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ORIGINAL ARTICLE

Feasibility of the contraction–relaxation coupling index in outcome prediction for patients with acute heart failure

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Abstract

Aims Contemporary heart failure (HF) classification based on left ventricular (LV) ejection fraction is limited for comprehensive assessment of LV function. We aimed to validate the feasibility of the contraction–relaxation coupling index (CRC) as a novel predictor for clinical outcomes in patients with acute HF.

Methods and results A total of 3266 consecutive patients (median age: 74 years, 53% male) with acute HF were included. CRC was defined as the ratio of end-diastolic elastance (LV end-diastolic pressure/stroke volume) to end-systolic elastance (LV end-systolic pressure/end-systolic volume). The risk for 1 year composite endpoint of all-cause mortality or hospitalization for HF (primary outcome) was compared after group categorization using CRC tertiles (Tertile 1: CRC $\leq$ 0.17, Tertile 2: 0.17 $<$ CRC $\leq$ 0.40, and Tertile 3: 0.40 $<$ CRC). The median CRC was 0.3 and the median LVEF was 42%. After adjustment for clinical and echocardiographic covariates, CRC was an independent predictor for the primary outcome (hazard ratio [HR]: 1.74, 95% confidence interval [CI]: 1.47–2.07 in Tertile 3 and HR: 1.21, 95% CI: 1.02–1.44 in Tertile 2 when compared with Tertile 1; HR: 1.23, 95% CI: 1.14–1.33 per one-standard deviation increment in CRC). The risk model with CRC showed better performance in outcome discrimination than the model with LVEF (c-statistic 0.701 vs. 0.699, *P* for difference $<$0.001). Patients with higher CRC demonstrated better effectiveness of neurohormonal blockade for the primary outcome compared with those with lower CRC (HR: 0.38, 95% CI: 0.29–0.50 in Tertile 3 and HR: 0.67, 95% CI: 0.52–0.89 in Tertile 1).

Conclusions CRC provides an independent value for outcome prediction in patients with acute HF. CRC would be a sensitive indicator for prognostic risk stratification and for predicting treatment response to the neurohormonal blockade.

Keywords Acute heart failure; Elastance; End-diastolic pressure–volume relationship; End-systolic pressure–volume relationship; Left ventricular ejection fraction

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Introduction

Accurate assessment of left ventricular (LV) function remains a cornerstone for risk stratification and optimal management of heart failure (HF).[1,2] The LV ejection fraction (LVEF) is a well-known and frequently used parameter expressed as a percentage of blood volume pumped out by the LV during contraction. LVEF has been indivisibly linked to the clinical diagnosis of HF and is considered a landmark to categorize HF into HFrEF (HF with reduced LVEF), HFpEF (HF with preserved LVEF), and even HFmrEF (HF with mid-range EF).[1] The diagnostic types of HF are now regarded as separate disease entities, with a growing body of evidence considering the different types as unrelated syndromes.[3,4] However, HF shows a heterogeneous clinical course with complex structural and functional derangements, unsuitable to be classified

using arbitrary LVEF cut-offs.[2] Direct measurement of the LV pressure–volume status has derived pressure–volume loop analysis, visualizing dynamic LV movement in response to loading conditions or myocardial contractility.[5] However, pressure–volume determination generally requires invasive measures, hindering its wide application for haemodynamic assessment in patients with HF. Several non-invasive modalities have been proposed based on a single-beat pressure–volume loop analysis,[6,7] estimating end-systolic or end-diastolic myocardial stiffness, arterial elastance, or vascular–ventricular coupling.[7–11] However, myocardial contraction and relaxation are coupled processes that simultaneously changes in response to LV dysfunction.[12] Thus, integrating the systolic and diastolic pressure–volume relationship would be an optimal approach for comprehensive haemodynamic assessment in HF. The present study aimed to evaluate the feasibility of a new haemodynamic index, the contraction–relaxation coupling index (CRC), as a novel predictor of clinical outcomes in patients with acute HF.

Methods

Study population

Patient data were derived from the STrain for Risk Assessment and Therapeutic Strategies in patients with Acute Heart Failure (STRATS-AHF) registry (NCT03513653).[13] The STRATS-AHF registry enrolled 4312 patients hospitalized for acute HF in three tertiary medical hospitals in Korea between 2009 and 2016. Patients presenting with symptoms or signs of HF and concurrent pulmonary congestion or objective findings of structural or functional LV abnormality were eligible for registration. Patients with acute coronary syndrome at the initial presentation were excluded. Transthoracic echocardiography was performed in 98% of the registered patients. The ethics committee at each participating centre approved the study protocol, which was conducted in accordance with the principles of the Declaration of Helsinki. The committee waived the requirement for informed consent due to the retrospective study design.

