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

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Potential Utility of Cardiorenal Biomarkers for Prediction and Prognostication of Worsening Renal Function in Acute Heart Failure

YU HORIUCHI, MD,[1,2] NICHOLAS WETTERSTEN, MD,[1] DIRK J. VAN VELDHUISEN, MD,[3] CHRISTIAN MUELLER, MD,[4] GERASIMOS FILIPPATOS, MD,[5] RICHARD NOWAK, MD,[6] CHRISTOPHER HOGAN, MD,[7] MICHAEL C. KONTOS, MD,[8] CHAD M. CANNON, MD,[9] GERHARD A. MÜELLER, MD, PhD,[10] ROBERT BIRKHAHN, MD,[11] PAM TAUB, MD,[1] GARY M. VILKE, MD,[12] OLGA BARNETT, MD,[13] KENNETH MCDONALD, MD,[14,15] NIALL MAHON, MD,[14,16] JULIO NUÑEZ, MD,[17,18] CARLO BRIGUORI, MD, PhD,[19] CLAUDIO PASSINO, MD,[20] ALAN MAISEL, MD,[1] AND PATRICK T. MURRAY, MD[21]

Tokyo, Japan; La Jolla, California; Groningen, the Netherlands; Basel, Switzerland; Athens, Greece; Detroit, Michigan; Richmond, Virginia; Kansas City, Kansas; Gottingen, Germany; Brooklyn, New York; Lviv, Ukraine; Valencia and Madrid, Spain; Naples and Pisa, Italy, and Dublin, Ireland.

ABSTRACT

Background: Multiple different pathophysiologic processes can contribute to worsening renal function (WRF) in acute heart failure.

Methods and Results: We retrospectively analyzed 787 patients with acute heart failure for the relationship between changes in serum creatinine and biomarkers including brain natriuretic peptide, high sensitivity cardiac troponin I, galectin 3, serum neutrophil gelatinase-associated lipocalin, and urine neutrophil gelatinase-associated lipocalin. WRF was defined as an increase of greater than or equal to 0.3 mg/dL or 50% in creatinine within first 5 days of hospitalization. WRF was observed in 25% of patients. Changes in biomarkers and creatinine were poorly correlated ($r \leq 0.21$) and no biomarker predicted WRF better than creatinine. In the multivariable Cox analysis, brain natriuretic peptide and high sensitivity cardiac troponin I, but not WRF, were significantly associated with the 1-year composite of death or heart failure hospitalization. WRF with an increasing urine neutrophil gelatinase-associated lipocalin predicted an increased risk of heart failure hospitalization.

Conclusions: Biomarkers were not able to predict WRF better than creatinine. The 1-year outcomes were associated with biomarkers of cardiac stress and injury but not with WRF, whereas a kidney injury biomarker may prognosticate WRF for heart failure hospitalization. (*J Cardiac Fail 2021;27:533−541*)

Key Words: Biomarkers, worsening renal function, acute heart failure, prognosis.

Acute kidney dysfunction is frequently observed in patients with acute heart failure (AHF). This has been termed worsening renal function (WRF), usually defined as a deterioration in kidney function reflected by increasing

From the [1]From the Division of Cardiovascular Medicine, University of California San Diego, La Jolla, California; [2]Division of Cardiology, Mitsui Memorial Hospital, Tokyo, Japan; [3]Department of Cardiology, University Medical Centre Groningen, University of Groningen, Groningen, the Netherlands; [4]Department of Cardiology, University Hospital Basel, University of Basel, Basel, Switzerland; [5]Department of Cardiology, Athens University Hospital Attikon, University of Athens, Athens, Greece; [6]Department of Emergency Medicine, Henry Ford Hospital System, Detroit, Michigan; [7]Division of Emergency Medicine and Acute Care Surgical Services, VCU Medical Center, Virginia Commonwealth University, Richmond, Virginia; [8]Division of Cardiology, VCU Medical Center, Virginia Commonwealth University, Richmond, Virginia; [9]Department of Emergency Medicine, University of Kansas Medical Center, Kansas City, Kansas; [10]Department of Nephrology and Rheumatology, University Medical Centre Göttingen, University of Göttingen, Göttingen, Germany; [11]Department of Emergency Medicine, New York Methodist Hospital, Brooklyn, New York; [12]Department of Emergency Medicine, University of California San Diego, La Jolla, California; [13]Division of Cardiology, Danylo Halytsky Lviv National Medical University, Lviv Oblast, Ukraine; [14]Department of Cardiology, School of Medicine, University College Dublin, Belfield, Dublin, Ireland; [15]Department of Cardiology, St Vincent's University Hospital, Dublin, Ireland; [16]Department of Cardiology, Mater Misericordiae University Hospital, Dublin, Ireland; [17]Department of Cardiology, Valencia University Hospital, INCLIVA, Valencia, Spain; [18]Centro de Investigación Biomédica en Red (CIBER) in Cardiovascular Diseases, Madrid, Spain; [19]Department of Cardiology, Mediterranea Cardiocentro, Naples, Italy; [20]Department of Cardiology and Cardiovascular Medicine, Fondazione Gabriele Monasterio, Pisa, Italy; and the and [21]Department of Medicine, School of Medicine, University College Dublin, Health Sciences Centre, Dublin, Ireland.

