ORIGINAL RESEARCH

Combination of Amino-Terminal Pro-BNP, Estimated GFR, and High-Sensitivity CRP for Predicting Cardiorenal Syndrome Type 1 in Acute Myocardial Infarction Patients

De-Qiang Zhang, MD; Hong-Wei Li, MD, PhD, FESC; Hai-Ping Chen, MD; Qing Ma, MD; Hui Chen, MD; Yun-Li Xing, MD; Xue-Qiao Zhao, MD, FACC

***Background*—**Cardiorenal syndrome type 1 (CRS1) as a complication of acute myocardial infarction can lead to adverse outcomes, and a method for early detection is needed. This study investigated the individual and integrated effectiveness of amino-terminal pro–brain natriuretic peptide (Pro-BNP), estimated glomerular filtration rate (eGFR), and high-sensitivity C-reactive protein (CRP) as predictive factors for CRS1 in patients with acute myocardial infarction.

***Methods and Results*—**In a retrospective analysis of 2094 patients with acute myocardial infarction, risk factors for CRS1 were analyzed by logistic regression. Receiver operating characteristic curves were constructed to determine the predictive ability of the biomarkers individually and in combination. Overall, 177 patients (8.45%) developed CRS1 during hospitalization. On multivariable analysis, all 3 biomarkers were independent predictors of CRS1 with odds radios and 95% confidence intervals for a 1-SD change of 1.792 (1.311-2.450) for log(amino-terminal pro–brain natriuretic peptide, 0.424 (0.310-0.576) for estimated glomerular filtration rate, and 1.429 (1.180-1.747) for high-sensitivity C-reactive peptide. After propensity score matching, the biomarkers individually and together significantly predicted CRS1 with areas under the curve of 0.719 for amino-terminal pro–brain natriuretic peptide, 0.843 for estimated glomerular filtration rate, 0.656 for high-sensitivity C-reactive peptide, and 0.863 for the 3-marker panel (all $P<0.001$). Also, the integrated 3-marker panel performed better than the individual markers ($P<0.05$). CRS1 risk correlated with the number of biomarkers showing abnormal levels. Abnormal measurements for at least 2 biomarkers indicated a greater risk of CRS1 (odds ratio 36.19, 95% confidence interval 8.534-153.455, $P<0.001$).

***Conclusions*—**The combination of amino-terminal pro–brain natriuretic peptide, estimated glomerular filtration rate, and high-sensitivity C-reactive peptide at presentation may assist in the prediction of CRS1 and corresponding risk stratification in patients with acute myocardial infarction. **(*J Am Heart Assoc*. 2018;7:e009162. DOI: 10.1161/JAHA.118.009162.)**

Key Words: cardiorenal syndrome • high-sensitivity C-reactive protein • amino-terminal pro–brain natriuretic peptide • prediction

Cardiorenal syndrome (CRS) is defined as "a complex pathophysiologic disorder of the heart and kidneys where acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ."[1,2] Five subtypes of CRS have been defined according to the primary organ, an acute versus chronic time frame, and whether cardiac and renal codysfunction occur secondary to systemic disease. CRS type 1 (CRS1) is characterized by acute worsening of heart function leading to acute kidney injury (AKI). The reported incidence of CRS1 ranges from 25% to 33% in patients admitted with acute decompensated heart failure,[3] and the reason for this variation may be the differences in the definitions of kidney dysfunction and the heterogeneity of populations. The pathophysiology of CRS1 is multifaceted and involves both hemodynamic and nonhemodynamic mechanisms that remain largely unknown.[4] However, it has been shown that passive central venous congestion and inflammatory activation play vital roles in the mechanisms leading to CRS1 in patients with acute heart failure.[5-7]

AKI is 1 of the most frequent in-hospital complications in patients with acute myocardial infarction (AMI) and is associated with adverse short-term and long-term outcomes.[8,9] At the same time, AMI is a common antecedent

From the Internal Medical Department, Medical Health Center, Beijing Friendship Hospital, Capital Medical University (D.-Q.Z., H.-W.L., H.-P.C., Q.M., Y.-L.X.), and Department of Cardiology, Beijing Friendship Hospital, Capital Medical University (H.-W.L., H.C.), Beijing, China; Clinical Atherosclerosis Research Laboratory, Division of Cardiology, University of Washington, Seattle, WA (X.-Q.Z.).

Correspondence to: Hong-Wei Li, MD, PhD, FESC, No. 95, Rd. Yong'an, XiCheng District Beijing, China 100050. E-mail: lhw19656@sina.com

Received March 14, 2018; accepted August 14, 2018.

Clinical Perspective

What Is New?

- Amino-terminal pro–brain natriuretic peptide, estimated glomerular filtration rate, and high-sensitivity C-reactive protein at admission significantly predicted the development of cardiorenal syndrome type 1 and showed good discriminative ability.
- The combination of the 3 biomarkers showed better predictive capability than any of the biomarkers individually.
- Abnormal levels of 2 or more of these markers according to the identified cutoff values were associated with an elevated risk of cardiorenal syndrome type 1.

What Are the Clinical Implications?

- Use of amino-terminal pro–brain natriuretic peptide, estimated glomerular filtration rate, and high-sensitivity C-reactive protein in combination may assist in the prediction of cardiorenal syndrome type 1 and corresponding risk stratification in patients with acute myocardial infarction.

event that predisposes patients to acute heart failure. Patients who experience both acute heart failure and AKI have worse outcomes than those who experience only 1 of these conditions.[10] Therefore, there is an urgent need to understand the risk factors for CRS1 and to establish an ideal biomarker for its prediction in AMI patients. Over the past decade researchers have evaluated many traditional and novel biomarkers, such as serum creatinine, cystatin C, the urea albumin creatinine ratio, neutrophil gelatinase-associated lipocalin, and others. However, whether these biomarkers possess adequate prognostic accuracy for early detection of CRS1 remains to be determined. Moreover, a multimarker panel may provide a more effective model for CSR1 risk prediction.

Toward the development of such a biomarker panel, we selected amino-terminal pro–brain natriuretic peptide (NT-proBNP), the estimated glomerular filtration rate (eGFR), and high-sensitivity C-reactive protein (hs-CRP) as promising markers of heart failure, renal injury, and inflammation, respectively, and investigated the predictive value of these biomarkers individually and in combination for CRS1 in AMI patients.

Methods

The data, analytic methods, and study materials for this study will be made available to other researchers for purposes of reproducing the results or replicating the procedure. The materials will be made available by the corresponding author on reasonable request.

Study Population

The study population for this retrospective, single-center observational study was identified from the AMI patient database of the Cardiovascular Center of Beijing Friendship Hospital, which includes patients treated from 2012 onward. From December 2012 to February 2017, 2712 patients were included in the database according to the following criteria: age of more than 18 years, confirmed diagnosis of AMI presenting with ST-segment elevation myocardial infarction or non–ST-elevation myocardial infarction and treated within 48 hours after the onset of symptoms. All medical data and study end points were collected by trained study coordinators. AMI was defined according to published guidelines.[11,12] The study protocol was performed in accordance with the principles of the Declaration of Helsinki and was approved by the local institutional ethics committee with a waiver for informed consent (No. 2017-P2-123-01), and permission was granted to use data for analysis. For the present analysis, exclusion criteria included (1) chronic renal failure and/or need for regular hemodialysis (n=22) or peritoneal dialysis (n=6); (2) serum creatinine ≥442 μmol/L at first admission (n=9); (3) prior treatment with renal transplantation (n=1); (4) presence of autoimmune disease and sepsis that might result in worsening renal function (n=6); and (5) absence of either the initial or peak creatinine values and admission data (n=574). According to these criteria, this study population consisted of the remaining 2094 patients (Figure 1).