Echocardiography and calculation of the contraction–relaxation coupling index

A standard ultrasound machine with a 2.5 MHz probe was used to obtain echocardiographic images. Standard protocols were applied to acquire two-dimensional, M-mode, and Doppler parameters, following the guideline recommendations.[14] The median time interval between the admission and the echocardiograms was 1 day [interquartile range (IQR) of 0 to 2 days]. To calculate the CRC, both LV end-systolic elastance (Ees) and LV end-diastolic elastance (Eed) were estimated (*Figure 1*). The Ees was derived using the pressure and volume data obtained at the end-systolic period using the formula: Ees = LV end-systolic pressure/LV end-systolic volume.[15] The estimation for Ees assumed a linear end-systolic pressure–volume relationship (ESPVR) and a constant volume axis intercept (V_0) of zero.[15,16] LV end-systolic pressure was approximated with a systolic blood pressure multiplied by 0.9, as previously validated.[7,17] For Eed estimation, we assumed the intraventricular pressure at the end of the isovolumic relaxation period to be zero. Based on the pressure–volume data obtained at the end-diastolic period, Eed was calculated using the formula: Eed = LV end-diastolic pressure/stroke volume. The LV end-diastolic pressure was approximated using the mitral Doppler flow parameters using the formula: LV end-diastolic pressure = 11.96 + 0.596 × E/e′, where E and e′ represent early diastolic mitral inflow velocity and mitral annular velocity, respectively.[9,18] We applied the modified Simpson's method to calculate the LV end-systolic and end-diastolic volumes.[14] Finally, CRC was defined as the ratio of Eed to Ees (CRC = Eed/Ees). LVEF was calculated as a percentage of stroke volume to LV end-diastolic volume.[14] We included patients whose blood pressure was measured at the time of echocardiography. Patients with missing values in either the end-systolic or the end-diastolic pressure–volume status were excluded, leaving a total of 3266 patients for further analysis.

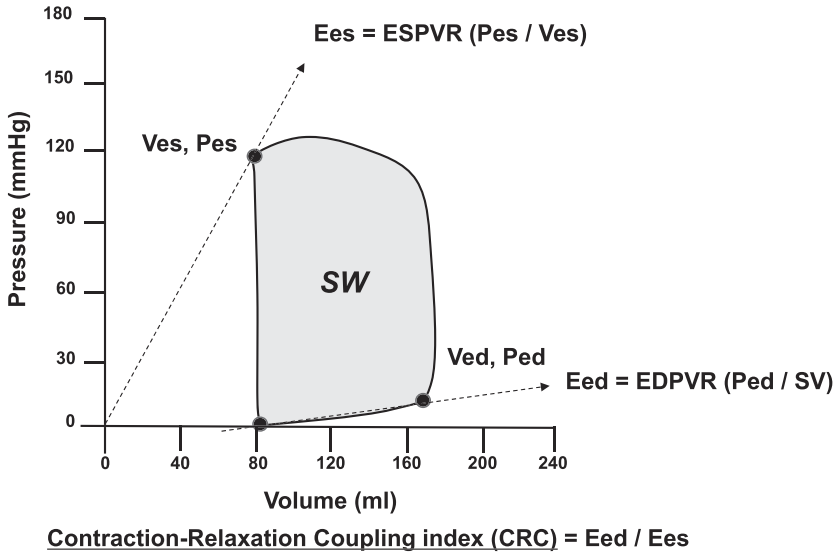
Study outcomes

The primary outcome was a composite endpoint of 1 year all-cause mortality or hospitalization for HF. The vitality status of the study population was obtained from the National Death Records. Patients were followed up and censored at the date of composite endpoint or at the last date of the 1 year follow-up period from the index hospitalization. Each component of the composite endpoint was defined as the secondary outcome. The complete follow-up rate was 97%.

Statistical analysis

For further analysis, we stratified the study population into three groups using CRC tertiles as cut-offs: Tertile 1 ($CRC \leq 0.17$), Tertile 2 ($0.17 < CRC \leq 0.40$), and Tertile 3 ($0.40 < CRC$). Baseline characteristics were presented as medians with IQR for continuous variables and as numbers and frequencies for categorical variables. Intergroup differences were compared using the Kruskal–Wallis test or the χ^2 test. We used the Cox proportional hazards regression model to estimate the hazard ratio (HR) of the primary outcome according to the CRC included as a continuous variable and as tertiles. HR was estimated with adjustment for

Figure 1 Definition of the contraction–relaxation coupling index. The diagram represents the left ventricular (LV) single-beat pressure–volume loop. The contraction–relaxation coupling index (CRC) was defined as the ratio of LV Eed to LV Ees. The detailed calculation of CRC is described in the Methods section. EDPVR, end-diastolic pressure–volume relationship; ESPVR, end-systolic pressure–volume relationship; Ped, end-diastolic pressure; Pes, end-systolic pressure; SV, stroke volume; SW, stroke work; Ved, end-diastolic volume; Ves, end-systolic volume.



