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Independent prognostic value of the congestion and renal index in patients with acute heart failure

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ABSTRACT

BACKGROUND Clinical outcomes are poor if patients with acute heart failure (AHF) are discharged with residual congestion in the presence of renal dysfunction. However, there is no single indication to reflect the combined effects of the two related pathophysiological processes. We, therefore, proposed an indicator, congestion and renal index (CRI), and examined the associations between the CRI and one-year outcomes and the incremental prognostic value of CRI compared with the established scoring systems in a multicenter prospective cohort of AHF.

METHODS We enrolled AHF patients and calculated the ratio of thoracic fluid content index divided by estimated glomerular filtration rate before discharge, as CRI. Then we examined the associations between CRI and one-year outcomes.

RESULTS A total of 944 patients were included in the analysis (mean age 63.3 ± 13.8 years, 39.3% women). Compared with patients with CRI ≤ 0.59 mL/min per kΩ, those with CRI > 0.59 mL/min per kΩ had higher risks of cardiovascular death or HF hospitalization (HR = 1.56 [1.13–2.15]) and all-cause death or all-cause hospitalization (HR = 1.33 [1.01–1.74]). CRI had an incremental prognostic value compared with the established scoring system.

CONCLUSIONS In patients with AHF, CRI is independently associated with the risk of death or hospitalization within one year, and improves the risk stratification of the established risk models.

Heart failure (HF) is a major global public health burden, affecting 64 million people worldwide.[1] An important component of this burden is acute HF (AHF) hospitalizations.[2] Patients hospitalized for AHF are at high risk of morbidity and mortality, with 90-day readmission rates and one-year mortality reaching 10%–30%.[3] Of those patients who survived to discharge, a further 10%-15% died within 90 days and about one-third were re-admitted for a variety of reasons.[4,5] Identification of patients at high risk for adverse outcomes before discharge is important for developing targeted therapeutic interventions, such as disease monitoring, device therapy, transplantation, or hospice care.[6–8]

Residual congestion and renal dysfunction are related and both associated with adverse outcomes in patients with AHF.[9,10] From the pathophysiologic perspective, renal dysfunction exacerbates fluid overload, and persistent congestion accelerates systemic

under-perfusion and conversely aggravates renal dysfunction.[11–13] However, there is no single indicator to reflect the combined effects of the two related pathophysiological processes, partly due to lacking an objective and quantitative measurement of congestion status. The traditional approach to evaluate congestion status is based on physical examination and has limited specificity and reliability.[14] Thoracic fluid content index (TFCI) is an objective and quantitative indicator of fluid volume in the thorax measured by impedance cardiography (ICG).[15–19] Several trials had investigated the value of thoracic impedance as an accurate way to assess volume status using impedance-based implantable devices.[20–22]

We hypothesize that a single novel indicator, congestion and renal index (CRI), which is calculated as TFCI divided by estimated glomerular filtration rate (eGFR), could discriminate high risk patients and serve as a potential tool for risk stratification in the clinical practice. Accordingly, in a multicenter prospective cohort of AHF, we measured CRI before index discharge, and examined the associations between CRI and one-year composite outcome of cardiovascular death or hospitalization for HF, and between CRI and a composite of all-cause death or all-cause hospitalization.

METHODS

Study Design and Population

In the China Patient-centered Evaluative Assessment of Cardiac Events Prospective Heart Failure Study (China PEACE 5p-HF Study), we included 996 patients from eight hospitals (Supplemental Table S1) who underwent standardized ICG test before discharge from the index hospitalization between September 2016 and April 2018. The protocol of China PEACE 5p-HF Study has been published.[23] Patients aged 18 years or older, hospitalized for HF (new-onset or decompensated chronic HF), and assessed by local physicians were enrolled in the study. After excluding 42 patients with missing serum creatinine data at discharge and 10 patients with serum creatinine or TFCI outliers, we finally included a total of 944 patients in the analyses. The patients completed a baseline interview during the index hospitalization and were followed-up at 1-, 6-, and 12-months after discharge.

The investigation conforms with the principles outlined in the Declaration of Helsinki. The ethics committee of Fuwai Hospital and the local ethics committees at sites approved the study. All the patients signed a written informed consent. The study was registered on www.clinicaltrials.gov (NCT02878811).