Data Collection and Biomarker Assays

On the basis of renal function and cardiac function, patients were assigned to either the CRS1 or no-CRS1 group. The collected clinical data included (1) basic information including age, sex, duration of hospitalization (days), classification of AMI, blood pressure, heart rate at admission, and body mass index at admission; (2) a medical history including coronary artery disease, percutaneous revascularization, coronary artery bypass grafting, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, peripheral arterial disease, and stroke; (3) treatment and prognosis involving an intra-aortic balloon pump, percutaneous revascularization, drug intervention (angiotensin-converting enzyme inhibitor/angiotensin receptor blocker [ACEI/ARB], diuretic, antiplatelet agent, β-blocker, statins), and clinical outcomes; (4) laboratory data and auxiliary examinations at admission, such as levels of NT-proBNP, creatinine, hs-CRP, hemoglobin, hematocrit, albumin, glucose, and glycated hemoglobin. NT-proBNP levels were assays based on a chemiluminescence enzyme immune assay and MAGTRATION methodology, and measurements were taken by a PATHFAST NT-proBNP analyzer (Mitsubishi Kagaku Iatron, Tokyo, Japan). Serum creatinine

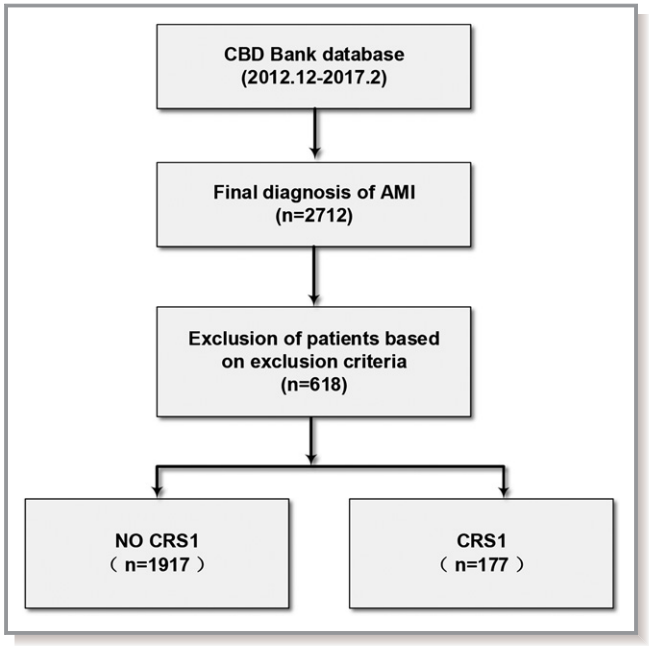

Figure 1. Selection of patient population. AMI indicates acute myocardial infarction; CBD, Cardiovascular Center of Beijing Friendship Hospital Database; CRS1, cardiorenal syndrome type 1.

concentrations were measured using a picric acid method and Beckman Coulter analyzers (Beckman Coulter Inc, Brea, CA). The hs-CRP was measured by an ultrasensitive method based on particle-enhanced immunoturbidimetry (DiaSys Diagnostic System, Holzheim, Germany). Troponin I was measured every 3 to 6 hours, and the peak value for each case was recorded. All the patients underwent echocardiography examination on admission, and the left ventricular ejection fraction was acquired via the modified Simpson method.

Heart Function and Kidney Function: CRS Definition

Heart function was evaluated using the Killip-Kimball classification during the episode, and heart failure was identified if the patient was considered class II or higher. Patients' eGFRs were calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[13] AKI was determined using the Acute Kidney Injury Network criteria[14] and defined as an increase in serum creatinine of ≥0.3 mg/dL or 1.5-fold higher than normal. The baseline serum creatinine was obtained on admission. For some patients, the serum creatinine concentration at discharge was lower than that at admission, and the serum creatinine concentration was considered to be the basal concentration. CRS1 was defined by the sum of these 2 components.[15,16] Acute heart failure was followed by AKI; that is, with a Killip–Kimball score ≥II and AKI. The primary end point of this study was the development of CRS1 during hospitalization.

Statistical Analysis

Continuous variables appeared to have non-Gaussian distributions, and therefore, the data are presented as median values with interquartile ranges. Comparisons between the study groups were performed by nonparametric rank test (Mann-Whitney U-test). Categorical variables are presented as numbers and percentages, and the chi-squared test was used to compare variables between the study groups. Because the distribution of NT-proBNP was highly skewed, log transformation of the data was carried out.

Logistic regression analysis was used to obtain odds ratios (ORs) and 95% confidence intervals (CIs) for the development of CRS1. To determine the factors that could independently predict CRS1, variables that were significant in the univariate logistic regression analysis were incorporated into the multivariate logistic regression analysis. Multivariable analysis was performed to evaluate the effects of the number of abnormal biomarker levels on the risk of developing CRS1.

The receiver operating characteristic (ROC) curve analysis was used to evaluate the discriminatory capability of the biomarkers for CRS1. To control for confounding factors, covariates were included in the ROC analysis, and propensity score matching analysis was performed. The cutoff value was defined for the maximum Youden index. Statistical analyses were performed with using SPSS version 19.0 (SPSS, Chicago, IL) and Med-calc software version 15.8 (MedCalc Software bvba, Mariakerke, Belgium). A 2-sided *P* value of less than 0.05 was considered to indicate a statistically significant difference.

Propensity Score Matching Analysis

Propensity score matching is used to reduce selection bias in observational studies. The matching process was conducted with a minimum-distance scoring method and a 1-to-1 match between the CRS1 group and the no-CRS1 group. In this study, propensity scores were calculated through a binary logistic regression model, including covariates of age, sex, hemoglobin, hematocrit, albumin, glucose, previous coronary artery disease, previous hypertension, previous diabetes mellitus, previous chronic kidney disease, angiography, ACEI and/or ARB use after admission, and diuretic use after admission. Ultimately, 120 CRS1 patients were individually matched to 120 no-CRS1 controls using nearest available score matching with SPSS version 22.0. The ROC curve analysis from the data set after matching was used to further evaluate the discriminatory capability of the biomarkers for CRS1.

Table 1. Distribution of Variables in Patients With AMI According to the Development of CRS1