demographics, comorbidities, initial laboratory tests, concomitant mediations, LVEF, and LV strain. For multivariable adjustment, correlation matrices across the covariates were checked and confirmed no significant interactions. In the secondary outcome, the risk of HF hospitalization was estimated, with death treated as a competing risk. Missing values in the covariates were replaced using multiple imputation methods. The incremental predictive value of the CRC was evaluated by constructing models with sequential addition of age and sex (Model 1), clinical variables (Model 2), LVEF (Model 3) or pressure–volume indices (Ees, Eed, and CRC) (Model 4), and both LVEF and pressure–volume indices (Model 5). The discriminatory performance of the models was assessed and compared using Harrell's concordance statistic (c-statistic). We additionally compared the discriminatory performance of Model 4 with CRC against the model with LV strain. We employed random permutations for a robust calculation of confidence intervals (CIs) for HRs, selecting random subsamples 1,000 times repeatedly. We applied Kaplan–Meier curves to plot the distribution of time-to-first event for any components of the primary outcome according to the CRC or LVEF tertiles, with differences in the event-free rate assessed using the log-rank test. The restricted cubic spline Cox regression analysis was applied with adjustment of covariates to discover a potential nonlinear association between CRC and the primary outcome. The spline analysis was further stratified by medical treatment at baseline including renin–angiotensin system (RAS) inhibitors, beta-blockers, and diuretics. We hypothesized that the prognostic effect of LVEF improvement would differ between patients with high and low CRC. Among the study population, 742 (22.7%) patients underwent follow-up echocardiography within 1 year after discharge (median interval: 8 months) and the difference in LVEF (ΔLVEF) between the initial examination and the follow-up was calculated. Additional spline analysis was employed to identify the difference in the association of ΔLVEF with the primary outcome between patients in Tertile 1 (high Ees and low Eed) and those in Tertile 3 (low Ees and high Eed). All statistical analyses were performed using R software, version 4.0.2 (R Development Core Team, Vienna, Austria). Statistical significance was set at $P < 0.05$.

Results

Baseline characteristics and echocardiographic parameters

The median age was 74 years, and 52.5% of the patients were men (*Table 1*). The median LVEF was 42% and HFrEF was present in 50.1% of the study population. The median CRC was 0.3, with a median Ees of 1.9 mmHg/mL and median Eed of 0.5 mmHg/mL. When compared with patients in Tertile 1, those in Tertile 3 were younger and had a higher proportion of male patients. HFpEF was the major type of HF in Tertile 1 (86.0%), while HFrEF was the major type (96.9%) in Tertile 3. However, a considerable overlap of the three HF types was found in Tertile 2 (*Figure 2*). LV end-systolic and end-diastolic volumes and left atrial diame-

Table 1 Baseline characteristics of the study population

Variable	All patients (*N* = 3266)	Tertile 1 (CRC ≤ 0.17) (*N* = 1075)	Tertile 2 (0.17 < CRC ≤ 0.40) (*N* = 1079)	Tertile 3 (0.40 < CRC) (*N* = 1112)	*P* for difference
Age, years	74 (64–81)	76 (68–82)	74 (64–81)	71 (60–78)	<0.001
Male, %	1714 (52.5)	455 (42.3)	566 (52.5)	693 (62.3)	<0.001
BMI, kg/m^2	23.1 (20.8–25.7)	23.8 (21.6–26.4)	23.1 (20.6–25.4)	22.5 (20.6–25.1)	<0.001
Medical history					
Hypertension	1906 (58.4)	697 (64.8)	642 (59.5)	567 (51.0)	<0.001
Diabetes mellitus	1117 (34.2)	346 (32.2)	363 (33.6)	408 (36.7)	0.076
Ischaemic heart disease	1097 (33.6)	320 (29.8)	377 (34.9)	400 (36.0)	0.005
Atrial fibrillation	886 (27.1)	310 (28.8)	320 (29.7)	256 (23.0)	0.001
NYHA functional Class IV	1279 (39.2)	404 (37.6)	436 (40.4)	439 (39.5)	0.392
Heart failure phenotype					
HFpEF	1108 (33.9)	924 (86.0)	178 (16.5)	6 (0.5)	<0.001
HFmrEF	514 (15.7)	109 (10.1)	378 (35.0)	27 (2.4)	
HFrEF	1637 (50.1)	38 (3.5)	522 (48.4)	1077 (96.9)	
Physical examination					
Systolic BP, mmHg	127 (110–146)	135 (118–135)	130 (113–149)	118 (104–134)	<0.001
Diastolic BP, mmHg	72 (63–83)	74 (64–84)	74 (63–84)	70 (60–80)	<0.001
Heart rate, beats/min	83 (70–99)	78 (65–92)	85 (70–101)	88 (75–102)	<0.001
Laboratory findings					
BUN, mg/dL	21 (16–30)	20 (15–28)	21 (16–31)	21 (16–32)	0.001
Creatinine, mg/dL	1.07 (0.82–1.52)	1.02 (0.79–1.45)	1.07 (0.82–1.53)	1.11 (0.86–1.60)	0.002
NT-proBNP, pg/mL	4403.5 (1636.3–11013.3)	2600.2 (970.4–6822.3)	4690.0 (1716.0–11535.0)	5971.4 (2661.4–14706.0)	<0.001
Echocardiographic parameters					
LV end-diastolic volume, mm^3	111 (78–155)	82 (60–108)	108 (80–143)	154 (118–199)	<0.001
LV end-systolic volume, mm^3	62 (35–104)	31 (22–44)	62 (44–87)	114 (85–152)	<0.001
LVEF, %	42 (29–57)	61 (56–66)	42 (36–47)	25 (21–30)	<0.001
LA diameter, mm	44 (39–50)	43 (37–49)	44 (39–50)	45 (41–51)	<0.001
E wave, m/s	0.8 (0.6–1.1)	0.8 (0.6–1.0)	0.8 (0.6–1.1)	0.9 (0.7–1.1)	<0.001
E/e′ ratio	16.5 (11.7–23.1)	13.1 (9.8–17.7)	16.3 (11.6–22.0)	21.1 (15.6–28.4)	<0.001
Ees, mmHg/mL	1.9 (1.1–3.3)	3.9 (2.8–5.5)	1.9 (1.4–2.6)	0.9 (0.7–1.3)	<0.001
Eed, mmHg/mL	0.5 (0.4–0.7)	0.4 (0.3–0.6)	0.5 (0.4–0.7)	0.7 (0.5–0.9)	<0.001
CRC (Eed/Ees)	0.3 (0.1–0.5)	0.1 (0.1–0.1)	0.3 (0.2–0.3)	0.7 (0.5–0.9)	<0.001
Medication at discharge					
RAS inhibitors	2286 (70.0)	668 (62.1)	767 (71.1)	851 (76.5)	<0.001
beta-blockers	1998 (61.2)	598 (55.6)	699 (64.8)	701 (63.0)	0.010
Diuretics	2399 (73.5)	758 (70.5)	758 (70.3)	883 (79.4)	<0.001
MRA	1475 (45.2)	405 (37.7)	42 (42.8)	608 (54.7)	<0.001
Follow-up echocardiography[a]	742 (22.7)	195 (18.1)	235 (21.8)	312 (28.1)	<0.001
Interval duration, months	8 (6–10)				