Patient Characteristics

Patient characteristics were collected from the medical record of the index hospitalization and face-to-face interviews during hospitalization. Clinical characteristics included medical history, symptoms and signs, laboratory tests, and medication treatment. Body mass index was calculated according to the height and weight measured before ICG test. Comorbidities were defined based on discharge diagnosis or medical history. Diabetes mellitus was also defined according to a glycated hemoglobin A1c ≥ 6.5 mmol/L from central laboratory examination (local laboratory if central laboratory tests were not available). Anemia was also defined according to hemoglobin at admission < 120 g/L for male and < 110 g/L for female. Current smoker was defined according to the medical records of the index hospitalization. Patients who had never smoked or had quit were non-current smokers.

Left ventricular ejection fraction (LVEF) was uniformly measured within 7-10 days of admission by trained physicians according to the standard protocol. HF was categorized by different LVEFs: HF with reduced ejection fraction (HFrEF, LVEF ≤ 40%), HF with mildly reduced ejection fraction (HFmrEF, LVEF 41%-49%), and HF with preserved ejection fraction (HFpEF, LVEF ≥ 50%). Kansas City Cardiomyopathy Questionnaire-12 (KCCQ-12), a short version of the original 23-item instrument, was performed within two days of admission. N-terminal pro-B-type natriuretic peptide (NT-proBNP) was analyzed in central laboratory. The results of local laboratory (0.8%) were used if central laboratory tests were not available.

Serum creatinine was determined by the last record before discharge, and transformed into eGFR with the modified abbreviated Modification of Diet in Renal Disease equation adapted for the Chinese patients.[24] We provided uniformed equipment of

ICG (CHM T3002/P3005 HDpro) to all sites. ICG was performed by a trained local physician after the patient reached a stable state before discharge. Four dual ICG sensors were placed on the patient in the supine position: above the base of neck, under each ear, and one on either side of thorax in the mid-axillary line at the level of the xiphoid. The ICG reports were checked and corrected with the original ICG waveform to ensure data reliability. Thoracic fluid content (/KΩ) was calculated from basis impedance (Z0) as its reciprocal (Thoracic fluid content = 1000/Z0), and indexed to body surface area to yield TFCI (kΩ/m^2). Body surface area was calculated according to the Stevenson formula (body surface area = 0.0061 × H + 0.0128 × BM – 0.1529), where BM was body mass in kilograms and H was height in centimeters. CRI was calculated by the ratios of TFCI and eGFR.

Outcomes

The primary outcome was the time to the first occurrence of a composite of cardiovascular death or HF hospitalization during the first year after discharge from the index hospitalization. We also included the time to the first occurrence of a composite of all-cause death or all-cause hospitalization as the secondary outcome. Information on patient survival status and hospitalization events were collected from interviews, medical documents, and death registry. Outcome events were centrally adjudicated by trained clinicians according to standard criteria.[25] Cardiovascular death was defined as sudden cardiac death, or death due to HF, cerebrovascular events, coronary heart disease, or other cardiovascular causes. If there is no evidence of a cardiovascular cause of death, we counted it as non-cardiovascular death.

Statistical Analyses

We used percentage to describe categorical variables and mean with standard deviation or median with interquartile to describe continuous variables where appropriate. We used restricted cubic splines to examine the non-linearity relationships between CRI and the outcomes (Supplemental Figure S1). Three knots were used and placed at the 10th, 50th, and 90th percentiles of CRI (at 0.30, 0.50, and 1.09 mL/min per kΩ, respectively). We identified non-linearity relationships between CRI and the outcomes (non-linear association: $P < 0.01$), and therefore included CRI as a categorical variable in the model. Cut-off scores balancing sensitivity and specificity were determined by using the Youden index, which was calculated by (sensitivity + specificity – 1). A CRI value of 0.59 mL/min per kΩ corresponded to the highest Youden index for the primary outcome. We divided patients into two groups based on the cut-off value of CRI, the lower group (CRI ≤ 0.59 mL/min per kΩ) and the higher group (CRI > 0.59 mL/min per kΩ), and compared the baseline characteristics between the two groups, using Wilcoxon test for continuous variables and chi-square test for categorical variables.