Characteristic	Total (N=2094)	NO CRS1 (n=1917)	CRS1 (n=177)	*P* Value
Age, y (median, interquartile range)	65 (57, 77)	64 (56, 76)	77 (67, 82)	<0.001
Female (n, %)	612 (29.2)	541 (28.2)	71 (40.1)	0.001
Hospital stay, d (median, interquartile range)	8 (6, 10)	7 (6, 9)	10 (7, 14)	<0.001
STEMI (n, %)	1003 (47.9)	916 (47.8)	87 (49.2)	0.727
Measurements (median, interquartile range)				
Systolic blood pressure at admission, mm Hg	130 (114, 143)	130 (115, 143)	125 (111, 148)	0.509
Diastolic blood pressure at admission, mm Hg	73 (65, 81)	73 (65, 81)	71 (64, 80)	0.142
Heart rate at admission, bpm	74 (65, 82)	74 (65, 84)	83 (69, 97)	<0.001
Body mass index, kg/m^2	25.4 (23.0, 27.7)	25.4 (23.1, 27.7)	24.3 (21.0, 27.6)	0.009
Left ventricular ejection fraction, %	62 (53, 67)	62 (55, 67)	50 (35, 64)	<0.001
Laboratory values (median, interquartile range)				
Hemoglobin at admission, g/L	134 (121, 148)	135 (122, 148)	124 (104.8136.0)	<0.001
Hematocrit at admission, %	40.2 (36.3, 44.0)	40.5 (36.6, 44.3)	37.4 (32.2, 41.1)	<0.001
Albumin at admission, g/dL	38.9 (35.8, 41.7)	39.0 (36.0, 41.8)	36.4 (33.4, 39.7)	<0.001
NT-proBNP at admission, pg/mL	738.0 (207.5, 2817.5)	626.5 (193.0, 2236.8)	5324.0 (2 357.5, 17 730.5)	<0.001
Creatinine at admission, μmol/L	78.0 (68.0, 96.3)	77.0 (67.5, 92.3)	113.0 (89.0147.5)	<0.001
eGFR at admission, mL/(min/1.73 m^2)	83.6 (64.3100.3)	85.6 (67.6101.5)	50.5 (32.9, 68.1)	<0.001
Peak troponin I, ng/mL	4.9 (1.1, 16.1)	3.9 (0.8, 12.4)	5.5 (1.3, 18.9)	0.081
Glucose at admission, mmol/L	7.9 (6.4, 10.8)	7.8 (6.4, 10.7)	8.5 (6.6, 11.8)	0.043
hs-CRP at admission, mg/L	6.6 (2.3, 17.3)	5.9 (2.2, 15.7)	16.5 (8.1, 30.1)	<0.001
Glycated hemoglobin at admission, %	6.0 (5.5, 7.1)	6.0 (5.5, 7.0)	6.2 (5.7, 7.4)	0.055
Medical history (n, %)				
Coronary artery disease	828 (39.5)	737 (38.4)	91 (51.4)	0.001
Percutaneous revascularization	326 (15.6)	290 (15.1)	36 (20.3)	0.067
Coronary artery bypass grafting	45 (2.1)	34 (1.8)	11 (6.2)	<0.001
Hypertension	1383 (66.0)	1244 (64.9)	139 (78.5)	<0.001
Diabetes mellitus	710 (33.9)	633 (33.0)	77 (43.5)	0.005
Dyslipidemia	934 (44.6)	849 (44.3)	85 (48.0)	0.339
Chronic kidney disease	118 (5.6)	81 (4.2)	37 (20.9)	<0.001
Peripheral arterial disease	124 (5.9)	99 (5.2)	25 (14.1)	<0.001
Stroke	356 (17.0)	316 (16.5)	40 (22.6)	0.038
Treatment after admission (n, %)				
IABP	41 (2.0)	30 (1.6)	11 (6.2)	<0.001
Angiography	1669 (79.7)	1587 (82.8)	82 (46.3)	<0.001
Percutaneous revascularization	1482 (70.8)	1417 (73.9)	65 (36.7)	<0.001
ACEI and/or ARB	1426 (68.1)	1339 (69.8)	87 (49.2)	<0.001
Diuretics	309 (14.8)	239 (12.5)	70 (39.5)	<0.001
Antiplatelet agent	1942 (92.7)	1810 (94.4)	132 (74.6)	<0.001
β-blocker	1512 (72.2)	1410 (73.6)	102 (57.6)	<0.001
Statins	1802 (86.1)	1686 (87.9)	116 (65.5)	<0.001

Continued

Table 1. Continued

Characteristic	Total (N=2094)	NO CRS1 (n=1917)	CRS1 (n=177)	*P* Value
Clinical end points (n, %)				
All-cause mortality	63 (3.0)	32 (1.7)	31 (17.5)	<0.001
Cardiac mortality	56 (2.7)	27 (1.4)	29 (16.4)	<0.001

ACEI indicates angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; bpm, beats/min; CRS1, cardiorenal syndrome type 1; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; IABP, intra-aortic balloon pump; NT-proBNP, amino-terminal pro–brain natriuretic peptide; STEMI, ST-segment–elevation myocardial infarction.

Results

Patient Characteristics and the Prevalence of CRS1

A total of 2094 patients presenting with AMI from December 2012 to February 2017 were included in this study. Among the affected inpatients, 656 (31.33%) developed acute heart failure, and 177 (8.45%) developed CRS1. A total of 63 (3%) patients died during hospitalization, and all-cause mortality was higher among those with CRS1 than among those without (17.5% versus 1.7%; $P<0.001$).

The demographic, clinical, and laboratory characteristics of the patients with and without CRS1 are provided in Table 1. There were no significant differences between the groups in the incidence of ST-elevation myocardial infarction, systolic blood pressure, diastolic blood pressure, prior percutaneous revascularization, dyslipidemia, or peak serum levels of troponin I and glycated hemoglobin. Compared with the patients without CRS1, patients who developed CRS1 were older, more often female, had a longer hospital stay, and more frequently presented with a medical history of coronary artery disease, coronary artery bypass grafting, hypertension, diabetes mellitus, chronic kidney disease, peripheral arterial disease, or stroke. The CRS1 group also had higher mean levels of NT-proBNP (5324.0 versus 626.5 pg/mL; $P<0.001$), creatinine (113.0 versus 77.0 μmol/L; $P<0.001$), hs-CRP (16.5 versus 5.9 mg/L; $P<0.001$), and glucose (8.5 versus 7.8 mmol/L; $P=0.043$), as well as lower levels of hemoglobin (124 versus 135 g/L; $P<0.001$), hematocrit (37.4% versus 40.5%; $P<0.001$), and albumin (36.4 versus 39.0 g/dL; $P<0.001$) and a lower eGFR (50.5 versus 85.6 mL/[min·1.73 m^2]; $P<0.001$). It should be noted that the treatment after admission was significantly different. A higher percentage of patients with CRS1 were treated with an intra-aortic balloon pump and diuretics ($P<0.001$), whereas treatments involving an ACEI and/or ARB, antiplatelet agent, β-blocker, statins, angiography, and percutaneous revascularization were used more often in patients without CRS1 (all $P<0.001$).

Predictors of CRS1

Table 2 shows the results of the univariate and multivariate logistic regression analyses. On univariate analysis, increased log(NT-proBNP) and hs-CRP levels and decreased eGFR at admission were significantly associated with CRS1, as were advanced age, female sex, history of coronary artery disease, hypertension, diabetes mellitus, chronic kidney disease, decreased hemoglobin, hematocrit, and albumin, angiography use, ACEI and/or ARB use, increased glucose, and diuretic use. After multivariable adjustment, increased log(NT-proBNP) (OR 2.136; 95% CI 1.422-3.209; $P<0.001$), glucose (OR 1.003; 95% CI 1.000-1.006; $P=0.03$), and hs-CRP (OR 1.031; 95% CI 1.014-1.048; $P<0.001$) as well as diuretic use (OR 1.811; 95% CI 1.130-2.902; $P=0.014$), decreased eGFR (OR 0.967; 95% CI 0.956-0.979; $P<0.001$), and ACEI and/or ARB use (OR 0.509; 95% CI 0.328-0.789; $P=0.003$) were determined to be independent predictors of CRS1 in AMI patients.

