.M. Bagshaw, et al., Cardio-renal syndromes: report from the consensus conference of the acute dialysis quality initiative, Eur. Heart J. 31 (2010) 703–711.
[2] K. Damman, M.A. Valente, A.A. Voors, C.M. O'Connor, D.J. van Veldhuisen, H. L. Hillege, Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis, Eur. Heart J. 35 (2014) 455–469.
[3] G. Filippatos, D. Farmakis, J. Parissis, Renal dysfunction and heart failure: things are seldom what they seem, Eur. Heart J. 35 (2014) 416–418.
[4] J.M. Testani, J. Chen, B.D. McCauley, S.E. Kimmel, R.P. Shannon, Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival, Circulation 122 (2010) 265–272.
[5] G.M. Felker, K.L. Lee, D.A. Bull, M.M. Redfield, L.W. Stevenson, S.R. Goldsmith, et al., Diuretic strategies in patients with acute decompensated heart failure, N. Engl. J. Med. 364 (2011) 797–805.
[6] M. Metra, B. Davison, L. Bettari, H. Sun, C. Edwards, V. Lazzarini, et al., Is worsening renal function an ominous prognostic sign in patients with acute heart failure? The role of congestion and its interaction with renal function, Circ. Heart Fail. 5 (2012) 54–62.
[7] A.P. Ambrosy, P.S. Pang, S. Khan, M.A. Konstam, G.C. Fonarow, B. Traver, et al., Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: findings from the EVEREST trial, Eur. Heart J. 34 (2013) 835–843.
[8] N. Wettersten, Y. Horiuchi, D.J. van Veldhuisen, C. Mueller, G. Filippatos, R. Nowak, et al., B-type natriuretic peptide trend predicts clinical significance of worsening renal function in acute heart failure, Eur. J. Heart Fail. 21 (2019) 1553–1560.
[9] T. Ahmad, K. Jackson, V.S. Rao, W.H.W. Tang, M.A. Brisco-Bacik, H.H. Chen, et al., Worsening renal function in patients with acute heart failure undergoing aggressive diuresis is not associated with tubular injury, Circulation 137 (2018) 2016–2028.
[10] V.S. Rao, T. Ahmad, M.A. Brisco-Bacik, J.V. Bonventre, F.P. Wilson, E.D. Siew, et al., Renal effects of intensive volume removal in heart failure patients with preexisting worsening renal function, Circ. Heart Fail. 12 (2019), e005552.
[11] Y.U. Horiuchi, N. Wettersten, D.J.V. Veldhuisen, C. Mueller, G. Filippatos, R. Nowak, et al., Potential utility of cardiorenal biomarkers for prediction and prognostication of worsening renal function in acute heart failure, J. Card. Fail. 27 (5) (2020 May) 533–541.
[12] W. Mullens, K. Damman, J.M. Testani, P. Martens, C. Mueller, J. Lassus, et al., Evaluation of kidney function throughout the heart failure trajectory - a position statement from the heart failure Association of the European Society of cardiology, Eur. J. Heart Fail. 22 (2020) 584–603.
[13] A.S. Maisel, N. Wettersten, D.J. van Veldhuisen, C. Mueller, G. Filippatos, R. Nowak, et al., Neutrophil gelatinase-associated Lipocalin for acute kidney injury during acute heart failure hospitalizations: the AKINESIS study, J. Am. Coll. Cardiol. 68 (2016) 1420–1431.
[14] L.B. Daniels, A.S. Maisel, Natriuretic peptides, J. Am. Coll. Cardiol. 50 (2007) 2357–2368.
[15] H.R. Omar, M. Guglin, Longitudinal BNP follow-up as a marker of treatment response in acute heart failure: relationship with objective markers of decongestion, Int. J. Cardiol. 221 (2016) 167–170.
[16] R. Kazanegra, V. Cheng, A. Garcia, P. Krishnaswamy, N. Gardetto, P. Clopton, et al., A rapid test for B-type natriuretic peptide correlates with falling wedge pressures in patients treated for decompensated heart failure: a pilot study, J. Card. Fail. 7 (2001) 21–29.
[17] P. Bettencourt, A. Azevedo, J. Pimenta, F. Frioes, S. Ferreira, A. Ferreira, N-terminal-pro-brain natriuretic peptide predicts outcome after hospital discharge in heart failure patients, Circulation 110 (2004) 2168–2174.
[18] F. Zhou, Q. Luo, L. Wang, L. Han, Diagnostic value of neutrophil gelatinase-associated lipocalin for early diagnosis of cardiac surgery-associated acute kidney injury: a meta-analysis, Eur. J. Cardiothorac. Surg. 49 (2016) 746–755.