As the lower and higher groups differed in clinical and demographic baseline variables (Supplemental Table S2), we used inverse probability treatment weighting (IPTW) to balance the differences in baseline characteristics between groups. A propensity score model was estimated using logistic regression, with the higher group as the 'treatment' group and the following characteristics as covariates: age, gender, systolic blood pressure, New York Heart Association class, LVEF class, presence of diabetes mellitus, coronary heart disease, anemia, valvular heart disease, chronic obstructive pulmonary disease, NT-proBNP, and in-hospital medication treatment (angiotensin-converting enzyme inhibitors or angiotensin receptor blocker, β blocker, and aldosterone antagonist). NT-proBNP was included in the model after logarithmic transformation. These variables were specified before outcome analyses based on clinical significance and univariate analyses. Standardized mean differences were examined to assess the balance between groups before and after weighting, and a value below 10% was considered as indicating the clinically meaningful balance of a covariate.[26] The crude and IPTW-weighted cumulative incidence rate curves were illustrated and Log-rank tests were used to compare the cumulative incidences of outcomes between the two groups. Treatment effects were assessed for the whole weighted population in terms of hazard ratio (HR) by Cox proportional hazard models and Fine-Gray proportional sub-distribution hazards model to account for non-cardiovascular death as a competing risk for cardiovascular death. The proportional hazards assumption was assessed by the curve of log[–logS(t)] to time, and the assumption was validated. We also performed subgroup analyses by introducing inter-

action terms, including age, sex, body mass index, New York Heart Association class, LVEF class, eGFR, TFCI, comorbidities, and the use of intravenous loop diuretic.

The incremental prognostic value was assessed by adding CRI to modified Get With the Guidelines–HF (GWTG-HF) scoring system[27,28] and Enhanced Feedback for Effective Cardiac Treatment (EFFECT) scoring system combined with NT-proBNP,[29] as both of the two scoring systems were derived from acute HF and had similar outcomes and modeling methods to our study with strong predictive power. The C statistic, continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were calculated. 95% confidence intervals (CIs) of NRIs and IDIs were obtained by bootstrapping. The cut-off value, the area under curve and the incremental prognostic value of CRI were validated by 1000 times of 10-folds cross-validations. For each cross-validation procedure, 850 patients were randomly selected as the training set, and the rest of the samples were treated as the testing set (94 patients).

Hemoglobin (n = 19), LVEF (n = 44), and NT-proBNP (n = 3) had missing values and were imputed by medians in the main analyses. The P-value < 0.05 (two-sided test) was considered statistically significant. SAS version 9.4 and R version 4.0.2 were used for data analysis.

RESULTS

Baseline Characteristics

The mean age of all 944 subjects was 63 ± 14 years, and 39% were women. There were 431 (46%) patients with HFrEF, 176 (19%) with HFmrEF, and 293 (31%) with HFpEF. At discharge, 176 (19%) patients had an eGFR < 60 mL/min per 1.73 m^2. The median value of TFCI was 24.6 (Interquartile range 21.0-29.3)/kΩ per m^2. The CRI ranged from 0.15 to 4.73 mL/min per kΩ (median = 0.50, interquartile range: 0.38-0.70) (Table 1).

Table 1 Baseline characteristics by cut-off value of congestion and renal index.