ROC Curve Analysis of the Value of NT-proBNP, eGFR, and hs-CRP, as Biomarkers

The results of the ROC analysis detailed in Table 3 revealed that all 3 biomarkers significantly predicted the development of CRS1 (area under the ROC curve [AUC]: NT-proBNP 0.813, eGFR 0.828, and hs-CRP 0.693; all $P<0.01$). According to the maximum Youden indexes, the cutoff values for eGFR, NT-proBNP, and hs-CRP were 71.29 mL/[min·1.73 m^2], 2573 pg/mL, and 8.03 mg/L, respectively. Notably, the specificity of hs-CRP (57.04%) was less than those of eGFR (71.31%) and NT-proBNP (77.82%). The AUC for the combination of eGFR, NT-proBNP, and hs-CRP was 0.856 ($P<0.01$), indicating very good discriminative ability for the prediction of CRS1. Table 4 shows the results of the covariate adjusted model analysis. After including the covariates, the biomarkers individually and together still significantly predicted CRS1 with AUC values of 0.858 for log(NT-proBNP), 0.866 for eGFR, 0.849 for hs-CRP, and 0.882 for the combination of these 3 markers

Table 2. Univariate and Multivariate Logistic Regression Analysis of CRS1 Occurrence in Patients With AMI

	Univariate		Multivariate	
	OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Age, y	1.073 (1.057-1.089)	<0.001	1.021 (0.999-1.045)	0.065
Female, %	1.704 (1.241-2.338)	0.001	0.801 (0.503-1.276)	0.350
Hemoglobin at admission, g/dL	0.969 (0.962-0.977)	<0.001	1.016 (0.974-1.060)	0.458
Hematocrit at admission, %	0.897 (0.874-0.921)	<0.001	0.978 (0.848-1.128)	0.763
Albumin at admission, g/dL	0.892 (0.862-0.923)	<0.001	1.041 (0.986-1.099)	0.146
log(NT-proBNP) at admission	6.005 (4.524-7.971)	<0.001	2.136 (1.422-3.209)*	<0.001
eGFR at admission, mL/(min·1.73 m^2)	0.95 (0.943-0.956)	<0.001	0.967 (0.956-0.979)†	<0.001
Glucose at admission, mmol/L	1.003 (1.001-1.005)	0.002	1.003 (1.000-1.006)	0.03
hs-CRP at admission, mg/L	1.046 (1.035-1.059)	<0.001	1.031 (1.014-1.048)‡	<0.001
Previous coronary artery disease	1.694 (1.244-2.307)	0.001	1.067 (0.691-1.646)	0.770
Previous hypertension	1.979 (1.366-2.867)	<0.001	1.378 (0.813-2.334)	0.234
Previous diabetes mellitus	1.562 (1.143-2.137)	0.005	0.666 (0.397-1.116)	0.123
Previous chronic kidney disease	5.99 (3.916-9.165)	<0.001	1.771 (0.924-3.396)	0.085
Angiography after admission	0.179 (0.131-0.247)	<0.001	0.744 (0.460-1.202)	0.227
ACEI and/or ARB after admission	0.417 (0.306-0.569)	<0.001	0.509 (0.328-0.789)	0.003
Diuretics after admission	4.593 (3.301-6.391)	<0.001	1.811 (1.130-2.902)	0.014

ACEI indicates angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; CI, confidence interval; CRS1, cardiorenal syndrome type 1; eGFR, estimated glomerular filtration rate; hs-CRP, high sensitivity C-reactive protein; NT-proBNP, amino-terminal pro–brain natriuretic peptide; OR, odds ratio.
*The odds ratio and 95%CI for 1 standard deviation change in the logNT-proBNP were 1.792 (1.311–2.450).
†The odds ratio and 95%CI for 1 standard deviation change in the eGFR was 0.424 (0.310–0.576).
‡The odds ratio and 95%CI for 1 standard deviation change in the hs-CRP was 1.429 (1.180–1.747).

(all $P<0.001$). The differences in the AUC values between the individual biomarkers and their combinations (Figure 2) were statistically significant ($P<0.05$), which indicated that the predictive capability of the 3-biomarker panel is better than each individual marker.

After propensity score matching, the baseline age and sex along with hemoglobin, hematocrit, albumin, glucose, history of coronary artery disease, hypertension, diabetes mellitus, chronic kidney disease, angiography use, ACEI and/or ARB use, and diuretic use were not statistically different between the CRS1 and no-CRS1 groups (Table 5). The results of ROC analysis (Table 6, Figure 3) still showed that the discriminatory capability of the 3-biomarker panel was good (AUC 0.863, 95% CI 0.816-0.910) and stronger than that of the individual biomarkers, with AUC values of 0.719 for NT-proBNP, 0.843 for eGFR, and 0.656 for hs-CRP (all $P<0.001$).

Table 3. Prematching Receiver Operating Characteristic Curve Analysis of NT-proBNP, eGFR, and hs-CRP for the Prediction of CRS1

	Cutoff Value	Abnormality (n, %)*		AUC	*P* Value	95% CI	Sensitivity	Specificity	Youden Index
		No-CRS1	CRS1						
eGFR at admission, mL/(min·1.73 m^2)	71.29	550 (28.7)	142 (80.2)	0.828	<0.001	0.811 to 0.844	0.8079	0.7131	0.521
NT-proBNP at admission, pg/mL	2573	385 (22.2)	120 (74.5)	0.813	<0.001	0.777 to 0.849	0.7453	0.7782	0.524
hs-CRP at admission, mg/L	8.03	806 (43.0)	125 (76.2)	0.693	<0.001	0.653 to 0.733	0.7622	0.5704	0.333
NT-proBNP +eGFR+ hs-CRP	…	…	…	0.856	<0.001	0.825 to 0.886	…	…	…

AUC indicates area under the receiver operating characteristic curve; CI, confidence interval; CRS1, cardiorenal syndrome type 1; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, amino-terminal pro–brain natriuretic peptide.
*Abnormal biomarkers levels were defined as eGFR≤71.29 mL/(min·1.73 m^2), NT-proBNP≥2573 pg/mL, and hs-CRP≥8.03 mg/L individually.

Table 4. Prematching Receiver Operating Characteristic Curve Analysis of NT-proBNP, eGFR, and hs-CRP Adjusted by Covariates for the Prediction of CRS1

	AUC	*P* Value	95% CI
Covariates	0.837	<0.001	0.804 to 0.870
eGFR+ covariates	0.866	<0.001	0.850 to 0.881
Log(NT-proBNP)+covariates	0.858	<0.001	0.824 to 0.892
hs-CRP+ covariates	0.849	<0.001	0.832 to 0.865
Log(NT-proBNP)+eGFR+ hs-CRP+covariates	0.882	<0.001	0.850 to 0.913

The covariates included age, sex, hemoglobin, hematocrit, albumin, glucose, previous coronary artery disease, previous hypertension, previous diabetes mellitus, previous chronic kidney disease, angiography, ACEI and/or ARB use after admission, and diuretic use after admission. The differences in the AUC values adjusted by covariates between the individual biomarkers and their combinations were statistically significant, with *P* values of 0.0330 (eGFR+covariates vs Log[NT-proBNP]+eGFR+hs-CRP+covariates), 0.0070 (Log[NT-proBNP]+covariates vs Log[NT-proBNP]+eGFR+hs-CRP+covariates), 0.0062 (hs-CRP+covariates vs Log[NT-proBNP]+eGFR+hs-CRP+covariates), and 0.0008 (covariates vs Log[NT-proBNP]+eGFR+hs-CRP+covariates). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AUC, area under the receiver operating characteristic curve; CI, confidence interval; CRS1, cardiorenal syndrome type 1; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, amino-terminal pro–brain natriuretic peptide.