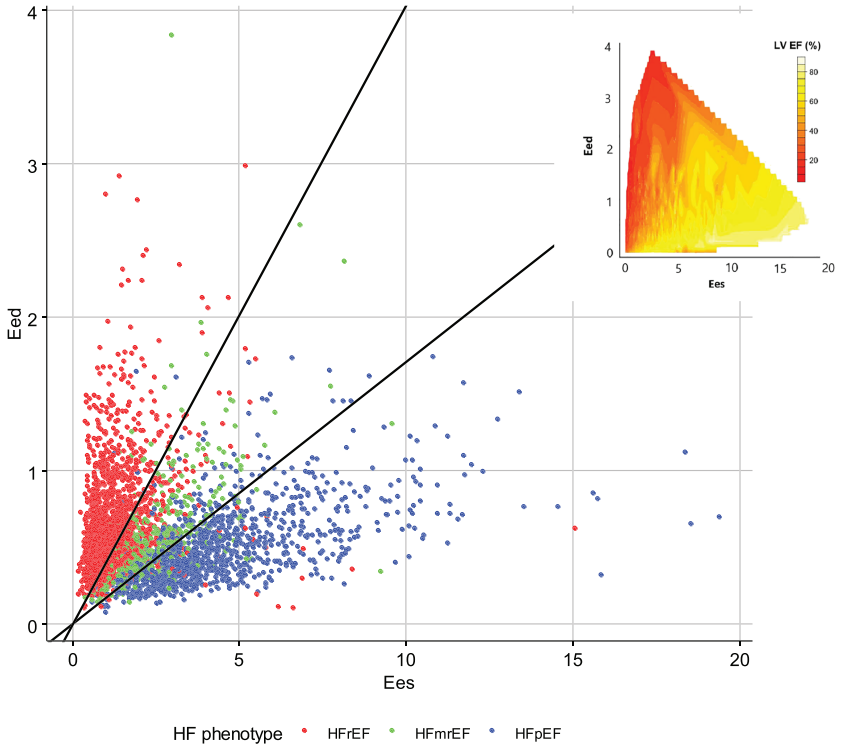
BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; CRC, contraction–relaxation coupling index; Eed, LV end-diastolic elastance; Ees, LV end-systolic elastance; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LA, left atrium; LV, left ventricle; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; RAS, renin–angiotensin system.
[a]Within 1 year after discharge.
[*]Values are given as numbers (percentage), or median (interquartile range) otherwise indicated.

ter were the highest in Tertile 3. The prescription rates for medical treatment were also the highest in Tertile 3.

Independent predictive value of contraction–relaxation coupling index

During a median follow-up of 12 months (IQR 8–12 months), 914 (28%) patients experienced the primary outcome. After adjusting for clinical variables; LVEF, Ees, Eed, and CRC were independently associated with a higher risk of the primary outcome (*Table 2*). However, with further adjustment for LVEF, a significant association was observed for CRC (HR: 1.73, 95% CI: 1.40–2.14), but not for Ees and Eed. An independent association was also observed for CRC with model adjustment for HF phenotypes (HR: 1.62, 95% CI: 1.35–1.95). A significant difference was observed in the event-free rate for the primary outcome among the tertile groups (log-rank $P < 0.001$) (*Figure 3*). With Tertile 1 as a reference, an increasing trend in the primary outcome was observed with the highest risk in Tertile 3 (HR: 1.74, 95% CI: 1.47–2.07). For LVEF, however, substantial overlap was found in survival curves between the mid-tertile

Figure 2 Scatterplot for distribution of patients by Ees and Eed. Patients were labelled according to their heart failure phenotypes. The solid lines represent the cut-off values of the contraction–relaxation coupling index (CRC) tertiles. Considerable overlap was observed among the three heart failure types across the cut-offs, especially in Tertile 2. HF, heart failure.



and high-tertile groups, showing no significant difference in the primary outcome risk (HR: 1.13, 95% CI: 0.95–1.33) (*Figure* S1). The independent association of CRC with the primary outcome was maintained after the adjustment for LV strain (*Table S1*). For the secondary outcome, higher CRC was an independent predictor for higher mortality risk at 1 year. The significant association of the CRC with HF hospitalization was attenuated after the adjustment for LVEF (*Table* S2).

