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ORIGINAL ARTICLE

Modified reverse shock index predicts early outcomes of heart failure with reduced ejection fraction

Gyu Chul Oh[1,2], Seokyung An[3,4], Hae-Young Lee[5]*, Hyun-Jai Cho[5], Eun-Seok Jeon[6], Sang Eun Lee[7], Jae-Joong Kim[7], Seok-Min Kang[8], Kyung-Kuk Hwang[9], Myeong-Chan Cho[9], Shung Chull Chae[10], Dong-Ju Choi[11], Byung-Su Yoo[12], Kye Hun Kim[13], Sue K. Park[4,14] and Sang Hong Baek[1]

[1]*Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, South Korea;* [2]*Catholic Research Institute for Intractable Cardiovascular Disease (CRID), College of Medicine, The Catholic University of Korea, Seoul, South Korea;* [3]*Department of Biomedical Science, Seoul National University Graduate School, Seoul, South Korea;* [4]*Cancer Research Institute, Seoul National University, Seoul, South Korea;* [5]*Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea;* [6]*Department of Internal Medicine, Sungkyunkwan University College of Medicine, Seoul, South Korea;* [7]*Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea;* [8]*Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea;* [9]*Department of Internal Medicine, Chungbuk National University College of Medicine, Cheongju, South Korea;* [10]*Department of Internal Medicine, School of Medicine, Kyungpook National University, Daegu, South Korea;* [11]*Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, South Korea;* [12]*Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju, South Korea;* [13]*Department of Internal Medicine, Heart Research Center of Chonnam National University, Gwangju, South Korea; and* [14]*Department of Integrated Major in Innovative Medical Science, Seoul National University Graduate School, Seoul, South Korea*

Abstract

Aims Increased blood pressure (BP) and decreased heart rate (HR) are signs of stabilization in patients admitted for acute HF. Changes in BP and HR during admission and their correlation with outcomes were assessed in hospitalized patients with heart failure (HF) with reduced ejection fraction (HFrEF).

Methods A novel modified reverse shock index (mRSI), defined as the ratio between changes in systolic BP and HR during admission, was devised, and its prognostic value in the early outcomes of acute HF was assessed using the Korean Acute HF registry.

Results Among 2697 patients with HFrEF (mean age 65.8 ± 14.9 years, 60.6% males), patients with mRSI ≥1.25 at discharge were significantly younger and were more likely to have *de novo* HF. An mRSI ≥1.25 was associated with a significantly lower incidence of 60-day and 180-day all-cause mortality [hazard ratio (HR) 0.49, 95% confidence interval (CI) 0.31–0.77; HR 0.62, 95% CI 0.45–0.85, respectively], compared with $1 \leq$ mRSI < 1.25 (all $P < 0.001$). Conversely, an mRSI <0.75 was associated with a significantly higher incidence of 60-day and 180-day all-cause mortality (adjusted HR 2.08, 95% CI 1.19–3.62; HR 2.24, 95% CI 1.53–3.27; all $P < 0.001$). The benefit associated with mRSI ≥1.25 was consistent in sub-group analyses. The correlation of mRSI and outcomes were also consistent regardless of admission SBP, presence of atrial fibrillation, or use of beta blockers at discharge.

Conclusions In patients hospitalized for HFrEF, the mRSI was a significant predictor of early outcomes. The mRSI could be used as a tool to assess patient status and guide physicians in treating patients with HFrEF.

Keywords Heart failure; Blood pressure; Heart rate; Mortality

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**Correspondence to: Hae-Young Lee, Department of Cardiology, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul, South Korea.*
Email: hylee612@snu.ac.kr
Gyu Chul Oh and Seokyung An contributed equally to the work.

Introduction

Managing blood pressure (BP) and heart rate (HR) are critical factors in treating critically ill patients. These are two critical components of what we term as vital signs. They are indicators of patients' disease status, diagnostic value, and treatment goal. Abnormal values can be recognized as red flags for deterioration, whereas improvement can signify patient recovery.

Patients with acute heart failure (HF) may present in a low perfusion state, accompanied by low BP and tachycardia.[1] For patients in shock, circulatory support is warranted with

inotropes such as dobutamine and dopamine to maintain tissue perfusion.[2] During a successful treatment for acute HF, inotropes are tapered off as the patients' BP increases, and signs of shock are recovered. In clinical practice, if the patient can tolerate guideline-directed medical treatments (GDMTs) such as renin–angiotensin system (RAS) inhibitors and/or beta blockers, they are ready to be discharged.