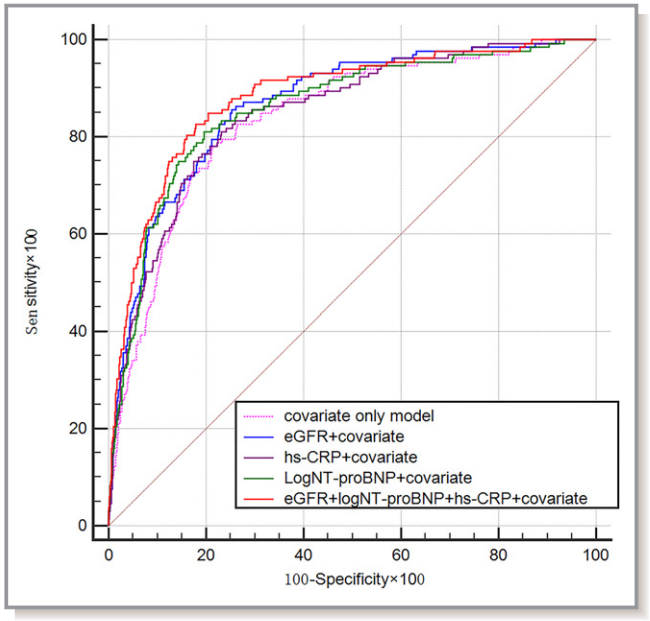

Figure 2. Prematching receiver operating characteristic curve analysis including covariates for the prediction of CRS1 by eGFR, NT-proBNP, and hs-CRP. CRS1 indicates cardiorenal syndrome type 1; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, amino-terminal pro–brain natriuretic peptide.

Association Between Number of Abnormal Biomarker Levels and CRS1

The data presented in Figure 4 illustrate the association between the number of abnormal biomarker levels and the risk of CRS1. Using the cutoff values derived from the ROC analysis to define biomarker levels as normal or abnormal, the risk of CRS1 increased significantly with an increasing number of abnormal biomarker levels. In a multivariate adjusted logistic regression model, the odds of CRS1 were increased by 35-fold if patients presented with abnormal levels of 2 or more biomarkers compared with no abnormal levels (Table 7). This finding implies that abnormal levels of the biomarkers at presentation may facilitate better CRS1 risk stratification.

Discussion

To our knowledge, this is the first study to examine the predictive ability of a combination of 3 traditional biomarkers of heart failure: (NT-proBNP), renal function (eGFR), and inflammation (hs-CRP) for CSR1. The major findings of this study were these: (1) abnormal levels of NT-proBNP, eGFR, and hs-CRP at admission were independent risk factors for in-hospital CRS1; (2) the sensitivity of NT-proBNP, eGFR, and hs-CRP were relatively high, but the specificity of hs-CRP was relatively poor; (3) the discriminatory capability of the 3-biomarker panel was stronger than those of the individual biomarkers; and (4) abnormal levels of 2 or more biomarkers based on the identified cutoff values were associated with an elevated risk of CRS1.

AMI is 1 of the critical conditions that can lead to CRS1. The majority of existing reports noted that CRS1 in patients with acute coronary syndrome was associated with longer hospital stay and higher in-hospital mortality.[17] Recently, in patients who were hospitalized for acute coronary syndrome, the risk of in-hospital mortality associated with CRS1 was greater than the sum of the risks associated with acute heart failure and AKI.[10] CRS1 also was responsible for more than half of all cases of in-hospital mortality. In contrast to acute coronary syndrome, there are few reports in the literature on CRS1 in the setting of only AMI. Our study provides evidence that CRS1 may adversely affect clinical outcomes in AMI patients. In our cohort the all-cause mortality and cardiovascular mortality in the CRS1 group were 9 times higher than those among the group of patients who did not develop CRS1. Therefore, it is important to understand the risk factors and develop methods for early prevention of the development of CRS1.

A large number of studies have evaluated the associations of various predictors with the occurrence of AKI in AMI patients and found that advanced age, hypertension, low body mass index, initial hemodynamic instability, extent of vessel disease, severe Killip class, abnormal heart rate, reduced GFR at presentation, longer door-to-needle time, increased spot urine albumin-to-creatinine ratio, hyperglycemia at admission,

Table 5. Pre- and Postmatching Distribution of Covariates in Patients With AMI According to the Development of CRS1

	Prematching			Postmatching		
Covariate	No-CRS1 (n=1917)	CRS1 (n=177)	*P* Value	No-CRS1 (n=120)	CRS1 (n=120)	*P* Value
Age, y (median, IQR)	64 (56, 76)	77 (67, 82)	<0.001	74 (61, 81)	76.5 (67, 82)	0.091
Min/max	25/99	42/98	…	29/99	50/91	…
≤60 (n, %)	741 (38.7)	22 (12.4)	<0.001	27 (22.5)	16 (13.3)	0.122
61 to 70 (n, %)	513 (26.8)	34 (19.2)		24 (20.0)	22 (18.3)	
71 to 80 (n, %)	405 (21.1)	59 (33.3)		32 (26.7)	47 (39.2)	
≥81 (n, %)	258 (13.5)	62 (35.0)		37 (30.8)	35 (29.2)	
Female (n, %)	541 (28.2)	71 (40.1)	0.001	36 (30)	48 (40)	0.104
Hemoglobin at admission, g/L (median, IQR)	135 (122, 148)	124 (104.8136.0)	<0.001	129 (117.3142.8)	126 (110, 137.8)	0.171
Hematocrit at admission, % (median, IQR)	40.5 (36.6, 44.3)	37.4 (32.2, 41.1)	<0.001	38.55 (35.4, 43.0)	38.35 (33.5, 42.0)	0.195
Albumin at admission, g/dL (median, IQR)	39.0 (36.0, 41.8)	36.4 (33.4, 39.7)	<0.001	37.9 (33.9, 40.7)	37.45 (34.5, 39.9)	0.677
Glucose at admission, mmol/L (median, IQR)	7.8 (6.4, 10.7)	8.5 (6.6, 11.8)	0.043	8.8 (6.7, 13.9)	8.6 (6.5, 12.1)	0.366
Previous coronary artery disease (n, %)	737 (38.4)	91 (51.4)	0.001	55 (45.8)	60 (50)	0.518
Previous hypertension (n, %)	1244 (64.9)	139 (78.5)	<0.001	89 (74.2)	96 (80)	0.282
Previous diabetes mellitus (n, %)	633 (33.0)	77 (43.5)	0.005	41 (34.2)	49 (40.8)	0.286
Previous chronic kidney disease (n, %)	81 (4.2)	37 (20.9)	<0.001	9 (7.5)	18 (15)	0.066
Angiography after admission (n, %)	1587 (82.8)	82 (46.3)	<0.001	61 (50.8)	63 (52.5)	0.796
ACEI and/or ARB after admission (n, %)	1339 (69.8)	87 (49.2)	<0.001	57 (47.5)	67 (55.8)	0.196
Diuretics after admission (n, %)	239 (12.5)	70 (39.5)	<0.001	55 (45.8)	42 (35)	0.087

ACEI indicates angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; CRS1, cardiorenal syndrome type 1; IQR, interquartile range.

history of chronic kidney disease, and decreased hemoglobin levels are associated with worsening renal function (or AKI).[17–22] In the present study we found that baseline cardiorenal dysfunction and inflammation were independent predictors of CRS1 in patients with AMI, which is consistent with previous results. Furthermore, we found that NT-proBNP, eGFR, and hs-CRP had good discriminative ability for the prediction of CRS1.