Characteristics	Total (n = 944)	CRI ≤ 0.59 mL/min per kΩ (n = 597)	CRI > 0.59 mL/min per kΩ (n = 347)	P
Age, yrs	63.3 ± 13.8	59.8 ± 14.0	69.2 ± 11.3	< 0.01
Women	371 (39.3%)	223 (37.4%)	148 (42.7%)	0.11
Current smokers	226 (23.9%)	161 (27.0%)	65 (18.7%)	< 0.01
BMI, kg/m^2				
BMI < 18.5	67 (7.1%)	28 (4.7%)	39 (11.2%)	< 0.01
18.5 ≤ BMI < 24.0	379 (40.1%)	220 (36.9%)	159 (45.8%)	< 0.01
BMI ≥ 24.0	498 (52.8%)	349 (58.5%)	149 (42.9%)	< 0.01
NYHA class				
Class II	89 (9.4%)	71 (11.9%)	18 (5.2%)	< 0.01
Class III	345 (36.5%)	234 (39.2%)	111 (32.0%)	0.03
Class IV	510 (54.0%)	292 (48.9%)	218 (62.8%)	< 0.01
KCCQ-12 score	45.2 (21.6%)	47.9 (21.6%)	40.5 (20.8%)	< 0.01
SBP, mmHg	132.0 ± 24.3	130.4 ± 23.2	134.7 ± 25.9	0.02
DBP, mmHg	81.0 ± 16.1	81.3 ± 15.9	80.4 ± 16.5	0.55
HR, beats/min	88.3 ± 23.3	88.9 ± 23.0	87.4 ± 23.8	0.16
Signs/Symptoms at admission				
Rales	386 (40.9%)	207 (34.7%)	179 (51.6%)	< 0.01
Orthopnea	392 (41.5%)	222 (37.2%)	170 (49.0%)	< 0.01
Edema	426 (45.1%)	243 (40.7%)	183 (52.7%)	< 0.01
Jugular vein distension	100 (10.6%)	53 (8.9%)	47 (13.5%)	0.03
EF, %	43.0 ± 14.7	42.1 ± 14.3	44.5 ± 15.2	0.03
LVEF				

Continued

Characteristics	Total (n = 944)	CRI ≤ 0.59 mL/min per kΩ (n = 597)	CRI > 0.59 mL/min per kΩ (n = 347)	P
HFrEF (LVEF ≤ 40%)	431 (45.7%)	288 (48.2%)	143 (41.2%)	0.04
HFmrEF (LVEF 41%-49%)	176 (18.6%)	102 (17.1%)	74 (21.3%)	0.11
HFpEF (LVEF ≥ 50%)	293 (31.0%)	182 (30.5%)	111 (32.0%)	0.63
Unrecorded	44 (4.70%)	25 (4.2%)	19 (5.5%)	0.37
Medical history				
Coronary heart disease	515 (54.6%)	305 (51.1%)	210 (60.5%)	< 0.01
Hypertension	499 (52.9%)	291 (48.7%)	208 (59.9%)	< 0.01
Atrial fibrillation	369 (39.1%)	228 (38.2%)	141 (40.6%)	0.46
Diabetes mellitus	323 (34.2%)	185 (31.0%)	138 (39.8%)	< 0.01
Valvular heart disease	235 (24.9%)	151 (25.3%)	84 (24.2%)	0.71
COPD	210 (22.2%)	124 (20.8%)	86 (24.8%)	0.15
Anemia	199 (21.1%)	84 (14.1%)	115 (33.1%)	< 0.01
Ischemic stroke	143 (15.1%)	83 (13.9%)	60 (17.3%)	0.16
Laboratory results				
eGFR at admission, mL/min per 1.73 m^2	79.4 ± 26.3	89.3 ± 23.2	62.4 ± 22.2	< 0.01
eGFR at discharge, mL/min per 1.73 m^2	87.9 ± 33.3	103.5 ± 28.8	60.9 ± 20.9	< 0.01
eGFR at discharge < 60, mL/min per 1.73 m^2	176 (18.6%)	8 (1.3%)	168 (48.4%)	< 0.01
NT-proBNP at admission, ng/L	1264 (576-2833)	901 (420-1929)	2409 (1171-5446)	< 0.01
TFCI, kΩ/m^2	24.6 (21.0-29.3)	22.4 (19.6-25.5)	29.2 (25.7-34.6)	< 0.01
CRI, mL/min/KΩ	0.50 (0.38-0.70)	0.41 (0.33-0.49)	0.80 (0.67-1.12)	< 0.01
In-hospital medication				
Aldosterone antagonist	852 (90.3%)	547 (91.6%)	305 (87.9%)	0.06
Intravenous loop diuretic	789 (83.6%)	494 (82.7%)	295 (85.0%)	0.37
β-blocker	753 (79.8%)	502 (84.1%)	251 (72.3%)	< 0.01
ACEI/ARB	702 (74.4%)	461 (77.2%)	241 (69.5%)	< 0.01
Statin	560 (59.3%)	352 (59.0%)	208 (59.9%)	0.77
Digoxin	477 (50.5%)	311 (52.1%)	166 (47.8%)	0.21
Length of stay, days	9 (7-12)	9 (7-11)	10 (7-13)	< 0.01

Data are presented as n (%), mean ± SD or median (IQR). ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blocker; BMI: body mass index; COPD: chronic obstructive pulmonary disease; CRI: congestion and renal index; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; HFmrEF: heart failure with mid-range ejection fraction; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; HR: heart rate; IQR: interquartile range; KCCQ: Kansas city cardiomyopathy questionnaire; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; SBP: systolic blood pressure; TFCI: thoracic fluid content index.