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Reprint requests: Patrick T. Murray, MD, University College Dublin Clinical Research Centre, UCD Catherine McAuley Education & Research Centre, Nelson Street, Dublin 7, Ireland. Tel: +353-1-7164504. E-mail: patrick.murray@ucd.ie

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creatinine and decreasing glomerular filtration rate (GFR).[1−5] WRF has been variably associated with worse, neutral, or even improved outcomes.[1−5] This variability is likely a product of different pathophysiologic processes driving alterations in renal function and potentially depends on whether acute tubular injury (ATI) is occurring.[5] Studies have recently shown WRF in the setting of aggressive and effective decongestive therapy in AHF is a result of benign functional changes in the GFR and not associated with ATI or a poor prognosis.[2−5] Although these studies focused on evaluating kidney specific biomarkers, a more global assessment of systemic processes that may affect kidney function, such as hemodynamic changes, inflammation, neurohormonal activation, and immune-mediated damage, may give improved insight into the causes and prognostic outcomes of WRF.[6]

The Acute Kidney Injury Neutrophil gelatinase-associated lipocalin (NGAL) Evaluation of Symptomatic heart faIlure Study (AKINESIS) is one of the largest international multicenter prospective cohort studies specifically designed to evaluate cardiorenal syndrome (CRS) in patients with AHF.[7] In addition to serial measurements of serum NGAL (sNGAL) and urine NGAL (uNGAL) for the assessment of ATI, other biomarkers including B-type natriuretic peptide (BNP), high sensitivity cardiac troponin I (hscTnI), and galectin 3 (Gal3) were analyzed from stored serum samples.[8−10] These biomarkers can reflect different detrimental pathophysiologic processes in CRS, including congestion, myocardial damage, myocardial fibrosis, kidney injury and fibrosis, and systemic inflammation.[11−16] In this study, we investigated the contribution of different pathophysiologic processes as reflected by biomarkers for the risk of developing WRF, and their prognostic significance in relation to WRF outcomes in patients with AHF.

Methods

Study Population

We retrospectively analyzed patients in AKINESIS, which has been previously described.[7] Briefly, from January 2011 through September 2013, 927 patients were enrolled at 16 sites in the United States and Europe. Patients had to have 1 or more signs or symptoms of HF, including dyspnea on exertion, rales or crackles, galloping heart rhythm, jugular venous distention, orthopnea, paroxysmal nocturnal dyspnea, using more than 2 pillows to sleep, fatigue, edema, frequent coughing, a cough that produces mucous or blood-tinged sputum, or a dry cough when lying flat. Patients must have received or planned treatment with intravenous diuretics. Exclusion criteria were (1) acute coronary syndrome, (2) patients on dialysis or initiation was planned during the current hospitalization, (3) major organ transplantation, (4) enrolment in a drug treatment study within the past 30 days or patients who had already enrolled in this study, or (5) were pregnant or belonging to an institutional review board−determined vulnerable population. In the current analysis, 6 patients lacked creatinine measurements, 29 patients lacked BNP measurements, 10 patients lacked hscTnI measurements, 3 patients lacked sNGAL measurements, and 92 patients lacked uNGAL measurements on admission; these patients were excluded. A total of 787 patients were included in this analysis.

Specimen Collection

Serum samples for biomarker assessment were collected with ethylenediaminetetraacetic acid plasma tubes, processed to plasma, frozen, and shipped to the core laboratory. Urine samples were centrifuged, frozen, and shipped to the core laboratory. Serum and urine specimens were collected up to 6 times, depending on the hospitalization duration. 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 third, fourth, and fifth specimens were collected on hospital days 1, 2, and 3, respectively. The sixth specimen was collected on the day of discharge or anticipated discharge. uNGAL

Table 1. Baseline Characteristics in Patients With or Without Nonsevere WRF

	WRF ($n = 193$)	No WRF ($n = 594$)	*P* value
Age (years)	70 ± 14	68 ± 14	.081
Male sex	123 (64)	376 (63)	.982
White race	379 (64)	124 (64)	.980
History of CAD	102 (53)	260 (44)	.034
History of hypertension	165 (86)	470 (79)	.065
History of hyperlipidemia	107 (55)	301 (51)	.285
History of diabetes mellitus	99 (51)	246 (41)	.020
History of COPD	44 (23)	159 (27)	.317
History of CKD	62 (32)	139 (23)	.020
Tobacco use	29 (15)	99 (17)	.671
ACE-I	83 (43)	263 (44)	.822
ARB	40 (21)	111 (19)	.603
β-Blocker	140 (73)	417 (70)	.597
Diuretics	128 (66)	430 (72)	.128
Systolic BP (mm Hg)	146 ± 31	139 ± 29	.003
Heart rate (bpm)	87 ± 22	88 ± 23	.720
Edema	147 (76)	441 (74)	.661
Rales present	87 (45)	248 (42)	.466
Sodium (mEq/L)	139 ± 5	138 ± 7	.546
Hemoglobin (g/dL)	11.2 [9.5−12.8]	12.0 [10.4−13.3]	<.001
BUN (mg/dL)	28 [20−44]	23 [16−33]	<.001
Creatinine (mg/dL)	1.35 [1.00−1.80]	1.15 [0.92−1.50]	<.001
eGFR (mL/min/1.73 m^2)	50 [36−68]	60 [43−82]	<.001
BNP (ng/l)	646 [285−1119]	509 [206−1108]	.029
hscTnI (ng/l)	31.9 [16.5−79.2]	23.9 [12.2−54.6]	.001
Gal3 (ng/mL)	26.6 [21.3−37.6]	24.5 [19.2−34.6]	.010
sNGAL (ng/mL)	170.4 [107.0−329.5]	123.9 [76.7−219.6]	<.001
uNGAL (ug/g)	38.1 [15.1−78.7]	23.1 [12.1−59.8]	.001