For HR, the initial response to low perfusion and shock is tachycardia, which is the intrinsic compensatory mechanism to maintain cardiac output even in a low stroke volume state.[3] As the patient stabilizes, HR returns to normal ranges, and beta blockers are initiated to improve outcomes. If intolerant to beta blockers, or if the target HR is not met, ivabradine may also be used to further control HR.[4]

Attempts to stabilize these critical vital signs have been previously accomplished in critically ill patients. Almost half a century ago, Allgöwer and Buri[5] first introduced the shock index (SI), defined as HR divided by systolic BP (SBP), and showed a simple method to evaluate the degree of hypovolaemia in shock patients. Increased values of SI have been correlated with low left ventricular (LV) end-diastolic pressure and circulatory volume, even when individual SBP and HR are within the normal limit.[6,7] The reverse shock index (RSI), the inverse of SI, has also been evaluated in adult trauma patients.[8,9] However, the SI and RSI are cross-sectional values and do not reflect the ongoing changes in patient status during admission. Furthermore, these indices have not been evaluated in patients with HF.

We hypothesized that the degree of BP and HR improvement at discharge would be associated with early outcomes in patients with acute HF with reduced ejection fraction (HFrEF). Using a dedicated acute HF registry, we analysed the prognostic effect of the ratio between changes in SBP and HR during admission and mortality up to 6 months.

Methods

Study population

The Korean Acute Heart Failure (KorAHF) registry is a prospective, multicentre study designed to assess the clinical features and outcomes of acute HF in Korea. A total of 5625 patients hospitalized for acute HF in 10 nationwide centres between March 2011 and February 2014 were enrolled and followed up until February 2019. Details on its design and results have been previously published.[10–12] Accurate data on mortality was acquired using information from the National Health Insurance Service or government-reported death records. All enrolled patients were referred to a cardiologist specializing in HF management, and optimal medical and device therapy according to current guidelines were encouraged at the discretion of the treating physician. Clinical events were monitored and verified by a separate committee composed of independent experts who had not participated in patient enrolment.[10] Among enrolled patients, those with LV ejection fraction (LVEF) $< 40\%$ were included in the current analysis. The study protocol required the investigators to record BP and HR values at admission and at discharge. The study was conducted in accordance with the Declaration of Helsinki. All study protocols were reviewed and approved by the institutional review board of each participating hospital and registered with ClinicalTrials.gov (NCT01389843).

Modified reverse shock index

We defined a novel modified reverse shock index (mRSI) as the ratio between SBP and HR changes from admission to discharge:

$$\text{mRSI} = (\text{SBP}_{\text{discharge}}/\text{SBP}_{\text{admission}})/(\text{HR}_{\text{discharge}}/\text{HR}_{\text{admission}})$$

For example, patients initially in shock and discharged with increased BP and decreased HR would have an mRSI >1, whereas those with decreased BP and increased HR would have an mRSI <1.

BP and HR measurements were performed using standard certified sphygmomanometers, and the first recorded values were used for the analysis. However, if SBP was >180 or <90 mmHg or HR was >160 or <60 beats/min, values were re-measured after 5 min of rest, and average values were recorded. For patients with atrial fibrillation, the average of two BP and HR measurements acquired at 5-min intervals were recorded.

Outcomes

Patients were enrolled at admission, and those with valid SBP and HR values at both admission and discharge were included in the analysis (*Figure S1*). The mRSI was calculated, and patients were grouped into mRSI ≥ 1.25, $1 \leq$ mRSI < 1.25, $0.75 \leq$ mRSI < 1, and mRSI < 0.75 categories. The primary outcome of all-cause mortality was assessed at 60 and 180 days after discharge, and the secondary composite outcome of mortality and HF re-admissions was assessed. Outcomes were compared in each group, with $1 \leq$ mRSI < 1.25 as the reference. Additionally, the traditional RSI was calculated in patients with valid SBP and HR values at admission, and its association with in-hospital outcomes was analysed.