Incremental predictive value of contraction–relaxation coupling index

The addition of clinical variables to Model 1 resulted in a significant improvement in the discrimination of outcome events (Model 2) (*Table* S3). When compared with Model 2, moderate but significant gains in model performance were observed with the addition of LVEF (Model 3) or pressure–volume indices (Model 4). The model with CRC showed the highest performance (c-statistic: 0.701, 95% CI: 0.696–0.705). However, the addition of LVEF to Model 4 with CRC did not result in a significant improvement in model performance (Model 5). The calibration plot of Model 4 with CRC demonstrated a linear relationship between the predicted outcome risk and the observed event rate (*Figure* S2). No significant difference in outcome discrimination was found for Model 4 with CRC against the model with LV strain (c-statistic: 0.703, 95% CI: 0.699–0.707) (*Table* S4).

Comparison of nonlinear association of contraction–relaxation coupling index with the primary outcome according to medical treatment

We observed a continuous increase in the risk of primary outcome with an increase in CRC (HR: 1.23, 95% CI: 1.14–1.33 per one-standard deviation increment) (*Figure 4A*). The estimated HRs in patients on RAS inhibitors demonstrated a relatively gentle curve across the range of CRC compared with those in patients not taking RAS inhibitors (*Figure 4B*). Patients with higher CRC (Tertile 3) demonstrated a better effectiveness of RAS inhibitors (HR: 0.52, 95% CI: 0.41–0.66) than those with lower CRC (Tertile 1) (HR: 0.75, 95% CI: 0.57–0.98) (*Table* S5). Similar trends were observed for beta-blockers (*Figure 4C*). For diuretics, divergence in the spline curves for HRs was observed with an increase in CRC over 0.7 (*Figure 4D*); however, no significant effect was observed in both high and low CRC group (*Table* S5). When the spline curves of the primary outcome were plotted based

Table 2 Predictors for 1 year mortality and hospitalization for heart failure

Variable	Univariable HR (95% CI)	*P*	Clinical variables adjustment HR (95% CI)	*P*	LV EF adjustment HR (95% CI)	*P*	LV EF adjustment (category) HR (95% CI)	*P*
Age, per 10 years increase	1.41 (1.33–1.49)	<0.001						
Male	1.10 (0.97–1.26)	0.145						
BMI, kg/m^2	0.93 (0.91–0.94)	<0.001						
Hypertension	0.98 (0.86–1.12)	0.766						
Diabetes mellitus	1.22 (1.07–1.39)	0.004						
Ischaemic heart disease	1.10 (0.96–1.26)	0.159						
Atrial fibrillation	1.14 (0.99–1.31)	0.074						
BUN, mg/dL	1.01 (1.01–1.02)	<0.001						
Creatinine, mg/dL	1.05 (1.02–1.07)	<0.001						
NT-proBNP, per 1000 pg/mL increase	1.01 (1.01–1.02)	<0.001						
RAS inhibitors	0.53 (0.46–0.60)	<0.001						
β-blockers	0.55 (0.48–0.62)	<0.001						
Diuretics	0.75 (0.65–0.87)	<0.001						
MRA	0.68 (0.60–0.78)	<0.001						
LVEF, per 10% decrease	1.07 (1.02–1.11)	0.002	1.13 (1.08–1.18)	<0.001				
HF phenotype: HFpEF	1 (reference)		1 (reference)					
HF phenotype: HFmrEF	1.03 (0.84–1.25)	0.790	1.06 (0.86–1.29)	0.605				
HF phenotype: HFrEF	1.30 (1.12–1.50)	<0.001	1.53 (1.31–1.80)	<0.001				
Ees, mmHg/mL	0.96 (0.92–0.99)	0.008	0.91 (0.87–0.95)	<0.001	0.96 (0.91–1.01)	0.079	0.95 (0.90–0.99)	0.030
Eed, mmHg/mL	1.41 (1.18–1.67)	<0.001	1.29 (1.07–1.55)	0.008	1.04 (0.84–1.29)	0.696	1.09 (0.89–1.34)	0.391
CRC (Eed/Ees)	1.54 (1.34–1.78)	<0.001	1.80 (1.56–2.09)	<0.001	1.73 (1.40–2.14)	<0.001	1.62 (1.35–1.95)	<0.001

BMI, body mass index; BUN, blood urea nitrogen; CI, confidence interval; CRC, contraction–relaxation coupling index; Eed, LV end-diastolic elastance; Ees, LV end-systolic elastance; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; RAS, renin–angiotensin system.

on LVEF, the risk of primary outcome gradually decreased with increasing LVEF (*Figure* S3). However, we could not observe any remarkable trends across the range of LVEF, regardless of the use of medications.