Table 6. Postmatching Receiver Operating Characteristic Curve Analysis of NT-proBNP, eGFR, and hs-CRP for the Prediction of CRS1

	AUC	*P* Value	95% CI
eGFR at admission, mL/(min·1.73 m^2)	0.843	<0.001	0.792 to 0.894
NT-proBNP at admission, pg/mL	0.719	<0.001	0.654 to 0.784
hs-CRP at admission, mg/L	0.656	<0.001	0.587 to 0.725
NT-proBNP+eGFR+hs-CRP	0.863	<0.001	0.816 to 0.910

The differences in the AUC values between the individual biomarkers and their combinations were statistically significant, with *P* values of 0.0372 (eGFR vs NT-proBNP+eGFR+hs-CRP), <0.0001 (NT-proBNP vs NT-proBNP+eGFR+hs-CRP), and <0.0001 (hs-CRP vs NT-proBNP+eGFR+hs-CRP). AUC indicates area under the receiver operating characteristic curve; CI, confidence interval; CRS1, cardiorenal syndrome type 1; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, amino-terminal pro–brain natriuretic peptide.

The reason may be based on the correlation of these markers with the pathophysiology mechanisms of CRS1.

Many studies have emerged in recent years trying to explain the pathophysiology of CRS1, and they have primarily focused on the hemodynamic and nonhemodynamic mechanisms. The traditional theory is that hypoperfusion of the kidneys followed by "forward failure" might lead to acute tubular necrosis, which is regarded as the key underlying mechanism contributing to renal dysfunction in the acute clinical setting.[23,24] However, a growing body of research indicates that elevations in right atrial pressure, which correlate with central venous pressure rather than a decline in cardiac output and/or cardiac index, are associated with declining renal function.[5,25–28] NT-proBNP has already been established as a diagnostic and prognostic marker in chronic as well as acute heart failure, and this protein is rapidly released from cardiomyocytes after stretching. Moreover, recent studies have reported that NT-proBNP is a strong independent predictor of worsening renal function within 18 months in patients with systolic heart failure[29] and a biochemical marker of integrated cardiorenal function in the chronic phase after myocardial infarction.[30] In the present study we hypothesized that NT-proBNP is an indirect indicator of elevations in central venous pressure and/or right atrial pressure during the pathophysiology of CRS1. Accordingly, we

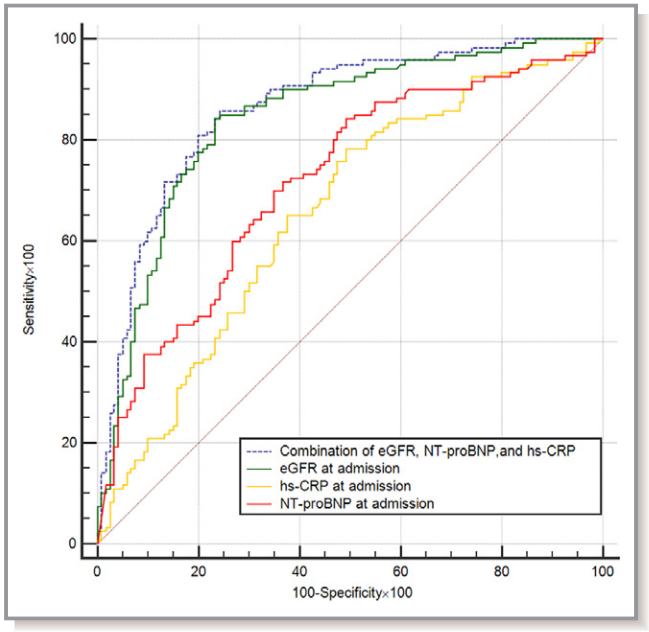

Figure 3. Postmatching receiver operating characteristic curve analysis for the prediction of CRS1 by eGFR, NT-proBNP, and hs-CRP. CRS1 indicates cardiorenal syndrome type 1; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, amino-terminal pro–brain natriuretic peptide.

found that NT-proBNP had good discriminatory ability and could serve as an indirect marker of CRS1 in patients with AMI.

In addition to hemodynamic pathways inflammation plays a pivotal role in the nonhemodynamic mechanisms of CRS1 pathophysiology. In a study by Virzi et al, serum levels of the proinflammatory cytokines tumor necrosis factor-α and interleukin-6 were significantly elevated in CRS1 patients compared with healthy controls.[31] Another recent study found that elevated levels of inflammatory factors such as interleukin-1β, endothelin-1, interleukin-10, and resolvin-D1 were positively correlated with worsening renal function in patients with ACS.[7] Among the various cytokines and mediators, hs-CRP has received significant attention due to its association with atherosclerosis and cardiac disease as well as its prognostic value for heart failure and long-term mortality.[32-34] The results of the current study indicate that hs-CRP is a powerful and independent predictor of CRS1. Despite its poor specificity, hs-CRP showed relatively good sensitivity at a cutoff value of 8.03 mg/L. Our results are consistent with those of a previous report indicating that hs-CRP >9 mg/L at admission is an independent predictor of AKI in patients with ST-elevation myocardial infarction following primary percutaneous coronary intervention.[35] Interestingly, elevation of hs-CRP not only is a marker of AKI but also plays a pathogenic role in AKI by inhibiting tubular epithelium cell regeneration and altering macrophage polarization.[36,37] Therefore, anti-inflammatory treatment targeting the hs-CRP pathway may offer a new therapeutic approach to preventing or treating CRS1.

So far, the ideal marker for early detection of CRS1 has remained elusive. Several novel biomarkers for early detection of AKI have been investigated in patients with heart failure, including cystatin C, neutrophil gelatinase-associated lipocalin, N-acetyl-β-D-glucosaminidase, kidney injury molecule-1, interleukin-18, and tissue inhibitor of metalloproteinase-2.[38,39] These indicators have different clinical significance and features. However, no single marker satisfied the conditions of high organ specificity, high sensitivity for diagnosis, and being reflective of the disease course. Therefore, a multimarker model has been proposed for risk prediction. The current analysis represents the first examination of the combination of NT-proBNP, eGFR, and hs-CRP for predicting CRS1 in patients with AMI. This combination of biomarkers may be used to predict CRS1 and to facilitate risk stratification of AMI patients.

Study Limitations

We acknowledge several limitations in our study. First, this was a single-center study, and our findings may not apply to other samples of patients in whom CRS1 was defined according to different criteria. Second, we did not investigate the contribution of nephrotoxic drugs to CRS1 development. Although we performed adjustment for pharmacological

Table 7. Multivariable Logistic Regression Analysis of Number of Abnormal Biomarker Levels and the Odds of Developing CRS1

No. of Abnormal Biomarkers*	No-CRS1 (n, %)	CRS1 (n, %)	Adjusted OR (95% CI)†	*P* Value
0	657 (99.4)	4 (0.6)	1	…
1	620 (96.3)	24 (3.7)	8.907 (2.065-38.409)	0.003
≥2	426 (77.5)	124 (22.5)	36.188 (8.534-153.455)	<0.001

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; CRS1, cardiorenal syndrome type 1; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, amino-terminal pro–brain natriuretic peptide; OR, odds ratio.

*Cutoff values for abnormal biomarker levels were eGFR≤71.29 mL/(min·1.73 m^2), NT-proBNP≥2573 pg/mL, and hs-CRP≥8.03 mg/L.