Statistical analyses

Continuous variables are expressed as mean ± standard deviation, and categorical variables are presented as numbers and percentages. We used the *t*-test for continuous variables and the chi-squared test for categorical variables to analyse

differences in clinical characteristics according to mRSI levels. Cox proportional hazards regression and Kaplan–Meier curves adjusted for age, sex, baseline SBP, baseline HR, body mass index, aetiology of HF (ischaemic vs. non-ischaemic), hypertension, serum creatinine (as a continuous variable), atrial fibrillation, and use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and beta blockers were used to estimate the associations between mRSI and risk of all-cause mortality. Cubic spline regression models were used to assess the non-proportional association between SBP, HR, and mRSI. Additionally, we stratified the findings by age, sex, presence of diabetes, use of GDMTs, atrial fibrillation, and SBP at discharge ($<$110 and $\geq$110 mmHg).

All statistical analyses were performed using the Statistical Analysis System (SAS) Version 9.4 (SAS Institute Inc., Cary, NC, USA). Spline regression and Kaplan–Meier plots were drawn using R Version 4.0.3 (http://cran.r-project.org/bin/windows/base/old/4.0.3/).

Patient and public involvement

Participants were not involved in determining the research question or outcome measures, nor were they involved in recruitment, design, or implementation of the study. Participants were not asked for advice on the interpretation of results.

Results

Patient characteristics

From 5625 patients with acute HF enrolled in the KorAHF registry, 2854 patients presented with LVEF $<$40%, and 2697 patients had both BP and HR values at admission and discharge. During the 4-year median follow-up (range, 0–7 years), there were 1292 (47.9%) deaths and 953 (35.3%) re-admissions for HF. The mean age of the patients was 65.8 ± 14.9 years, and 1635 (60.6%) were males. Patients were divided into Groups I–IV according to predefined mRSI values (mRSI $\geq$1.25 for Group I, $1 \leq$ mRSI $<$ 1.25 for Group II, $0.75 \leq$ mRSI $<$ 1 for Group III, and mRSI $<$0.75 for Group IV). Patients in Group I were significantly younger, had a higher prevalence of atrial fibrillation, and had an increased proportion of *de novo* HF. In Group I, intravenous inotropes were used more frequently, and an increased proportion of patients were prescribed mineralocorticoid antagonists at discharge. In contrast, prescription of RAS inhibitors was numerically lower than the other groups. Detailed information on patient characteristics according to mRSI is presented in *Table 1*.

BP at admission was significantly lower in Group I than those in Groups II–IV, whereas baseline HR was significantly higher in Group I than those in Groups II–IV. For the whole study population, the mean SBP and HR at admission and discharge were 129.1 and 112.8 mmHg and 95.5 and 77.4 beats/min, respectively. Changes in BP and HR are summarized in *Table 1*. Although mean SBP decreased from admission to discharge in all groups, the proportion of patients with an increase in SBP was higher in Group I (354/761, 46.5%) compared with Group IV (17/270, 6.3%). The proportion of patients with an increase in SBP during the admission period are shown in *Table S1*.

mRSI and outcomes

An mRSI $\geq$1.25 was associated with a significantly lower risk of the primary outcome of all-cause mortality at 60 and 180 days after discharge compared with $1 \leq$ mRSI $<$ 1.25 [adjusted hazard ratio (HR) 0.49, 95% confidence interval (CI) 0.31–0.77; adjusted HR 0.62, 95% CI 0.45–0.85, respectively; all $P < 0.001$]. In contrast, an mRSI $<$0.75 correlated with a significantly higher incidence of the primary outcome at 60 and 180 days after discharge, compared with $1 \leq$ mRSI $<$ 1.25 (adjusted HR 2.08, 95% CI 1.19–3.62; adjusted HR 2.24, 95% CI 1.53–3.27; all $P < 0.001$). Cubic spline curves drawn to assess the non-proportional effect of mRSI showed a curvilinear association with all-cause mortality (*Figure 1A*). Kaplan–Meier curves for 180-day mortality according to the mRSI groups are presented in *Figure 1B*.

For the composite outcome of mortality and HF re-admissions, patients with an mRSI $\geq$1.25 showed a significantly lower incidence of events compared with those with $1 \leq$ mRSI $<$ 1.25. The risk of events for patients with mRSI $<$0.75 was significantly increased at 180 days, but not at 60 days after discharge. Results of the multivariate Cox regression analyses for all-cause mortality and composite outcomes are presented in *Tables 2* and *S2*.