Prognostic impact of left ventricular ejection fraction improvement on the primary outcome according to contraction–relaxation coupling index tertiles

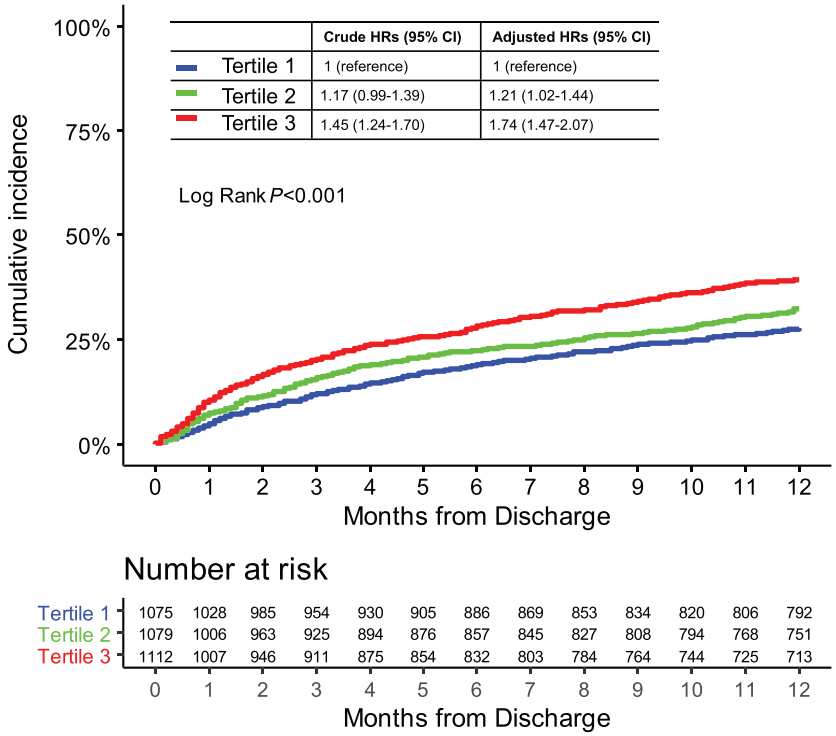
Spline curves for the association between ΔLVEF and the primary outcome are shown in *Figure* S4. For patients in Tertile 3, there was a continuous decrease in the primary outcome over the range of ΔLVEF. In Tertile 1, the primary outcome decreased with an increase in ΔLVEF up to 0. However, it remained constant afterwards despite an improvement in the LV systolic function.

Discussion

In the present study, we developed CRC, a novel haemodynamic index, for outcome prediction in patients with acute HF. CRC was an independent predictor of 1 year risk of all-cause mortality or hospitalization for HF. CRC could predict the treatment response to neurohormonal blockade and a higher CRC value was associated with better effectiveness of neurohormonal blockade. Additionally, CRC could determine the prognostic effect of improvement in the LV systolic function, which reduces the primary outcome in patients with high CRC, but not in those with low CRC.

Direct measurement of the LV pressure–volume relationship enables accurate haemodynamic assessment in HF.[5] However, such measures inevitably require invasive procedures for multiple cardiac cycles under varying loading conditions, limiting their applicability in clinical practice. Senzaki *et al*. invented single-beat estimation for ESPVR using a normalized time-varying elastance curve during early isovolumic contraction.[6] The estimated values were strongly correlated with the measured ESPVR from the multi-beat analysis. With the assistance of non-invasive modalities for chamber volume and pressure assessments, non-invasive single-beat measures for ESPVR have been validated.[7,9] Chen *et al*. derived single-beat ESPVR with a non-invasive approach using systolic and diastolic arm-cuff pressures, stroke volume derived by Doppler echocardiography, and normalized LV elastance at the onset of ejection.[7] The estimated ESPVR was highly correlated with the invasive measures, with little variance to inotropic stimulation. In the current study, we defined Ees as a ratio between the end-systolic pressure and volume, non-invasively obtained by echocardiography.[15,16] Without the invasive measures of V_0, we universally set V_0 as constant value of zero for simpler calculation, based on that the V_0 is relatively stable under the alteration in LV contractility.[19]

Figure 3 Kaplan–Meier curve for 1 year composite endpoint according to the contraction–relaxation coupling index (CRC) tertiles. A significant difference was observed in the event-free rate among the CRC tertiles during the follow-up period. After adjustment for covariates, Tertile 3 showed the highest risk of the primary outcome. CI, confidence interval.