†Adjusted by age, sex, hemoglobin at admission, hematocrit at admission, albumin at admission, glucose at admission, previous coronary artery disease, previous hypertension, previous diabetes mellitus, previous chronic kidney disease, angiography, ACEI and/or ARB use after admission, and diuretic use after admission.

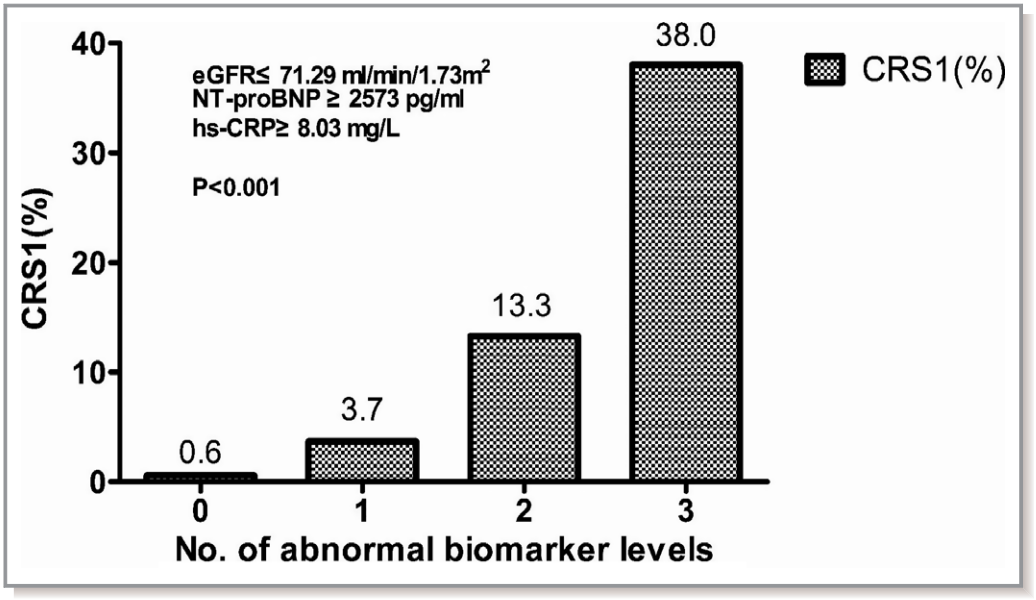

Figure 4. Association of the number of abnormal biomarker levels based on the identified cutoff values and the risk of CRS1. The risk of developing CRS1 increased significantly with an increase in the number of biomarkers showing abnormal levels according to the identified cutoff values. CRS1 indicates cardiorenal syndrome type 1; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, amino-terminal pro–brain natriuretic peptide.

treatments and the catheter laboratory procedure, the amount of contrast agent was unknown. Third, as discussed in other studies on CRS1, the measurement of serum creatinine for evaluation of dynamic changes in renal function was performed at variable time intervals in our study. Fourth, some baseline clinical variables may have been missed. Therefore, it is possible that unmeasured or residual confounding factors may explain some of our results. Last, it should be noted that our study was an observational study and not an interventional study. The characteristics and clinical course of CRS1 may have been influenced by different treatments, causing our results to differ slightly from those of later trials. Further prospective multicenter studies are needed to validate our findings and identify even better multimarker models including other existing biomarkers and parameters.

In summary, we assessed the performance of 3 traditional markers (NT-proBNP, eGFR, and hs-CRP) for detecting the development of CRS1 in a cohort of 2094 patients with AMI. These 3 simple markers are easy to measure and apply in clinical practice. Because of their relation to the pathophysiology of CRS1, NT-proBNP, eGFR, and hs-CRP at admission were found to be independent risk factors for in-hospital CRS1 and to show good discriminative ability. The combination of the 3 biomarkers showed better predictive capability than any of the biomarkers individually. Abnormal levels of 2 or more of these markers according to the identified cutoff values were associated with an elevated risk of CRS1. Therefore, the multimarker panel of NT-proBNP, eGFR, and hs-CRP may assist in the prediction of CRS1 and the corresponding risk stratification of patients with AMI.

Disclosures

None.

References

1. Ronco C, McCullough P, Anker SD, Anand I, Aspromonte N, Bagshaw SM, Bellomo R, Berl T, Bobek I, Cruz DN, Daliento L, Davenport A, Haapio M, Hillege H, House AA, Katz N, Maisel A, Mankad S, Zanco P, Mebazaa A, Palazzuoli A, Ronco F, Shaw A, Sheinfeld G, Soni S, Vescovo G, Zamperetti N, Ponikowski P; Acute Dialysis Quality Initiative consensus. Cardio-renal syndromes: report from the consensus conference of the acute dialysis quality initiative. *Eur Heart J*. 2010;31:703–711.
2. Ronco C. The cardiorenal syndrome: basis and common ground for a multidisciplinary patient-oriented therapy. *Cardiorenal Med*. 2011;1:3–4.
3. Roy AK, Mc Gorrian C, Treacy C, Kavanaugh E, Brennan A, Mahon NG, Murray PT. A comparison of traditional and novel definitions (RIFLE, AKIN, and KDIGO) of acute kidney injury for the prediction of outcomes in acute decompensated heart failure. *Cardiorenal Med*. 2013;3:26–37.
4. Virzi GM, Clementi A, Brocca A, de Cal M, Vescovo G, Granata A, Ronco C. The hemodynamic and nonhemodynamic crosstalk in cardiorenal syndrome type 1. *Cardiorenal Med*. 2014;4:103–112.
5. Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, Young JB, Tang WH. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. *J Am Coll Cardiol*. 2009;53:589–596.
6. Cho E, Kim M, Ko YS, Lee HY, Song M, Kim MG, Kim HK, Cho WY, Jo SK. Role of inflammation in the pathogenesis of cardiorenal syndrome in a rat myocardial infarction model. *Nephrol Dial Transpl*. 2013;28:2766–2778.
7. Ortega-Hernandez J, Springall R, Sanchez-Munoz F, Arana-Martinez JC, Gonzalez-Pacheco H, Bojalil R. Acute coronary syndrome and acute kidney injury: role of inflammation in worsening renal function. *BMC Cardiovasc Disord*. 2017;17:202.
8. Fox CS, Muntner P, Chen AY, Alexander KP, Roe MT, Wiviott SD. Short-term outcomes of acute myocardial infarction in patients with acute kidney injury: a

report from the National Cardiovascular Data Registry. *Circulation*. 2012;125:497–504.