Sub-group analysis

Associations of mRSI values with outcomes according to various sub-groups were assessed. Where mRSI $\geq$1.25 was associated with a significantly lower rate of events in men (adjusted HR 0.52, 95% CI 0.35–0.78). Association between mRSI and outcomes was also more obvious in patients aged $\geq$70 years (adjusted HR 0.63, 95% CI 0.43–0.92) and in patients without DM (adjusted HR 0.56, 95% CI 0.36–0.87). There was no difference in events according to admission SBP, presence of atrial fibrillation, or use of beta blockers at discharge (*Figure 2*).

The association between mRSI and outcomes was also analysed according to medications at discharge. Although an mRSI $\geq$1.25 was not associated with a significant improvement in outcomes for patients not prescribed with any GDMTs (adjusted HR 0.56, 95% CI 0.26–1.24), the interaction

Table 1 Baseline characteristics, drug management, changes in BP and HR from admission to discharge according to mRSI among patients in the KorAHF-based cohort study

Variables	mRSI ≥1.25 (*N* = 761) (I)	1 ≤ mRSI <1.25 (*N* = 833) (II)	0.75 ≤ mRSI <1 (*N* = 833) (III)	mRSI <0.75 (*N* = 270) (IV)	*P* value[a]
Baseline characteristics					
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Age (years)	64.3 ± 16.1	65.7 ± 14.4	67.3 ± 14.2	65.8 ± 14.8	<0.001
BMI (kg/m^2)	23.2 ± 3.7	23.2 ± 4.1	23.1 ± 3.7	23.2 ± 4.1	0.940
LVEF, %	26.0 ± 8.0	26.8 ± 8.0	27.2 ± 8.3	27.8 ± 8.1	0.005
BUN, mg/dL	26.7 ± 17.0	26.6 ± 15.8	25.5 ± 15.1	26.6 ± 18.1	0.409
Creatinine, mg/dL	1.5 ± 1.7	1.5 ± 1.6	1.4 ± 1.2	1.5 ± 1.7	0.380
	N (%)	*N* (%)	*N* (%)	*N* (%)	
Sex (male)	451 (59.3)	529 (63.5)	503 (60.4)	152 (56.3)	0.125
Hypertension	418 (54.9)	482 (57.9)	508 (61.0)	162 (60.0)	0.094
Diabetes mellitus	301 (39.6)	351 (42.1)	348 (41.8)	93 (34.4)	0.118
Atrial fibrillation	207 (27.2)	200 (24.0)	163 (19.6)	74 (27.4)	0.002
Chronic kidney disease	105 (13.8)	121 (14.5)	127 (15.3)	34 (12.6)	0.698
Cerebrovascular disease	104 (13.7)	109 (13.1)	124 (14.9)	38 (14.1)	0.762
Previous heart failure	320 (42.1)	269 (44.3)	392 (47.1)	138 (51.1)	0.040
NYHA Classes III and IV	669 (87.9)	702 (84.3)	711 (85.4)	237 (87.8)	0.147
Drugs					
	N (%)	*N* (%)	*N* (%)	*N* (%)	
During admission					
Parenteral diuretics	717 (94.2)	783 (94.0)	791 (95.0)	259 (95.9)	0.590
Parenteral inotropes	280 (36.8)	249 (29.9)	255 (30.6)	90 (33.3)	0.052
Parenteral vasodilators	396 (52.0)	466 (55.9)	479 (57.7)	158 (58.5)	0.094
At discharge					
RAS inhibitors	575 (75.6)	636 (76.4)	657 (78.9)	207 (76.7)	0.433
Beta blockers	449 (59.0)	490 (58.8)	484 (58.1)	146 (54.1)	0.527
Aldosterone antagonists	417 (54.8)	448 (53.8)	446 (53.5)	119 (44.1)	0.019
BP and HR					
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
At admission					
SBP, mmHg	117.4 ± 26.6	128.4 ± 28.2	135.9 ± 29.2	142.7 ± 30.1	<0.001
DBP, mmHg	76.2 ± 18.0	79.7 ± 18.5	81.9 ± 18.7	85.6 ± 21.0	<0.001
Heart rate, beats/minute	112.8 ± 25.9	95.7 ± 19.6	86.9 ± 19.2	72.4 ± 19.8	<0.001
At discharge					
SBP, mmHg	116.7 ± 17.5	113.7 ± 17.7	110.4 ± 15.3	106.6 ± 15.6	<0.001
DBP, mmHg	68.4 ± 11.9	67.7 ± 11.4	66.3 ± 10.8	66.2 ± 11.0	<0.001
Heart rate, beats/minute	71.7 ± 12.1	77.1 ± 13.4	80.0 ± 13.6	85.9 ± 15.6	<0.001
Change from baseline					
SBP, mmHg	−0.7 ± 24.1	−14.7 ± 22.5	−25.6 ± 24.6	−36.2 ± 26.6	<0.001
DBP, mmHg	−7.8 ± 18.9	−12.0 ± 17.2	−15.6 ± 18.4	−19.4 ± 21.8	<0.001
Heart rate, beats/minute	−41.1 ± 25.0	−18.7 ± 16.7	−6.9 ± 15.7	13.5 ± 19.2	<0.001
Percentage change from baseline					
SBP, mmHg	2.9 ± 22.3	−9.1 ± 15.6	−16.5 ± 14.4	−23.0 ± 15.6	<0.001
DBP, mmHg	−6.0 ± 25.6	−11.8 ± 20.1	−15.8 ± 20.0	−18.2 ± 24.4	<0.001
Heart rate, beats/minute	−33.8 ± 15.6	−17.7 ± 14.7	−5.5 ± 16.7	25.0 ± 34.0	<0.001

BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; DBP, diastolic blood pressure; HF, heart failure; HR, heart rate; KorAHF, Korean Acute Heart Failure registry; LVEF, left ventricular ejection fraction; mRSI, modified reverse shock index; NYHA, New York Heart Association; RAS, renin–angiotensin system; SBP, systolic blood pressure.
[a]*P* values in ANOVA for continuous variables and chi-squared test for categorical variables.

P value was not significant (*Figure 3*). Subgroup analyses of mRSI and outcomes are presented in *Table S3*.

Cross-sectional RSI at admission and in-hospital outcomes

Among 2697 patients with valid SBP and HR values at admission, traditional RSI was calculated, and its association with in-hospital outcomes was evaluated. Admission RSI, defined as the ratio of SBP to HR, was not a significant predictor of in-hospital mortality in the Cox regression analysis after adjusting for pre-defined variables. The spline curve for in-hospital outcomes according to RSI on admission is shown in *Figure S2*.

Discussion

In our registry of hospitalized patients with acute HF and LV dysfunction, mRSI at discharge, a ratio between BP and HR changes during admission, was associated with favourable early and long-term outcomes of all-cause mortality and HF

Figure 1 (A) Spline curve and (B) Kaplan–Meier curve for primary outcome at 6 months according to the modified reverse shock index (mRSI). Patients with mRSI ≥1.25 were associated with a lower risk of the primary outcome. CI, confidence interval; HR, hazard ratio; mRSI, modified reverse shock index.

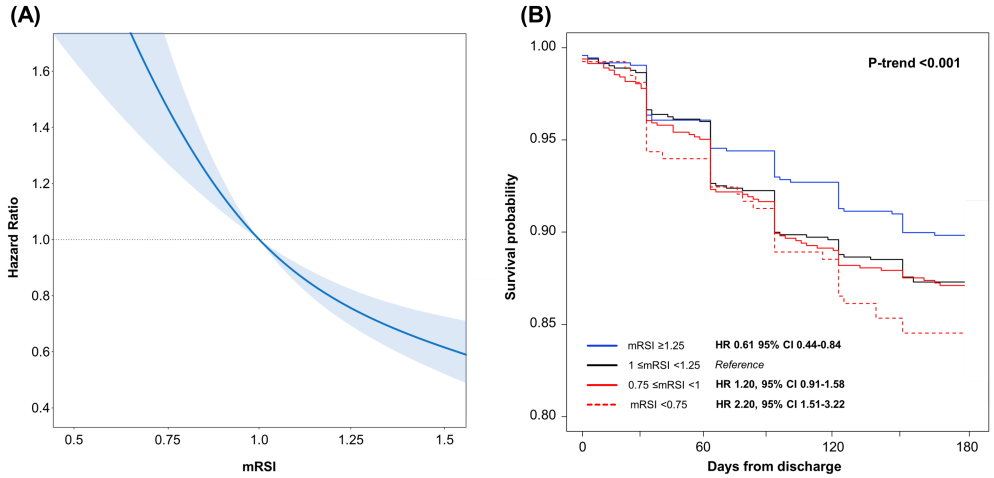


Table 2 Risk for all-cause mortality according to mRSI among patients in the KorAHF-based cohort study