ACE-I, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; BNP, B-type natriuretic peptide; BP, blood pressure; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; Gal3, galectin 3; hscTnI, high sensitivity cardiac troponin I; sNGAL, serum neutrophil gelatinase-associated lipocalin; uNGAL, urine neutrophil gelatinase-associated lipocalin; WRF, worsening renal function.

Values are mean ± standard deviation, number (%), or median [interquartile range].

was indexed to urine creatinine to account for urine tonicity. Levels of serum creatinine were measured each day during hospitalization.

Biomarker Assessment

Specimens were analyzed at the core laboratory with the Alere Triage platform for sNGAL and ARCHITECT platform (Abbott Laboratories) for BNP, hscTnI, Gal3, and uNGAL. The coefficient of variance (CV) and the lower limit of detection (LLD) of these assays are as follows: BNP, CV less than 12%, LLD 10 ng/L; hscTnI, CV less than 10%, LLD 1.1−1.9 ng/L; Gal3 less than 10%, LLD 1.0 ng/mL; sNGAL, CV 2.1%, LLD 0.7 ng/mL; uNGAL, CV 3.1%, LLD 0 ng/mL.

Clinical End Point

The end points were WRF and a composite of 1-year mortality or HF hospitalization. Mortality and HF

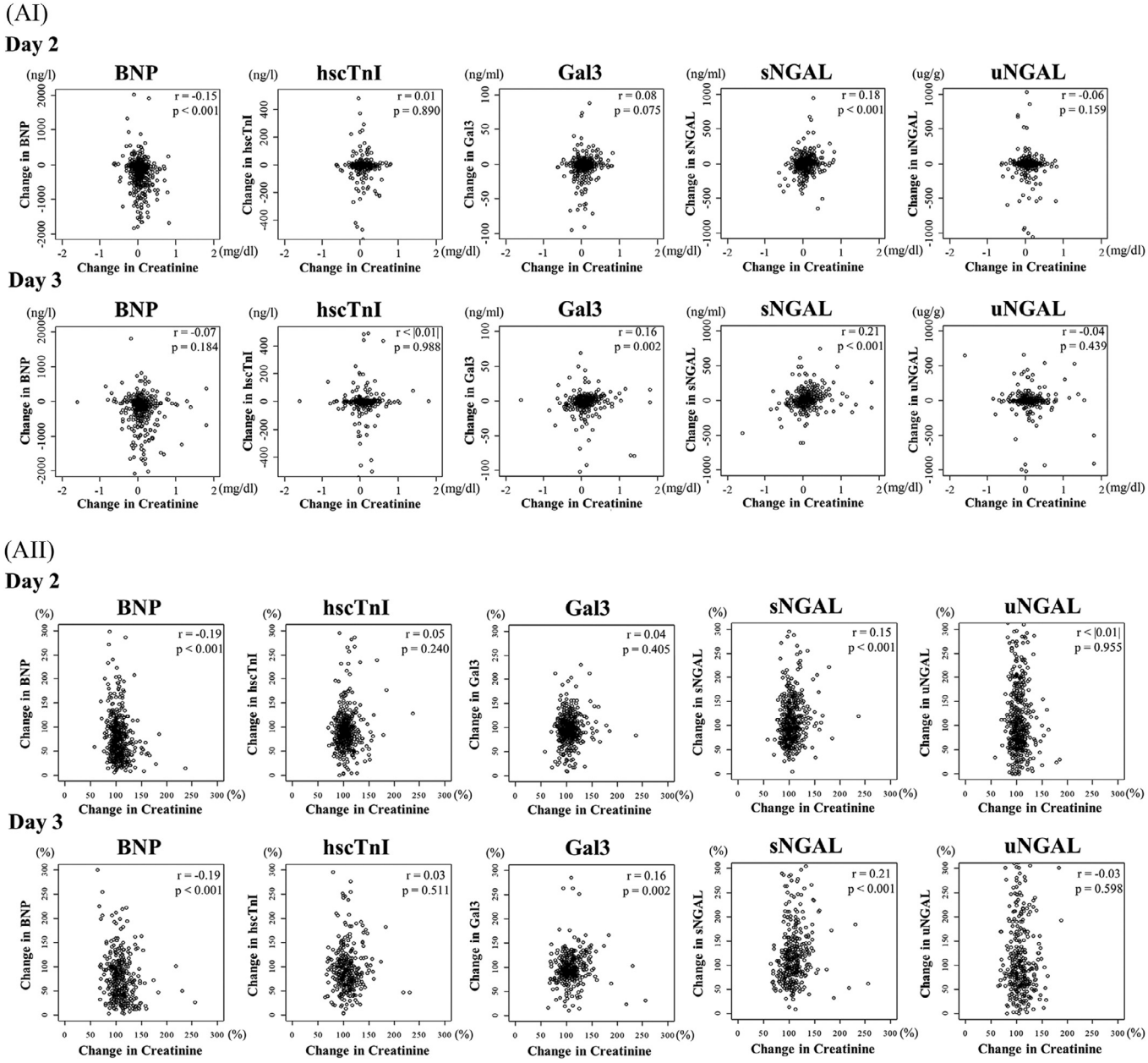
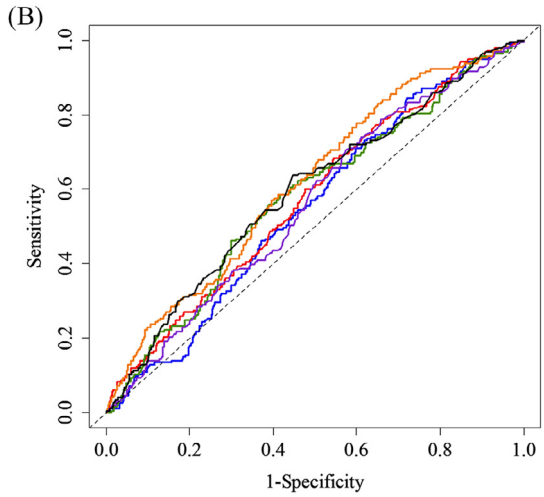