We performed 1000 times of computational 10-folds cross-validation based on the large sample cohort. The median cut-off value of CRI for the primary outcome was 0.59 mL/min per kΩ, which was consistent with the results obtained in the whole population. And the median area under curve of CRI for the primary outcome was 0.67 (Figure 1). Compared with those with CRI ≤ 0.59 mL/min per kΩ, patients with CRI > 0.59 mL/min per kΩ were older, and more likely to be admitted with congestion signs/symptoms (rales, orthopnea, edema, and jugular vein distension) or comorbidities and have a higher NT-proBNP level at admission (P < 0.05), (Table 1).

Association between CRI and Outcomes

During the one-year follow-up after discharge, cardiovascular death or HF hospitalization occurred in

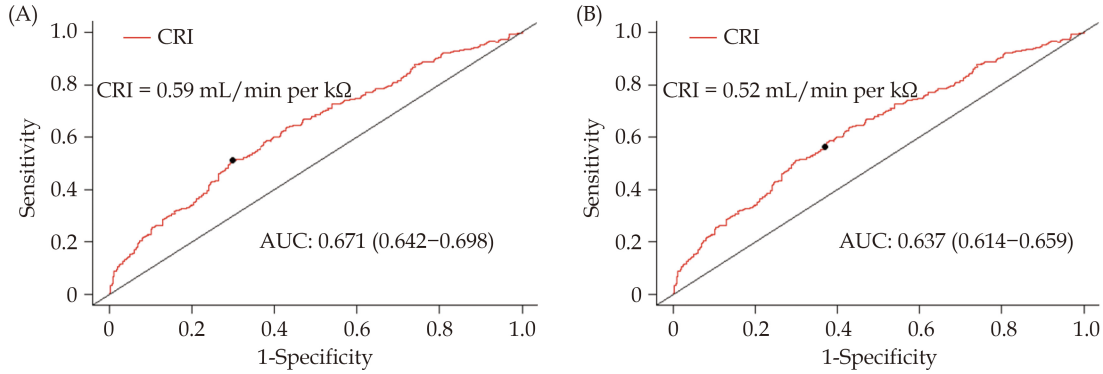

Figure 1 Receiver operating characteristic curves of congestion and renal index. (A): One-year cardiovascular death or HF hospitalization; and (B): one-year all-cause death or all-cause hospitalization. The AUCs of CRI were 0.671 and 0.637 for both the primary and secondary outcomes, respectively. AUC: area under curve; CRI: congestion and renal index; HF: heart failure.

308 (33%) patients, and all-cause death or all-cause hospitalization occurred in 460 (49%) patients (Table 2). The imbalance of baseline characteristics was adequately corrected by IPTW (all standardized mean differences less than 10%) (Supplemental Table S2). As shown in Figure 2, cumulative incidences were significantly higher in patients with CRI > 0.59 mL/min per kΩ for both the primary and secondary outcomes, either before or after weighting ($P < 0.01$). After weighted by IPTW, compared with the patients with CRI ≤ 0.59 mL/min per kΩ, those with CRI > 0.59 mL/min per kΩ had a 56% higher risk of the primary outcome (adjusted HR = 1.56; 95% CI: 1.13-2.15; $P < 0.05$), and a 33% higher risk of the secondary outcome (adjusted HR = 1.33; 95% CI: 1.01-1.74; $P < 0.05$) (Table 2). There was no heterogeneity in the associations between CRI and the primary outcome across all subgroups (All $P > 0.05$) (Supplemental Figure S2). Associations between CRI and the secondary outcome were in general consistent across most patient subgroups, while the associations were slightly stronger in patients with age < 65 years compared with the older patients (P for interaction < 0.05) (Supplemental Figure S3).