All-cause mortality	Person-years	Events (%)	HR (95% CI)[a]	HR (95% CI)[b]	*P* value[c]
60 days					<0.001
mRSI ≥1.25	122.6	37 (4.9)	0.48 (0.31–0.77)	0.47 (0.30–0.76)	
1 ≤ mRSI < 1.25	134.4	57 (6.8)	1.00	1.00	
0.75 ≤ mRSI < 1	134.3	61 (7.3)	1.29 (0.89–1.88)	1.37 (0.94–2.00)	
mRSI <0.75	43.3	21 (7.8)	1.96 (1.13–3.39)	2.05 (1.17–3.56)	
180 days					<0.001
mRSI ≥1.25	346.6	87 (11.4)	0.62 (0.45–0.85)	0.61 (0.44–0.84)	
1 ≤ mRSI < 1.25	375.7	110 (13.2)	1.00	1.00	
0.75 ≤ mRSI < 1	375.3	109 (13.1)	1.15 (0.88–1.51)	1.20 (0.91–1.58)	
mRSI <0.75	121.6	47 (17.4)	2.10 (1.44–3.05)	2.20 (1.51–3.22)	

CI, confidence interval; HR, hazard ratio; KorAHF, Korean Acute Heart Failure registry; mRSI, modified reverse shock index.
[a]Adjusted for age, sex, and baseline SBP and HR.
[b]Adjusted for age, sex, and baseline SBP and HR, body mass index, heart failure aetiology (ischaemic vs. non-ischaemic), serum creatinine, left ventricular ejection fraction, atrial fibrillation, use of ACEi/ARB, and use of beta blockers.
[c]*P* trend in Cox proportional hazards models.

re-admissions. An mRSI value ≥1.25 was associated with a lower rate of the composite outcome of mortality and re-admissions at 60 and 180 days after discharge. To the best of our knowledge, this is the first study to utilize complex changes in BP and HR during the admission period in patients with acute HF.

Increased HR has been associated with poor outcomes in all cardiovascular diseases, especially HF.[13] Lowering HR has been a target for HF treatment for a long time, with medications such as beta blockers and ivabradine. However, although it is a critical component in assessing patient status, BP has been overlooked in patients with HF. Patients with acute HF present with low perfusion and often low BP. As these patients are stabilized with medical treatment, an increase in BP is observed. Nevertheless, there is no consensus on the optimal targets for BP. Some studies have suggested a *J*-curve phenomenon, reporting that an excessively low BP was associated with poor outcomes.[14,15] However, these findings have mostly been derived from observational studies and cannot exclude the contribution of reverse causality.[16]

Using readily available BP and HR values, we were able to define a novel mRSI and show its association with early and long-term outcomes. A patient with an increase of 10% in SBP and a 10% decrease in HR during the admission period had an mRSI of approximately 1.22. Thus, a cut-off value of 0.75 and 1.25 was used, and outcomes were compared according to mRSI group. Through our analysis, we identified that an increase of ≥25% in mRSI was associated with a lower risk of all-cause mortality and HF re-admissions both in the early period and up to 6 months. In contrast, a decrease in mRSI of ≥25% was associated with poor patient outcomes. Previous studies have shown that changes in BP are associated with outcomes, there has been no specific target, and

Figure 2 Spline curves for primary outcome at 6 months according to mRSI, stratified by (A) presence of atrial fibrillation, (B) use of beta blockers, and (C) SBP at admission. The association between mRSI and the incidence of the primary outcome was consistent regardless of presence of atrial fibrillation, use of beta blockers, or SBP at admission. mRSI, modified reverse shock index; SBP, systolic blood pressure.