Fig. 1. (**A**) Correlations of absolute and relative changes in biomarkers and creatinine. (**AI**) Absolute changes in biomarkers and creatinine. (**AII**) Relative changes in biomarkers and creatinine. Absolute (**AI**) and relative (**AII**) changes in serum creatinine were weakly correlated with those in BNP, Gal3, and sNGAL, and were not correlated with hscTnI and uNGAL. BNP, B-type natriuretic peptide; Gal3, galectin 3; hscTnI, high sensitivity cardiac troponin I; uNGAL, urine neutrophil gelatinase-associated lipocalin; sNGAL, serum neutrophil gelatinase-associated lipocalin. (**B**) Prediction of WRF with admission values of biomarkers. AUCs of admission values of biomarkers for predicting WRF were poorly discriminatory, with highest AUC of 0.62 and were not better than admission serum creatinine. AUC, area under the receiver operating curve; BNP, B-type natriuretic peptide; Gal3, galectin 3; hscTnI, high sensitivity cardiac troponin I; uNGAL, urine neutrophil gelatinase-associated lipocalin; sNGAL, serum neutrophil gelatinase-associated lipocalin; WRF, worsening renal function.



	AUC	95% CI
BNP	0.55	0.51-0.60
hscTnI	0.58	0.53-0.62
Gal3	0.56	0.52-0.61
sNGAL	0.62	0.57-0.66
uNGAL	0.58	0.53-0.63
Creatinine	0.59	0.55-0.64

Fig. 1 Continued.

hospitalization were also analyzed individually. WRF was defined as an increase in creatinine of greater than or equal to 0.3 mg/dL or 50% from the first creatinine during the first 5 days. This definition was chosen because it is the most commonly used in literature.[1]

Statistical Analysis

Continuous variables were described as means with standard deviations, or medians with interquartile ranges if non-normally distributed. Categorical variables were described as counts and percentages. The Student t test, Mann−Whitney U test, and χ^2 test were used for group comparison as appropriate. Relationships between absolute and relative changes from admission to day 2 or 3 in creatinine and other biomarkers were analyzed using Spearman's correlation coefficient. The area under the receiver operating characteristic curves were used to investigate the usefulness of admission values of biomarkers for predicting WRF. Relationships between biomarkers and WRF were also investigated using multivariable logistic regression analysis, with each biomarker adjusted for risk factors for WRF including age, gender, history of hypertension, diabetes mellitus, coronary artery disease (CAD), creatinine, and hemoglobin, which have previously been identified in a meta-analysis.[1] Diuretic use was not included, because AKINESIS enrolled patients who must have received or planned treatment with intravenous diuretics, and 780 patients (99%) included in the current analysis received diuretic therapy. A model only adjusting for biomarkers was also analyzed. Log-rank, Kaplan−Meier, and Cox analyses were used to investigate the relationship between WRF and clinical outcomes. We evaluated the risk of 1-year outcomes in patients with combinations of WRF and changes in biomarkers with change analyzed using tertiles of relative changes from admission to peak values during the first 3 days of hospitalization. For BNP, the lowest value was used, considering the previous study investigating a relationship between BNP decrease and WRF.[17] In the multivariable Cox analysis, WRF was adjusted for clinical variables and admission values of biomarkers. Clinical variables included age, race, history of chronic obstructive disease, edema, systolic blood pressure, heart rate, sodium, hemoglobin, and blood urea nitrogen based on prior studies.[18−22] BNP, hscTnI, Gal3, sNGAL, uNGAL, and creatinine were log-2 transformed so that each increase represents a doubling in the value. All statistical analyses were performed using R x64 3.6.3 for Windows.