Incremental Value of CRI

Compared with the modified GWTG-HF scoring system and EFFECT scoring system, the prognostic values of CRI > 0.59 mL/min per kΩ were improved significantly according to NRIs and IDIs for both the primary and secondary outcomes (Table 3). According to the results of the cross-validation, compared with the modified GWTG-HF scoring system and EFFECT scoring system, the medians of NRI were 0.21 and 0.22 with the addition of the CRI for the primary outcome, respectively, and 0.19 and 0.21 for the secondary outcome, respectively. For both outcomes, the median IDI was 0.01 compared with the two scoring systems.

DISCUSSION

Using data from a multicenter, prospective cohort of 944 patients with AHF, we proposed a novel indicator of CRI, which quantitatively reflected the combined effects of residual congestion and renal function, and demonstrated its prognostic value in AHF. AHF patients with CRI > 0.59 mL/min per kΩ at index discharge had a 56% higher risk of cardi-

Table 2 Associations between congestion and renal index and the outcomes.

Analysis	Cardiovascular death or HF hospitalization	All-cause death or all-cause hospitalization
No. of events	308 (32.6%)	460 (48.7%)
CRI ≤ 0.59 mL/min/kΩ	153 (25.6%)	247 (41.4%)
CRI > 0.59 mL/min/kΩ	155 (44.7%)	213 (61.4%)
With inverse probability treatment weighting	1.56 (1.13-2.15), $P < 0.01$	1.33 (1.01-1.74), $P = 0.04$

Data are presented as *n* (%) or OR (95% CI). CRI: congestion and renal index; HF: heart failure; HR: hazard ratio.