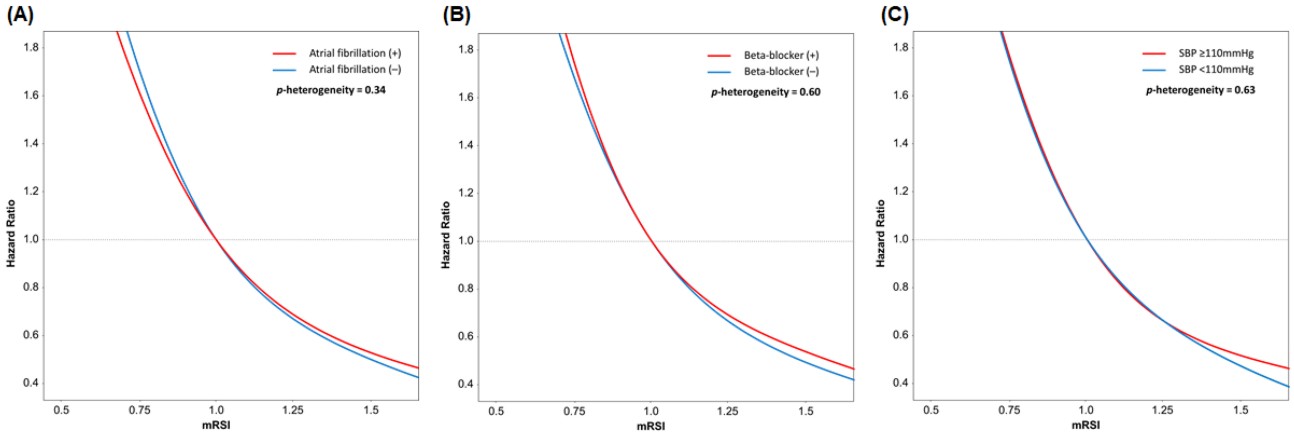
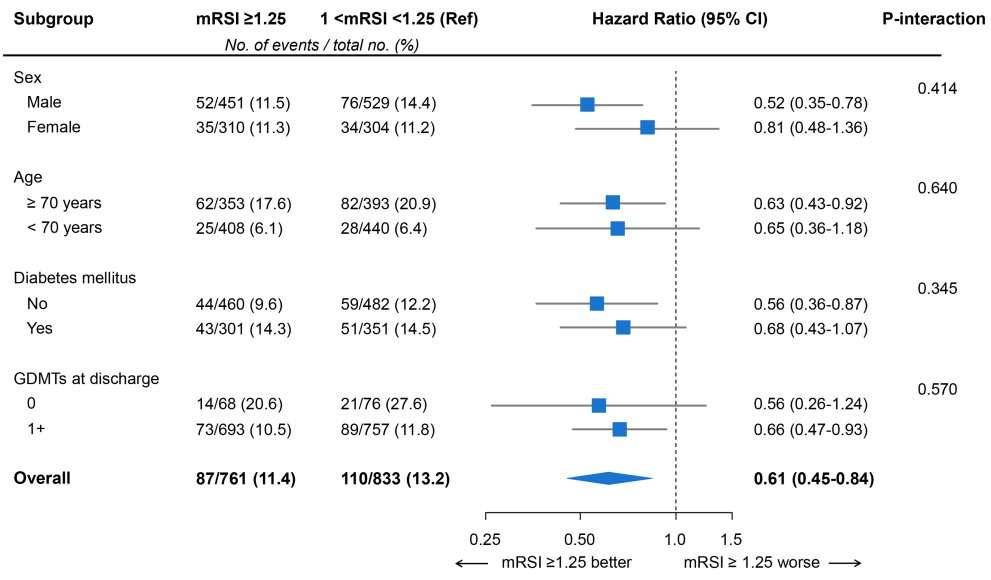


Figure 3 Forest plot for primary outcome for sub-groups. An mRSI ≥1.25 better correlated with outcomes in males, patients aged ≥70 years, non-diabetics, and those prescribed with 1 + GDMT at discharge. CI, confidence interval; GDMT, guideline-directed medical treatment; HR, hazard ratio; No, number.



no study has evaluated BP and HR as a combination.[17,18] Although we hypothesized that a higher mRSI may be associated with an increase in SBP and better outcomes, it is also important to note that preventing excessive reduction in BP is also important. The mRSI can be easily calculated and used throughout the admission process as a dynamic indicator of patients' status.