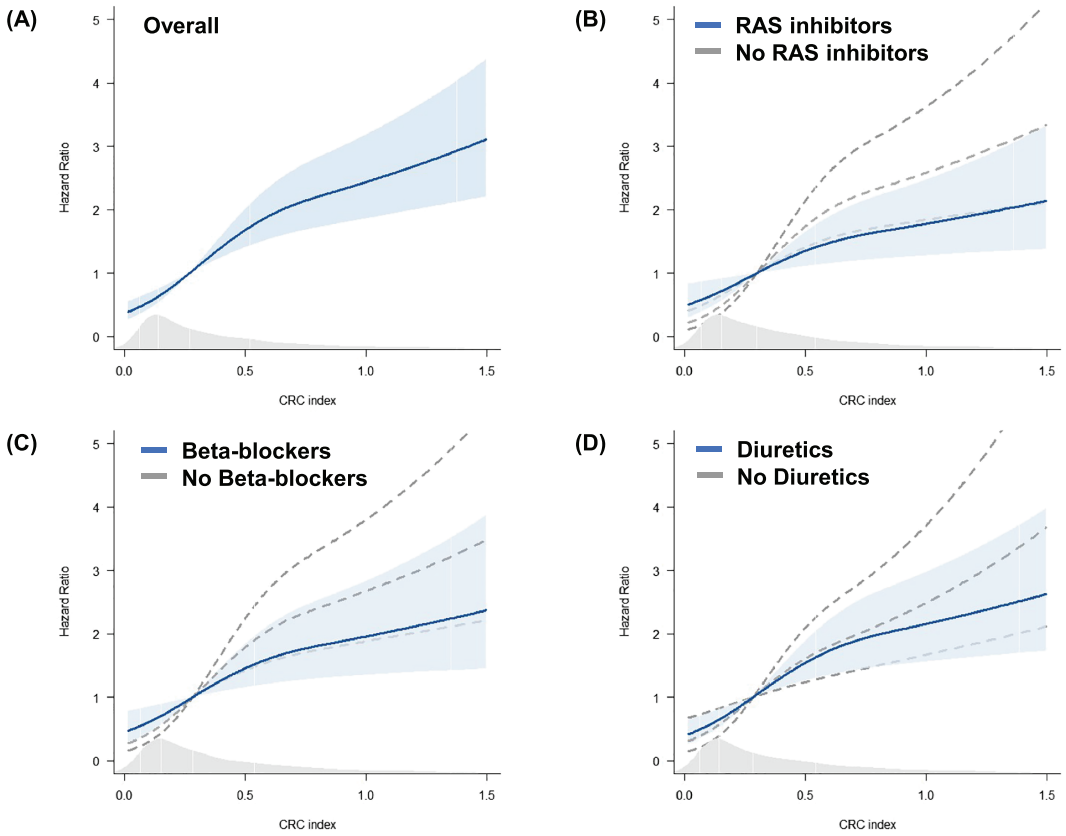


We observed that Ees was independently associated with the primary outcome after adjustment for clinical variables. However, the significant association was attenuated after adjustment for LVEF, showing no improvement in model performance. Because Ees and LVEF are correlated (r = 0.707) both representing LV systolic functions, additional information on LV diastolic function would be necessary for better outcome prediction.

Myocardial contraction and relaxation are coupled processes and a change in one might predict a change in the other. Both contraction and relaxation are modulated by common cyclic AMP.[20] However, most of the HF studies have analysed the contraction and relaxation functions separately. LVEF has been shown to be useful in demarcating subgroups with reduced LV contractility indicated for medical treatment with proven outcome benefits.[1] However, the definitions of HFrEF are different to some extent across treatment guidelines.[21] Additionally, there has been sparse evidence of treatment strategies demonstrating clear outcome benefits for patients with HFpEF.[22] The controversial findings may be related to the various clinical features in these patients[23] and it would be inappropriate to group these patients under the same category of HFpEF. The ambiguities in HF classification based on LVEF can be overcome by a joint evaluation of the contraction and relaxation functions. The advantage of CRC comes from its comprehensiveness, reflecting both the end-systolic and the end-diastolic pressure–volume statuses of the failing heart. Additionally, we derived CRC based on echocardiographic parameters that were obtained during routine examination, suggesting its convenience and cost-effectiveness. Therefore, our results underline the clinical applicability of CRC for comprehensive haemodynamic assessment of HF. The clinical benefit of comprehensive assessment of LV pressure–volume relationship had also been exhibited in patients with transthyretin cardiac amyloidosis (ATTR).[24] Bhuiyan *et al*. had invented the isovolumic PV area (PVA_{iso}), indicating the area between the slope of the end-systolic and end-diastolic pressure–volume relations. The PVA_{iso} was significantly lower in patients with the Val122Ile variant compared with those with wild-type ATTR, which correlated with low survival rate in those with the Val122Ile variant ATTR.

In the spline curve analysis stratified by medical treatment, we observed that higher CRC value was associated with better effectiveness of neurohormonal blockade. Eichhorn *et al*. developed a mathematical model of ventricular coupling, demonstrating a hyperbolic relationship between LV contraction and relaxation.[12] In patients with preserved contractility (Ees), the improvement in LV contraction resulted in only a small enhancement in LV relaxation. However, for

Figure 4 Spline curves for estimated risk of the primary outcome according to contraction–relaxation coupling index (CRC). The spline curves represent the estimated hazard ratios (HRs) (blue solid line) and 95% confidence band (blue shade) for the primary outcome across the CRC range in the overall study population (A) and after stratification by medical treatment including RAS inhibitors (B), beta-blockers (C), and diuretics (D). The spline curves with confidence bands in patients without medical treatment are presented with grey dotted lines. HRs were estimated using the median CRC as a reference with adjustment for covariates.



patients with severe LV systolic dysfunction, a subtle improvement in LV contraction occurred with a larger recovery in LV relaxation. Reverse remodelling or improvement in the LV systolic function in systolic HF can be successfully achieved by neurohormonal blockades such as beta-blockers and RAS inhibitors.[25,26] In patients with a stiff Eed/Ees slope (high CRC), diastolic stiffness improves significantly even with a small improvement in LVEF. Hence, higher CRCs showed a better drug response. Decreased LVEF imposes an elevated risk for clinical events that can coincidently benefit from optimal medical treatments, complicating the interpretation of LVEF for outcome prediction in secondary prevention.[27] However, CRC is valuable for monitoring medical therapy for secondary prevention of HF. Therefore, these findings would also extend the clinical implications of CRC as a prognostic indicator to patients with HF undergoing medical treatment.