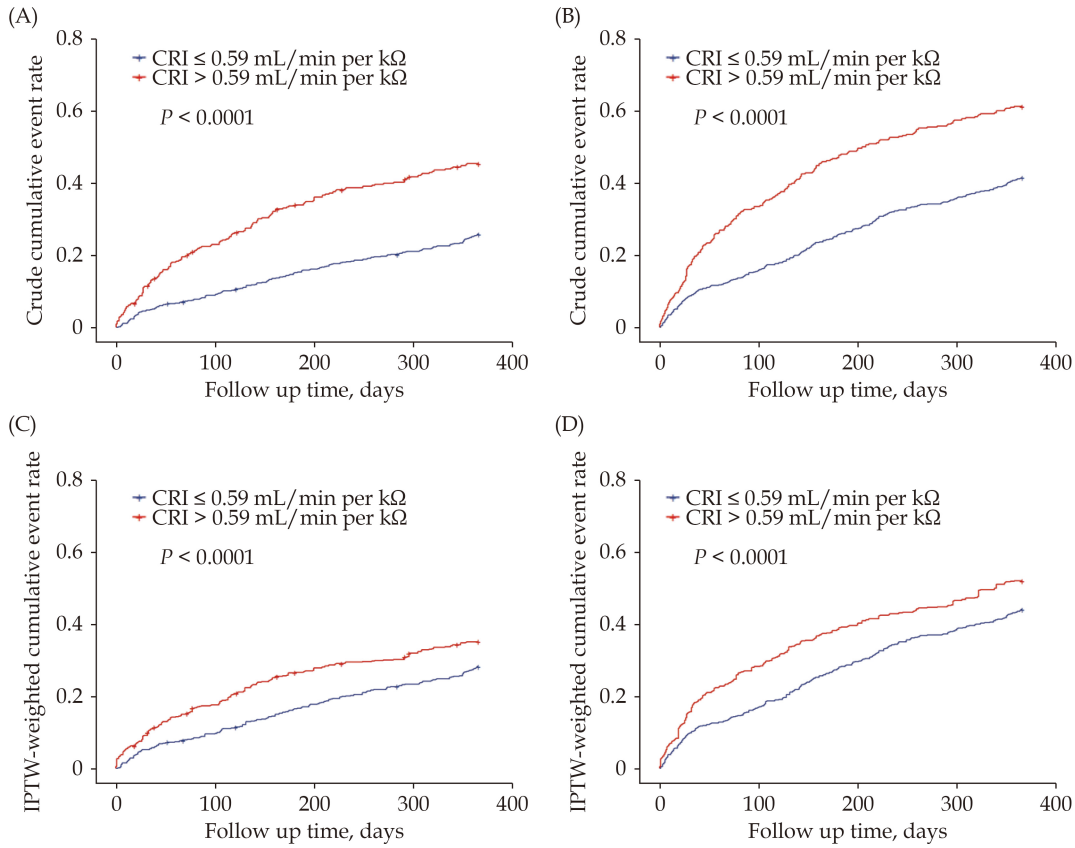

Figure 2 Cumulative incidences of outcomes grouped by cut-off value of congestion and renal index. (A): Cardiovascular death or HF hospitalization; (B): all-cause death or all-cause hospitalization; (C): cardiovascular death or HF hospitalization; and (D): all-cause death or all-cause hospitalization. The blue line indicates patients with CRI ≤ 0.59 mL/min per kΩ, and red line indicates patients with CRI > 0.59 mL/min per kΩ. The upper panels (A&B) shows crude cumulative incidences, and the lower panels (C&D) shows the inverse probability treatment-weighted cumulative incidences. CRI: congestion and renal index; HF: heart failure; IPTW: inverse probability treatment weighting.

Table 3 Incremental prognostic value of congestion and renal index.

	Modified GWTG-HF scoring system*		EFFECT scoring system**	
	Modified GWTG-HF	Modified GWTG-HF+CRI	EFFECT+ NT-proBNP	EFFECT+ NT-proBNP+CRI
C statistic				
Cardiovascular death or HF hospitalization	0.65 (0.62-0.68)	0.66 (0.63-0.69)	0.65 (0.62-0.69)	0.66 (0.63-0.69)
All-cause death or all-cause hospitalization	0.61 (0.58-0.64)	0.62 (0.59-0.65)	0.64 (0.61-0.66)	0.64 (0.62-0.67)
NRI				
Cardiovascular death or HF hospitalization	Reference	0.24 (0.12-0.42)	Reference	0.25 (0.09-0.41)
All-cause death or all-cause hospitalization	Reference	0.24 (0.14-0.40)	Reference	0.28 (0.14-0.40)
IDI				
Cardiovascular death or HF hospitalization	Reference	0.02 (0.00-0.04)	Reference	0.01 (0.00-0.03)
All-cause death or all-cause hospitalization	Reference	0.02 (0.00-0.03)	Reference	0.01 (0.00-0.03)

CRI: congestion and renal index; HF: heart failure; IDI: integrated discrimination improvement; NRI: net reclassification improvement. *Modified GWTG prediction model: age, systolic blood pressure, heart rate, left ventricular ejection fraction, New York Heart Association functional class, blood urea nitrogen, serum sodium, black race, presence of chronic obstructive pulmonary disease, anemia, N-terminal pro-B-type natriuretic peptide; **EFFECT scoring system: age, systolic blood pressure, respiratory rate, hyponatremia, blood urea nitrogen, presence of stroke, dementia, chronic obstructive pulmonary disease, cirrhosis and cancer.

ovascular death or HF hospitalization within the first-year post discharge than those with CRI ≤ 0.59 mL/min per kΩ. We also observed a similar 33% increased risk of all-cause death or all-cause hospitalization among these patients. Moreover, CRI provided incremental prognostic information over established HF risk scoring systems. Our results were confirmed by cross-validation and indicated that CRI was a promising marker to improve risk stratification of AHF before discharge.

This study extended previous literature[30–33] by demonstrating the prognostic value of the quantitative combination of residual congestion and renal dysfunction among AHF patients. Several studies demonstrated that congestion persisted in nearly half of AHF patients at discharge.[9,34,35] The presence of significant residual congestion at day seven or discharge was independently associated with a 90% increased risk of readmissions for HF by day 60 and a 50% increased risk of all-cause death by day 180.[35] Nearly half of the patients with HF had a persistent reduced eGFR[36] and an increased risk of death or HF hospitalization during a three-year follow-up.[37] Although the interaction between congestion and renal impairment has been elucidated pathophysiologically, little is known about how high the risk would be if a patient has both residual congestion and renal dysfunction, and if these conditions are mild but coexist.