[19] M. Haase, R. Bellomo, P. Devarajan, P. Schlattmann, A. Haase-Fielitz, Group NM-aI. Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: a systematic review and meta-analysis, Am. J. Kidney Dis. 54 (2009) 1012–1024.
[20] C. Quintavalle, C.V. Anselmi, F. De Micco, G. Roscigno, G. Visconti, B. Golia, et al., Neutrophil gelatinase-associated Lipocalin and contrast-induced acute kidney injury, Circ Cardiovasc. Interv. 8 (2015), e002673.
[21] P.T. Murray, N. Wettersten, D.J. van Veldhuisen, C. Mueller, G. Filippatos, R. Nowak, et al., Utility of urine neutrophil gelatinase-associated Lipocalin for worsening renal function during hospitalization for acute heart failure: primary findings of the urine N-gal acute kidney injury N-gal evaluation of symptomatic heart failure study (AKINESIS), J. Card. Fail. 25 (2019) 654–665.
[22] K. Salah, W.E. Kok, L.W. Eurlings, P. Bettencourt, J.M. Pimenta, M. Metra, et al., A novel discharge risk model for patients hospitalised for acute decompensated heart failure incorporating N-terminal pro-B-type natriuretic peptide levels: a European coLlaboration on acute decompeNsated heart failure: ELAN-HF score, Heart. 100 (2014) 115–125.
[23] K. Salah, W.E. Kok, L.W. Eurlings, P. Bettencourt, J.M. Pimenta, M. Metra, et al., Competing risk of cardiac status and renal function during hospitalization for acute decompensated heart failure, JACC Heart Fail. 3 (2015) 751–761.
[24] D.S. Lee, P.C. Austin, J.L. Rouleau, P.P. Liu, D. Naimark, J.V. Tu, Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model, JAMA 290 (2003) 2581–2587.
[25] G.M. Felker, J.D. Leimberger, R.M. Califf, M.S. Cuffe, B.M. Massie, K.F. Adams Jr., et al., Risk stratification after hospitalization for decompensated heart failure, J. Card. Fail. 10 (2004) 460–466.
[26] C.M. O'Connor, V. Hasselblad, R.H. Mehta, G. Tasissa, R.M. Califf, M. Fiuzat, et al., Triage after hospitalization with advanced heart failure: the ESCAPE (evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness) risk model and discharge score, J. Am. Coll. Cardiol. 55 (2010) 872–878.
[27] Peacock WFT, T. De Marco, G.C. Fonarow, D. Diercks, J. Wynne, F.S. Apple, et al., Cardiac troponin and outcome in acute heart failure, N. Engl. J. Med. 358 (2008) 2117–2126.
[28] P.T. Murray, R.L. Mehta, A. Shaw, C. Ronco, Z. Endre, J.A. Kellum, et al., Potential use of biomarkers in acute kidney injury: report and summary of recommendations from the 10th acute Dialysis quality initiative consensus conference, Kidney Int. 85 (2014) 513–521.

[29] D. Bolignano, V. Donato, G. Coppolino, S. Campo, A. Buemi, A. Lacquaniti, et al., Neutrophil gelatinase-associated lipocalin (NGAL) as a marker of kidney damage, Am. J. Kidney Dis. 52 (2008) 595–605.
[30] S.P. Collins, K.W. Hart, C.J. Lindsell, G.J. Fermann, N.L. Weintraub, K.F. Miller, et al., Elevated urinary neutrophil gelatinase-associated lipocalcin after acute heart failure treatment is associated with worsening renal function and adverse events, Eur. J. Heart Fail. 14 (2012) 1020–1029.
[31] Y. Nakada, R. Kawakami, M. Matsui, T. Ueda, T. Nakano, A. Takitsume, et al., Prognostic value of urinary neutrophil gelatinase-associated Lipocalin on the first day of admission for adverse events in patients with acute decompensated heart failure, J. Am. Heart Assoc. 6 (2017).
[32] N. Wettersten, Y. Horiuchi, D.J. van Veldhuisen, C. Mueller, G. Filippatos, R. Nowak, et al., Short-term prognostic implications of serum and urine neutrophil gelatinase-associated lipocalin in acute heart failure: findings from the AKINESIS study, Eur. J. Heart Fail. 22 (2020) 251–263.
[33] J.D. Frizzell, L. Liang, P.J. Schulte, C.W. Yancy, P.A. Heidenreich, A.F. Hernandez, et al., Prediction of 30-day all-cause readmissions in patients hospitalized for heart failure: comparison of machine learning and other statistical approaches, JAMA Cardiol. 2 (2017) 204–209.
[34] D. Kansagara, H. Englander, A. Salanitro, D. Kagen, C. Theobald, M. Freeman, et al., Risk prediction models for hospital readmission: a systematic review, JAMA. 306 (2011) 1688–1698.