Results

Patient Characteristics

Of the 787 patients included, the mean age was 68 ± 14 years, 63% were male, 46% had a history of CAD, and 44% had a history of diabetes mellitus. A history of chronic kidney disease was reported in 26%, with a median serum creatinine and estimated GFR on admission of 1.19 mg/dL (interquartile range, 0.93−1.59 mg/dL) and 57 mL/min/1.73 m^2 (interquartile range, 41−79 mL/min/1.73 m^2), respectively.

Table 2. Logistic Regression Analysis for WRF

	Univariable			Multivariable model 1			Multivariable model 2		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value
BNP	1.12	1.02−1.23	.022	1.08	0.97−1.19	.157	1.07	0.96−1.19	.235
hscTnI	1.15	1.06−1.26	<.001	1.13	1.03−1.23	.009	1.12	1.02−1.23	.015
Gal3	1.27	1.02−1.58	.035	1.00	0.76−1.30	.972	0.94	0.71−1.23	.639
sNGAL	1.41	1.22−1.61	<.001	1.28	1.08−1.51	.004	1.36	1.14−1.62	<.001
uNGAL	1.13	1.04−1.22	.004	1.07	0.98−1.17	.123	1.06	0.97−1.16	.180
Creatinine	1.64	1.27−2.13	<.001		—		1.04	0.74−1.47	.822

Model 1. Each biomarker was adjusted for age, gender, history of hypertension, diabetes mellitus, coronary artery disease, creatinine and hemoglobin
Model 2. Only biomarkers are included.
CI, confidence interval; OR, odds ratio. Other abbreviations as in Table 1.