CRI could identify a subgroup of HF patients who have been neglected but have increased risk, i.e., patients with subclinical pulmonary congestion complicated with modest renal dysfunction. These patients may not be classified as high risk if merely by the individual indicator of congestion or renal dysfunction. When congestion and renal dysfunction coexist, the interactions between the two could lead to an increased risk of mortality. The inability of the failing heart to generate forward flow results in prerenal hypoperfusion which impairs renal function. Inadequate renal afferent flow further activates the renin-angiotensin-aldosterone system axis, the sympathetic nervous system, and arginine vasopressin secretion; thus further leads to fluid retention, increases preload, and worsens pump failure.[11,12]

CRI is easy to measure and feasible for wide application, and improves risk stratification capabilities of the established risk scoring systems. Measuring CRI before discharge could help physicians identify high-risk patients. Physical examination is insufficient to evaluate residual congestion.[38] The combination of rales, edema, and elevated mean jugular venous pressure only had a sensitivity of 58% to detect elevated pulmonary capillary wedge pressures.[14,39] A *post hoc* analysis from two randomized controlled trials found that patients with orthodema at discharge had a statistically significant but modestly higher 60-day adverse event rate than those without congestion.[9] ICG is a non-invasive, quantifiable, and accurate tool, and is less subject to the operator.[19] It can be quickly mastered by the operator after a brief training. Thoracic fluid content tested by ICG has a good correlation with lung ultrasound score (R = 0.82)[15] and pulmonary wedge pressure (R = 0.87),[40] and shows excellent sensitivity and specificity together with B-lines in predicting pulmonary congestion on the chest radiograph.[41] It should be noted that monitoring of the patients' fluid volume was based on changes in intrathoracic impedance, and the threshold has not been determined. This accounted for the negative results of some clinical trials, even the larger of which were negative.[20–22] However, these findings suggest that monitoring of intrathoracic impedance may provide useful information for a general risk assessment in HF. And the additional input of renal function improves the prognostic ability of TFCI as suggested by NRI and IDI. Future studies are warranted to explore the utility of CRI in dynamic monitoring and guiding treatment.

LIMITATIONS

The following points should be noted when interpreting the results of this study. First, although we adjusted extensive clinical characteristics in the analyses, we cannot rule out the possibility of residual confounding factors given the observational nature of the analysis. Second, the prognostic value of CRI and optimal cut-off point are required to be examined in an external cohort to validate the results of our study. Third, whether CRI can be extrapolated to chronic HF patients still needs to be verified in future studies. Therefore, the results should be interpreted with caution.

CONCLUSIONS

In patients with AHF, those with CRI > 0.59 mL/min per kΩ had a nearly 60% higher risk of cardiovascular death or hospitalization for HF and a more than 30% increased risk of all-cause death or all-cause hospitalization. CRI is promising to serve as a convenient tool for AHF risk stratification before discharge.

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DISCLOSURES

Potential Conflicts of Interest

Jing LI reported receiving research grants, through Fuwai Hospital, from the Chinese government for work to improve the management of hypertension and blood lipids, to improve care quality and patient outcomes of cardiovascular disease, and to improve care for COVID-19 infection; receiving research agreements, through the National Center for Cardiovascular Diseases and Fuwai Hospital, from Amgen for a multicenter clinical trial assessing the efficacy and safety of omecamtiv mecarbil and for dyslipidemic patient registration; receiving a research agreement, through Fuwai Hospital, from Sanofi for a multicenter clinical trial on the effects of sotagliflozin; receiving a research agreement, through Fuwai Hospital, with the University of Oxford for a multicenter clinical trial of empagliflozin; receiving a research agreement, through the National Center for Cardiovascular Diseases, from AstraZeneca for clinical research methods training outside the submitted work; and receiving a research agreement, through the National Center for Cardiovascular Diseases, from Lilly for physician training outside the submitted work. Impedance cardiography devices (CHM T3002/P3005 HDpro) were manufactured and provided by Shandong Baolihao Medical Appliances, Ltd. The company did not participate in the design and conduct the study; collection, management, analysis, and interpretation of the data; or preparation of the manuscript. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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