Considering the limitation of LVEF, previous studies have suggested considering HF as a spectrum of ventricular dysfunction.[2] This concept suggests that LVEF is a time-varying index affected by triggering factors or disease-modifying therapeutics. Among patients with available records of follow-up LVEF, we observed an inverse relationship between the primary outcome and ΔLVEF in patients from Tertile 3. However, no improvement in the primary outcome was observed with a recovery in the LV systolic function (ΔLVEF >0) in Tertile 1. As discussed earlier, in patients with severe LV dysfunction (stiffer Eed/Ees slope), a small improvement in LV contraction may result in a larger improvement in LV relaxation.[12] These findings support our data explaining the differences in the association of LVEF improvement with primary outcome between patients in Tertile 1 (low CRC with high Ees) and those in Tertile 3 (high CRC with low Ees). In Tertile 1, the improvement in LVEF would lead to only a slight change in relaxation, which is insufficient to achieve better outcomes. Therefore, interpreting LVEF improvement as a positive sign for patient outcomes would be appropriate while considering CRC, especially for patients with preserved systolic function at initial presentation.

Limitations

Our results should be interpreted considering the following limitations. Due to the retrospective study design, potential confounders may exist despite adjustment for covariates. However, the STRATS-AHF registry consecutively enrolled patients from three tertiary medical centres representing real-world patients with acute HF. Although we observed independent and incremental values of CRC for outcome prediction, our results warrant further validation in different populations with a prospective collection for broader applications. The estimation for Ees was performed based on the assumption of ESPVR with a volume axis intercept of 0, which could have overestimated the actual values, particularly in patients with high Ees.[7] However, such concerns would be reduced in case of CRC due to reflection of both systolic and diastolic pressure–volume relationships. Concerns may exist regarding the practical usefulness of CRC beyond conventional LVEF, given that both indices are based on LV volume data obtained at end-systolic and the end-diastolic phases. However, CRC concurrently reflects LV pressure change during the cardiac cycle, which has an independent contribution to outcome prediction over volumetric measures (*Table* S6). Therefore, CRC can be a comprehensive index for patients with acute HF better than LVEF not only for risk stratification but also for predicting treatment response or determining the prognostic effect of improvement in the LV systolic function. Finally, pressure–volume data from right heart catheterization were not available in the current study. Therefore, further validation is required for CRC as referenced to invasive haemodynamic measures.

Conclusions

We developed CRC, a novel indicator, in patients with acute HF using both LV end-systolic and end-diastolic pressure–volume relationships. CRC provided independent and incremental values in 1 year outcome prediction for all-cause mortality or hospitalization for HF. Moreover, CRC is a sensitive indicator for predicting the treatment response to neurohormonal blockade and for determining the prognostic effect of improvement in the LV systolic function.

Conflict of interest

None declared.

Funding

None declared.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Primary endpoint associated with LV GLS
Table S2. Association of CRC with individual clinical outcomes.
Table S3. Model performance in discrimination for 1-year mortality and hospitalization for heart failure.
Table S4. Prediction performance of risk model with LV GLS.
Table S5. Treatment effect of neurohormonal blockades and diuretics in patients with high or low CRC.
Table S6. Independent association of pressure-volume indices for 1-year all-cause mortality and hospitalization for heart failure.
Figure S1. KM curve for 1-year all-cause mortality and hospitalization for heart failure by LVEF tertiles. After stratifying patients according to the LVEF tertiles, substantial overlap was found in survival curves between the mid- and high-tertile groups, showing no significant difference in the primary outcome risk. CI: confidence interval, HR: hazard ratios, LVEF: left ventricular ejection fraction.
Figure S2. Calibration plot of the final risk model with CRC. The calibration plot demonstrated a linear relationship with the predicted outcome risk and the observed event rate. CRC: contraction-relaxation coupling index.
Figure S3. Spline curves for estimated HRs of 1-year all-cause mortality and hospitalization for heart failure according to LVEF stratified by medical treatment of RAS inhibitor, beta-blocker, and diuretics. The spline curves represent the estimated HRs (blue solid line) and 95% confidence band (blue shade) for the primary outcome across the LVEF range in the overall study population (A) and after stratification by medical treatment including RAS inhibitors (B), beta-blockers (C), and diuretics (D). The spline curves with confidence bands in patients without medical treatment are presented with gray dotted lines. HRs were estimated using the median LVEF as a reference with adjustment for covariates. LVEF: left ventricular ejection fraction, RAS: renin-angiotensin system
Figure S4. Spline curve for estimated risk of the primary outcome according to LVEF improvement in the lowest and highest CRC tertiles. The spline curves represent the nonlinear association between ΔLVEF (difference in LVEF between baseline and follow-up echocardiography) and the primary outcome in tertile 1 (left panel) and tertile 3 (right panel).

In tertile 3, there was a continuous decrease in the primary outcome over the range of ΔLVEF. However, no improvement was observed in the primary outcome with improvement in the systolic function (ΔLVEF $>$ 0) in tertile 1. Hazard ratios were estimated using the median ΔLVEF in each tertile as a reference with adjustment for covariates. CRC: contraction-relaxation coupling index, LVEF: left ventricular ejection fraction

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