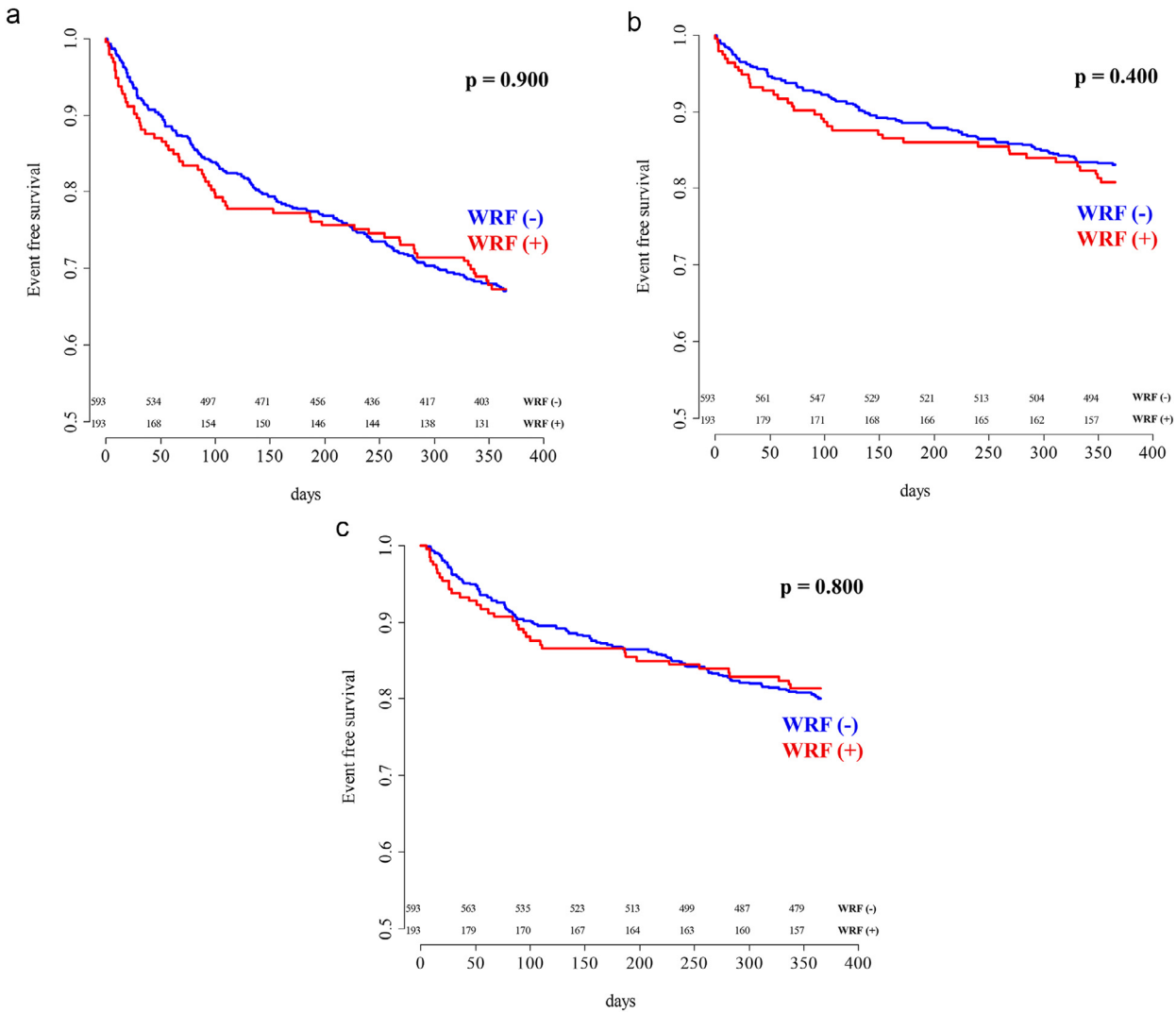


Fig. 2. WRF and 1-year clinical outcomes. (**A**) Death or heart failure hospitalization within 1 year. (**B**). Death within 1 year. (**C**). Heart failure hospitalization within 1 year. WRF was not associated with any clinical outcomes at 1 year. WRF, worsening renal function.

Characteristics of Patients With WRF

WRF occurred in 193 patients (25%). Patients with WRF more frequently had a history of CAD, diabetes mellitus, and chronic kidney disease and had higher systolic blood pressure on admission (Table 1). WRF was associated with higher levels of creatinine and blood urea nitrogen, and lower levels of hemoglobin and estimated GFR on admission. Levels of all biomarkers on admission were higher in those with WRF.

Biomarkers for Predicting WRF

During the second or third day of hospitalization, absolute and relative changes in serum creatinine were weakly correlated with those in BNP, Gal3, and sNGAL, but were not correlated with hscTnI or uNGAL (Fig. 1A). The areas under the receiver operating curve of admission values of biomarkers for predicting WRF were poorly discriminatory with the highest area under the receiver operating curve of 0.62, and were not better than admission serum creatinine (Fig. 1B). In multivariable logistic regression analysis, the admission values of hscTnI and sNGAL were significantly associated with WRF after adjustment for confounders (Table 2).

Biomarkers and WRF for Predicting Outcomes

During follow-up, 139 patients (18%) died and 154 patients (20%) were hospitalized because of HF; 260 patients (33%) developed the composite of death or HF hospitalization at 1 year. WRF did not predict the composite end point and HF hospitalization at 1 year (Fig. 2). The admission BNP was associated with all 1-year outcomes, hscTnI was associated with the composite end point and mortality, and Gal3 was associated with mortality after adjustment for clinical variables and biomarkers (Table 3). None of the biomarkers modified the risk of WRF for the composite outcome and death (Fig. 3A and 3B). However, patients with WRF in the higher tertiles of the ratio of peak

Table 3. Cox Analysis for Clinical Outcomes at the 1-Year Composite End Point

Univariable model	HR	95% CI	*P* Value
WRF	1.01	0.76−1.35	.934
Multivariable model 1			
WRF	1.03	0.77−1.38	.828
Multivariable model 2			
WRF	0.99	0.73−1.33	.93
BNP	1.23	1.13−1.33	<.001
hscTnI	1.08	1.01−1.16	.018
Gal3	1.09	0.89−1.34	.423
sNGAL	1.04	0.92−1.18	.506
uNGAL	0.98	0.92−1.05	.583
Death			
Univariable model			
WRF	1.16	0.80−1.69	.439
Multivariable model 1			
WRF	1.10	0.74−1.62	.64
Multivariable model 2			
WRF	1.06	0.71−1.57	.793
BNP	1.24	1.1−1.39	<.001
hscTnI	1.12	1.03−1.22	.012
Gal3	1.61	1.26−2.06	<.001
sNGAL	1.03	0.88−1.22	.708
uNGAL	0.96	0.88−1.05	.368
Heart failure hospitalization			
Univariable model			
WRF	0.95	0.65−1.38	.783
Multivariable model 1			
WRF	0.98	0.67−1.44	.928
Multivariable model 2			
WRF	0.99	0.67−1.47	.966
BNP	1.21	1.09−1.35	<.001
hscTnI	0.99	0.9−1.08	.794
Gal3	0.87	0.66−1.14	.300
sNGAL	1.02	0.87−1.2	.775
uNGAL	0.97	0.88−1.06	.469

Multivariable model 1 is adjusted for age, Black race, history of chronic obstructive disease, oedema, systolic blood pressure, heart rate, sodium, hemoglobin, and blood urea nitrogen.

Multivariable model 2 is adjusted for factors included in model 1 and BNP, hscTnI, sNGAL, uNGAL, and Gal3.

HF, heart failure; HR, hazard ratio. Other abbreviations as in Tables 1 and 2.

to admission uNGAL had a higher incidence of HF hospitalization (Fig. 3C).

Discussion

In this subanalysis of AKINESIS, we evaluated whether biomarkers reflective of systemic pathophysiologic processes in AHF and potentially CRS can predict and discriminate WRF. Changes in biomarkers and creatinine were not well correlated, and the admission values of biomarkers were not able to predict WRF better than serum creatinine. hscTnI and sNGAL were independent predictors of WRF. WRF was not associated with 1-year outcomes after adjusting for clinical variables; however, biomarkers were associated with 1-year clinical outcomes and patients with WRF and increasing uNGAL had an increased risk of HF hospitalization.