9. Amin AP, Spertus JA, Reid KJ, Lan X, Buchanan DM, Decker C, Masoudi FA. The prognostic importance of worsening renal function during an acute myocardial infarction on long-term mortality. *Am Heart J*. 2010;160:1065–1071.
10. Gonzalez RP, Comba PC, Esteban MR, Sanchez JJA, Afonso JH, Perez MDR, Rodriguez IM, Diaz BB, Elosua R, de Leon AC. Incidence, mortality and positive predictive value of type 1 cardiorenal syndrome in acute coronary syndrome. *PLoS One*. 2016;11:e0167166.
11. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, Caso P, Dudek D, Gielen S, Huber K, Ohman M, Petrie MC, Sonntag F, Uva MS, Storey RF, Wijns W, Zahger D. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the task force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2011;32:2999–3054.
12. Steg PG, James SK, Atar D, Badano LP, Blomstrom-Lundqvist C, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F, Gershlick AH, Giannuzzi P, Halvorsen S, Huber K, Juni P, Kastrati A, Knuuti J, Lenzen MJ, Mahaffey KW, Valgimigli M, van't Hof A, Widimsky P, Zahger D. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2012;33:2569–2619.
13. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF III, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612.
14. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A. Acute kidney injury network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care*. 2007;11:R31.
15. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. *J Am Coll Cardiol*. 2008;52:1527–1539.
16. McCullough PA, Kellum JA, Haase M, Muller C, Damman K, Murray PT, Cruz D, House AA, Schmidt-Otti KM, Vescovo G, Bagshaw SM, Hoste EA, Briguori C, Braam B, Chawla LS, Costanzo MR, Tumlin JA, Herzog CA, Mehta RL, Rabb H, Shaw AD, Singbartl K, Ronco C. Pathophysiology of the cardiorenal syndromes: executive summary from the eleventh consensus conference of the Acute Dialysis Quality Initiative (ADQI). *Contrib Nephrol*. 2013;182:82–98.
17. Eren Z, Ozveren O, Buyukoner E, Kaspar E, Degertekin M, Kantarci G. A single-centre study of acute cardiorenal syndrome: incidence, risk factors and consequences. *Cardiorenal Med*. 2012;2:168–176.
18. Choe JC, Cha KS, Ahn J, Park JS, Lee HW, Oh J-H, Kim JS, Choi JH, Park YH, Lee HC, Kim JH, Chun KJ, Hong TJ, Ahn Y, Jeong MH. Persistent renal dysfunction after percutaneous coronary intervention in patients with acute myocardial infarction: incidence, predictors, and impact on prognosis. *Angiology*. 2017;68:159–167.
19. Vavalle JP, van Diepen S, Clare RM, Hochman JS, Weaver WD, Mehta RH, Pieper KS, Patel MR, Patel UD, Armstrong PW, Granger CB, Lopes RD. Renal failure in patients with ST-segment elevation acute myocardial infarction treated with primary percutaneous coronary intervention: predictors, clinical and angiographic features, and outcomes. *Am Heart J*. 2016;173:57–66.
20. Tziakas D, Chalikias G, Kareli D, Tsigalou C, Risgits A, Kikas P, Makrygiannis D, Chatzikyriakou S, Kampouromiti G, Symeonidis D, Voudris V, Konstantinides S. Spot urine albumin to creatinine ratio outperforms novel acute kidney injury biomarkers in patients with acute myocardial infarction. *Int J Cardiol*. 2015;197:48–55.
21. Moriyama N, Ishihara M, Noguchi T, Nakanishi M, Arakawa T, Asaumi Y, Kumasaka L, Kanaya T, Miyagi T, Nagai T, Yamane T, Fujino M, Honda S, Fujiwara R, Anzai T, Kusano K, Goto Y, Yasuda S, Ogawa H. Admission hyperglycemia is an independent predictor of acute kidney injury in patients with acute myocardial infarction. *Circ J*. 2014;78:1475–1480.
22. Queiroz RE, de Oliveira LS, de Albuquerque CA, Santana C DE A, Brasil PM, Carneiro LL, Liborio AB. Acute kidney injury risk in patients with ST-segment elevation myocardial infarction at presentation to the ED. *Am J Emerg Med*. 2012;30:1921–1927.
23. Ronco C, Cicoira M, McCullough PA. Cardiorenal syndrome type 1. *J Am Coll Cardiol*. 2012;60:1031–1042.
24. Schefold JC, Filippatos G, Hasenfuss G, Anker SD, von Haehling S. Heart failure and kidney dysfunction: epidemiology, mechanisms and management. *Nat Rev Nephrol*. 2016;12:610–623.
25. Nohria A, Hasselblad V, Stebbins A, Pauly DF, Fonarow GC, Shah M, Yancy CW, Califf RM, Stevenson LW, Hill JA. Cardiorenal interactions: insights from the escape trial. *J Am Coll Cardiol*. 2008;51:1268–1274.
26. Gnanaraj JF, von Haehling S, Anker SD, Raj DS, Radhakrishnan J. The relevance of congestion in the cardio-renal syndrome. *Kidney Int*. 2013;83:384–391.
27. Chen KP, Cavender S, Lee J, Feng M, Mark RG, Celi LA, Mukamal KJ, Danziger J. Peripheral edema, central venous pressure, and risk of AKI in critical illness. *Clin J Am Soc Nephrol*. 2016;11:602–608.
28. Damman K, van Deursen VM, Navis G, Voors AA, van Veldhuisen DJ, Hillege HL. Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. *J Am Coll Cardiol*. 2009;53:582–588.
29. Pfister R, Muller-Ehmsen J, Hagemeister J, Hellmich M, Erdmann E, Schneider CA. NT-pro-BNP predicts worsening renal function in patients with chronic systolic heart failure. *Intern Med J*. 2011;41:467–472.
30. Luchner A, Hengstenberg C, Lowel H, Trawinski J, Baumann M, Riegger GA, Schunkert H, Holmer S. N-terminal pro-brain natriuretic peptide after myocardial infarction: a marker of cardio-renal function. *Hypertension*. 2002;39:99–104.
31. Virzi GM, Torregrossa R, Cruz DN, Chionh CY, de Cal M, Soni SS, Dominici M, Vescovo G, Rosner MH, Ronco C. Cardiorenal syndrome type 1 may be immunologically mediated: a pilot evaluation of monocyte apoptosis. *Cardiorenal Med*. 2012;2:33–42.
32. Araujo JP, Lourenco P, Azevedo A, Frioes F, Rocha-Goncalves F, Ferreira A, Bettencourt P. Prognostic value of high-sensitivity C-reactive protein in heart failure: a systematic review. *J Card Fail*. 2009;15:256–266.
33. Kozdag G, Ertas G, Kilic T, Acar E, Agir A, Sahin T, Cetin M, Bildirici U, Ural D. Elevated level of high-sensitivity C-reactive protein is important in determining prognosis in chronic heart failure. *Med Sci Monit*. 2010;16:Cr156–Cr161.
34. Suleiman M, Khatib R, Agmon Y, Mahamid R, Boulos M, Kapeliovich M, Levy Y, Beyar R, Markiewicz W, Hammerman H, Aronson D. Early inflammation and risk of long-term development of heart failure and mortality in survivors of acute myocardial infarction: predictive role of C-reactive protein. *J Am Coll Cardiol*. 2006;47:962–968.
35. Shacham Y, Leshem-Rubinow E, Steinvil A, Keren G, Roth A, Arbel Y. High sensitive C-reactive protein and the risk of acute kidney injury among ST elevation myocardial infarction patients undergoing primary percutaneous intervention. *Clin Exp Nephrol*. 2015;19:838–843.
36. Tang Y, Huang XR, Lv J, Chung AC, Zhang Y, Chen JZ, Szalai AJ, Xu A, Lan HY. C-reactive protein promotes acute kidney injury by impairing g1/s-dependent tubular epithelium cell regeneration. *Clin Sci (Lond)*. 2014;126:645–659.
37. Pegues MA, McCrory MA, Zarjou A, Szalai AJ. C-reactive protein exacerbates renal ischemia-reperfusion injury. *Am J Physiol Renal Physiol*. 2013;304:F1358–F1365.
38. McCullough PA, Jefferies JL. Novel markers and therapies for patients with acute heart failure and renal dysfunction. *Am J Med*. 2015;128:312.e1–312.e22.
39. Palazzuoli A, McCullough PA, Ronco C, Nuti R. Kidney disease in heart failure: the importance of novel biomarkers for type 1 cardio-renal syndrome detection. *Intern Emerg Med*. 2015;10:543–554.