The KorAHF registry enrolled HF patients regardless of their LVEF. In our analysis of HFrEF patients, mRSI ≥1.25 was associated with better outcomes, but there was no significant association in patients with HF and preserved ejection fraction (HFpEF) patients (data not shown). This again shows that these two HF entities are significantly different in aetiology and presentation.[19] In contrast to patients with HFpEF who mostly have elevated or preserved BP,[20] patients with LV dysfunction are more likely to present with hypoperfusion with low BP and tachycardia. In HFrEF patients, an increase in mRSI can be interpreted as an increase in BP and a decrease in HR, suggesting haemodynamic stability. In contrast, acute HF in patients with preserved LV function is mostly due to diastolic dysfunction, and changes in BP and HR may not be profound.

Another important finding was that the predictive value of mRSI was analysed in various sub-groups and did not show any difference according to patient characteristics or treatment. Medications such as RAS inhibitors and beta blockers affect BP and/or HR to some extent. An mRSI ≥1.25 was associated with reduced mortality at 180 days in the total study population, and although results were not significant for patients not on any GDMTs (interaction *P* value = 0.570), there still was a tendency for favourable outcomes. A cut-off of mRSI ≥1.25 could be ubiquitously used for initiation and titration of medications in patients admitted for acute HF.

The decision to discharge patients with acute HF is not straightforward. Recent guidelines have introduced a discharge checklist to help the process,[21] but the optimal timing and medications remain elusive. Complex changes in BP and HR are correlated to patients' volume status and renal function, and the mRSI could be used as a dynamic marker for improvement in haemodynamic status. Furthermore, previous population-based studies have shown a 35–40% mortality rate at 1 year[22,23] and a re-admission rate of 11–38% at 60–90 days after discharge.[24,25] Using the mRSI could aid physicians in determining whether a patient is suitable for discharge. Even though initiating GDMTs before discharge are recommended, careful evaluation of BP and HF should also be performed. Patients with an mRSI ≥1.25 at discharge were associated with a lower incidence of mortality and re-admissions, whereas those with mRSI <0.75 were associated with poor outcomes.

Limitations

The BP and HR values used in the analyses are continuous variables. However, measurements in the KorAHF registry only utilized the values at admission and discharge. A prospective, well-designed trial is needed to fully evaluate the role of admission and discharge BP and HR in patients with HF. Additionally, there is the possibility of selection bias, as mRSI could only be calculated in patients surviving to discharge. In a previous report, we have shown that 6.0% (4.8% in-hospital mortality, 1.2% heart transplantation) of patients enrolled in the KorAHF registry experienced in-hospital events.[11]

Although data on the use of RAS inhibitors, beta blockers, and aldosterone antagonists were used to adjust for the outcome, dosage, timing of initiation, and type of medications were not used in the analysis. Thus, it is unclear whether the beneficial effect was due to the appropriate use of GDMTs in patients with increased mRSI. Level of B-type natriuretic peptide (BNP) were not used as a co-variable in Cox regression analysis, as there were mixed measurements of BNP and N-terminal proBNP (NT-proBNP) among study participants. Additionally, data on use of implantable cardioverter-defibrillator (ICD) or cardiac re-synchronization therapy (CRT) were not used in the analysis, which could have led to bias in interpreting HR.

The current study utilized data from a nationwide acute HF registry and were not designed to assess haemodynamic changes during admission period. Only measurements at admission and discharge were available, limiting the assessment of serial changes in mRSI. In clinical practice, the mRSI could be used as a part of a multimodal decision tool to aid physicians in evaluating patients' haemodynamic status when starting and modifying medications.

Conclusions

In patients hospitalized with HFrEF, mRSI, defined as the ratio between SBP and HR changes during admission, was a significant predictor of early mortality. Physicians should be aware of the changes in BP and HR during admission and optimize medications accordingly.

Conflict of interest

None declared.

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Author contributions

G.C.O. and S.A. conceptualized the study design and methods. S.A. and S.K.P. conducted the statistical analysis. G.C.O. wrote the first draft of the manuscript. H-Y.L. managed the study. All study authors contributed to data collection, interpretation, and revising the final manuscript.

Supporting information

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

Table S1. Proportion of patients with an increase in SBP during admission period according to mRSI group.
Table S2. Risk for HF readmission and composite outcome according to mRSI among patients in the KorAHF- based cohort study.
Table S3. Cox regression analysis for 6-month all-cause mortality according to subgroups.

Figure S1. Study design

Figure S2. Cubic spline curve for in-hospital mortality according to RSI at admission.
RSI, reverse shock index.

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