Given the reported variability in the clinical significance of WRF in AHF, studies have been trying to discriminate the impact of AHF on kidney health using biomarkers of ATI.[5,7,23,24] These studies have overall found a lack of predictive usefulness of ATI biomarkers for WRF, largely owing to a dissociation between renal functional change and injury. NGAL (both serum and urine), *N*-acetyl-β-d-glycosaminidase, and kidney injury molecule 1 have repeatedly failed to show these biomarkers can predict impending WRF.[5,23,24] However, these studies are looking at the end-organ damage of AHF on the kidney and, if injury does occur, they may not capture the systemic pathophysiologic processes behind WRF. Our study examined CRS by evaluating systemic dysfunction from AHF as reflected by biomarkers of congestion, myocardial damage, kidney injury, inflammation, and fibrosis. These systemic processes in AHF similarly impact the kidney, contributing to hemodynamic perturbations that decrease the driving force for fluid and salt excretion in the kidney, and neurohormonal activation and immune-mediated damage that lead to kidney injury and fibrosis.[6,25−28]

Despite capturing a broad spectrum of pathophysiologic process, none of the individual admission biomarker values predicted subsequent WRF better than serum creatinine, and changes in these biomarkers were not meaningfully correlated with creatinine. This outcome is likely because no single pathophysiologic process causes CRS in AHF, but WRF is a culmination of the various processes measured in this study, as well as others that were unmeasured. In the multivariate analysis as well, most of the biomarkers were not significant for developing WRF. Intriguingly, admission hscTnI significantly predicted an increased odds of WRF, suggesting the presence of myocardial injury in AHF may translate to a more severe impact of AHF on the kidney. Of note, patients presenting with acute coronary syndrome and AHF were excluded from enrolment in the AKINESIS study. The relationship between hscTnI and WRF may not simply be the result of reduced hscTnI clearance with impaired renal function, because the multivariable model included serum creatinine. Myocardial injury reflected by elevated troponin in AHF is thought to result from numerous different processes including CAD, demand ischemia, microvascular dysfunction, myocardial stretch, inflammation, and oxidative stress.[12] These systemic processes could concurrently be impacting the kidney. This finding expands on the already described prognostic usefulness of hscTn in AHF for mortality to now potentially include prognostic usefulness of the systemic impact of myocardial injury on AHF.

Although admission sNGAL was associated with WRF, this finding may not be indicative of the kidney injury occurring with WRF, because sNGAL can reflect systemic inflammation and decreased glomerular filtration of NGAL from extrarenal sources, in addition to renal tubular injury.[13−15] If kidney injury was associated with WRF, we would have expected to see similar or even greater findings with uNGAL, which is more specific for kidney injury, given its inducible production at the site of injury.[14]

Conflicting findings regarding the impact of WRF on outcomes have been reported, which is likely because of the

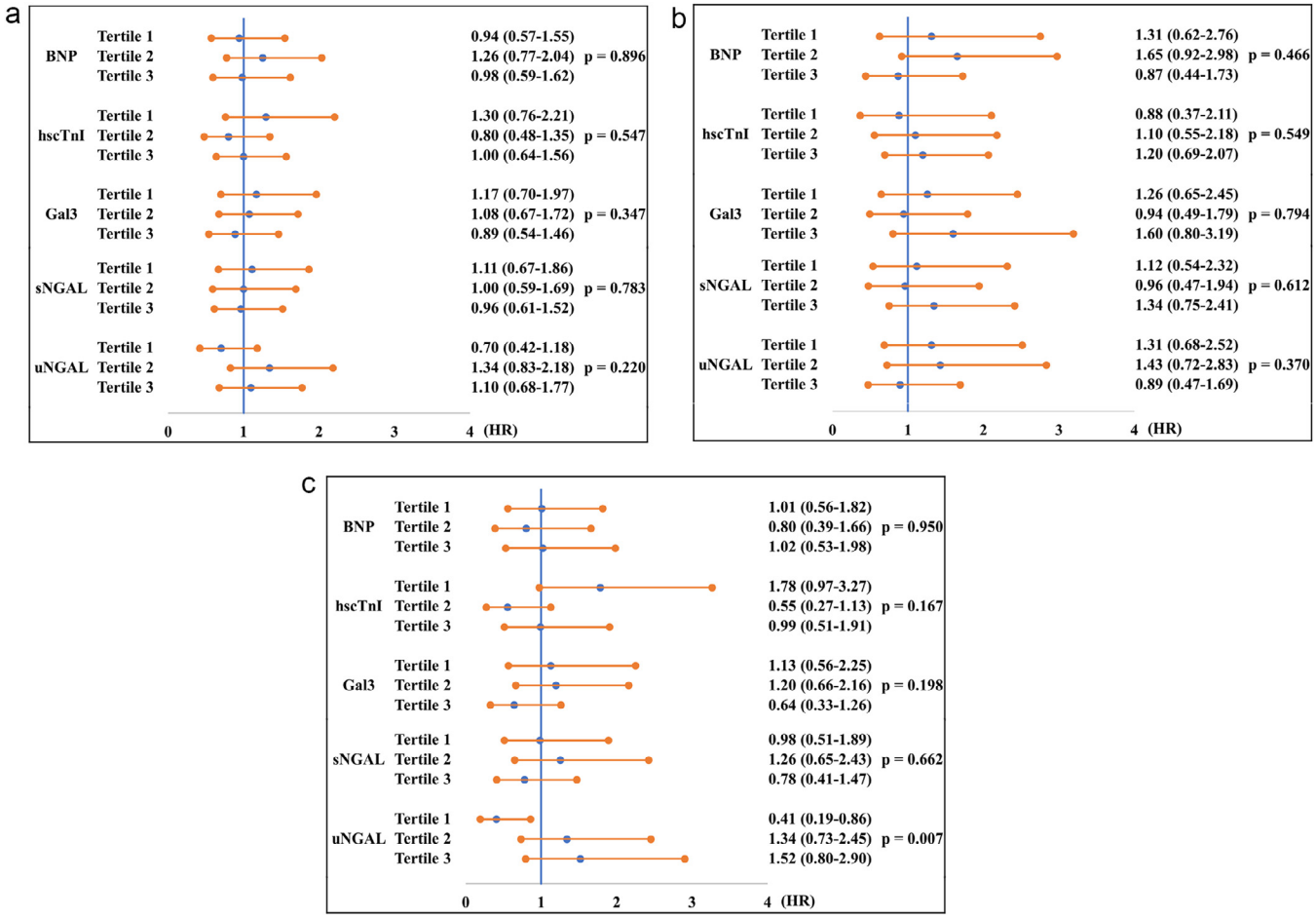


Fig. 3. Risk for 1-year clinical outcomes by biomarker tertiles in patients with WRF. (**A**) Death or heart failure hospitalization within 1 year. (**B**) Death within 1 year. (**C**) Heart failure hospitalization within 1 year. The risk of 1-year clinical outcomes in patients with combinations of WRF and changes in biomarkers was analyzed. Changes in biomarkers were evaluated using tertiles of relative changes from admission to peak values during the first 3 days of hospitalization. For BNP, the lowest value was used. None of the biomarkers modified the risk of WRF for the composite outcome and death (**A** and **B**). WRF in higher tertiles of the ratio of peak to admission uNGAL had a higher incidence of heart failure hospitalization (**C**). BNP, B-type natriuretic peptide; Gal3, galectin 3; hscTnI, high sensitivity cardiac troponin I; uNGAL, urine neutrophil gelatinase-associated lipocalin; sNGAL, serum neutrophil gelatinase-associated lipocalin; WRF, worsening renal function.

heterogeneity of mechanisms causing WRF.[1–5] There has been a growing appreciation for the mechanisms causing WRF in determining the clinical impact and prognostic significance of WRF. In the current analysis, in contrast with WRF, biomarkers such as BNP, hscTnI, and Gal3 were associated with clinical outcomes. Biomarkers reflecting severity of congestion, myocardial injury, fibrosis, and inflammation, which are proposed pathophysiologic processes of CRS in AHF, were able to predict 1-year clinical outcomes beyond WRF.[6] This finding supports the hypothesis that the pathophysiologic mechanisms driving WRF determine the clinical significance.

Despite the general lack of prognostic significance of WRF and uNGAL in our study, this result should not be interpreted as finding that CRS in AHF is not clinically meaningful. We demonstrated that patients with WRF who experienced greater increases in uNGAL from admission were more likely to experience HF hospitalization within 1 year. This finding may indicate that WRF with substantial kidney injury is a more clinically meaningful form of kidney dysfunction. One hypothesis is that those experiencing substantial renal tubular injury may not respond well to diuretic therapy and may become more likely to reaccumulate fluid and be readmitted. Considering the relatively high blood pressure on admission in patients with WRF and the lack of prognostic impact of WRF with elevated uNGAL on mortality, WRF with kidney injury seems less likely to be due to impaired renal perfusion with low output syndrome, which is generally associated with low blood pressure and a poor prognosis. Thus, WRF patients with elevated uNGAL have features less consistent with an increased risk of mortality, but more likely to present with other events, such as HF readmission. Although other markers did not improve prognostication of WRF, further research is required to investigate the pathophysiologic process behind WRF through hemodynamic and nonhemodynamic contributors, incorporating various clinical findings as well as biomarker values to

refine and identify patients with WRF who are at high risk for adverse outcomes.

Limitations

Although this is one of the largest cohort studies investigating cardiorenal biomarker trajectories in AHF patients, the lack of a urine sample in 92 patients may have affected the results. Our study is a post hoc analysis of a prospective AHF cohort; thus, the result is only hypothesis generating, and unmeasured confounding factors need to be considered in the multivariable analysis. Biomarker collection beyond the first few days of hospitalization may have found other significant trends not captured in the current analysis. Unfortunately, AKINESIS did not include serial measurements of hemodynamic parameters such as blood pressure, physical findings of congestion, or invasive hemodynamic monitoring.

Conclusions

Among patients with AHF treated with diuretic therapy, biomarkers were not able to predict WRF better than serum creatinine. One-year outcomes were associated with different pathophysiologic biomarkers, but not with WRF. Patients with WRF and increasing uNGAL during hospitalization had an increased risk of HF hospitalization within 1 year.

Disclosures

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