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Prognostic Value of Shock Index, Modified Shock Index, and Age-Adjusted Derivatives in Prediction of In-Hospital Mortality in Patients with Acute Decompensated Heart Failure: Persian Registry of Cardiovascular Disease/ Heart Failure Study

ORIGINAL INVESTIGATION

ABSTRACT

Background: Introduction of simple bedside tools for assessing patients' condition in different settings improves triaging. However, these indices are less frequently used in heart failure. This study aims to evaluate the utility of shock index, age shock index, modified shock index, and age-modified shock index in the prediction of in-hospital mortality in acute decompensated heart failure individuals.

Methods: We conducted this retrospective study on 3652 acute decompensated heart failure individuals in the context of Persian Registry of Cardiovascular Disease/heart failure. Shock index, age shock index, modified shock index, and age-modified shock index were assessed during admission. Receiver operating characteristic curve was used to define the optimum cut-off point. Odds ratio models were used for investigating the association of in-hospital mortality according to each specified cut-off value.

Results: Mean age was 70.12 ± 12.56 years (males: 62.6%). Optimum cut-off point for shock index, age shock index, modified shock index, and age-modified shock index were set to be 0.71 (sensitivity: 63%, specificity: 60%), 50.5 (sensitivity: 65%, specificity: 60%), 0.94 (sensitivity: 60%, specificity: 60%), and 66.7 (sensitivity: 62%, specificity: 60%), respectively. Participants with higher shock index derivatives in all domains had significantly higher likelihood of death. Compared to those with shock index, age shock index, modified shock index, and age-modified shock index values of less than cut-off points, adjusted model revealed patients with higher values had 2.59 (95% CI: 1.94-3.46, $P < .001$), 2.61 (95% CI: 1.95-3.48, $P < .001$), 2.14 (95% CI: 1.61-2.84, $P < .001$), and 2.28 (95% CI: 1.72-3.03, $P < .001$) times increase in-hospital death risk, respectively.

Conclusions: Shock index, age shock index, modified shock index, and age-modified shock index are simple bedside tools to reliably predict in-hospital mortality in acute decompensated heart failure patients to better prioritize high-risk subjects.

Keywords: Heart failure, mortality, shock index, age shock index, modified shock index, age-modified shock index, hospital mortality

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INTRODUCTION

One of the leading causes of death around the globe is cardiovascular diseases (CVDs). Approximately one-third of total deaths were related to CVDs.[1] Of note, one of the most common entities in CVDs mainly observed among the elderly population is heart failure (HF).[2]

This disease is a complicated clinical syndrome characterized by insufficient pump function of the heart through the entire body. Reduction in cardiac output occurs as a consequence of structural and/or functional abnormalities in the heart.[3,4]

Around 70% of acute HF (AHF) patients admitted to the emergency department (ED) diagnosed with acute decompensated HF (ADHF) mostly manifested with dyspnea caused by pulmonary edema.[5] Pulmonary edema is an emergency

medical condition in which the air sacs of the lungs were filled with fluid preventing sufficient oxygen delivery and subsequent breath shortness.[6,7] In most patients, symptoms started to appear about 1 week prior to hospitalization.[8]

The main goals of HF therapy are proficient symptom control and risk reduction of death in patients.[9] Despite all recent improvements in the management of HF, increase in the number of deaths in the context of ADHF, both in hospitalized and discharged patients, has been observed.[8] Previous studies revealed that the in-hospital mortality rates for ADHFs ranged between 3.8% and 9.3%.[10]

Early assessment of admitted ADHF patients leads to reducing the morbidity and mortality rates. The challenging step is to identify low- and high-risk patients and make the right decision for hospital discharge.[11] Several studies reported that patients discharged with normal vital signs while they were at high risk of death and required a longer hospital stay.[12,13]

In this regard, bedside predictive factors can play an important role in triaging patients.[14,15] In 1967, the shock index (SI) was proposed for the first time in the management of hemorrhagic and septic shock.[16] It remains as a bedside tool for more than 50 years and its predictive role for different situations including hospital stay, activation of massive transfusion protocol in trauma patients, and mortality were reported in literature.[17,18]

Shock index is defined as the heart rate divided by systolic blood pressure. It can be used as a quick and noninvasive predictor of mortality in patients admitted to ED. Previous studies concluded there is an inverse relationship between SI and mean arterial pressure (MAP), cardiac index, and left ventricular stroke volume.[19,20] They also reported several high-risk patients had abnormal SI range with normal vital signs.[21]

Replacing blood pressure by mean blood pressure turns SI into modified shock index (MSI). Earlier studies claimed that in comparison to SI and some vital signs including heart rate and blood pressure, MSI predicts mortality rate more precisely.[22]

Aging is often accompanied by raised morbidity and mortality risk, and age shock index (ASI) is another recently introduced index that might be practical in mortality prediction.[23] It is defined as age in years multiplied by SI.[24]

There is inadequate data on applying these indices as predictive tools in ADHF. The purpose of this study was to assess the relation between SI, ASI, MSI, and age MSI (AMSI) with in-hospital mortality in patients who were admitted to the ED diagnosed with ADHF.

HIGHLIGHTS

- Shock index derivatives are simple bedside tools for assessment of patients with ADHF, especially in low-income countries.
- SI, ASI, MSI and AMSI cut-off values of 0.71, 50.5, 0.94 and 66.7 appropriately identifies high risk individuals, respectively.
- The higher the shock index derivatives was associated with lower in-hospital survival rate.

METHODS

Study Population

We used registered data from "Persian Registry Of cardio-Vascular diseasE/HF (PROVE/HF)," an Iranian CVDs database started in 2015.[25] This database included all data from admitted HF patients. This retrospective study was conducted on patients aged 18 years and older admitted to the ED of one of the tertiary heart centers in Isfahan, Iran, during a 4-year period from March 2016 to March 2020. Patients younger than 18 years old or those with a pacemaker, acute liver failure, hepatic encephalopathy, and malignancy were excluded from the current study. We also discarded patients who were unwilling to participate in this research. Finally, 3652 patients were enrolled in this study after the implementation of all inclusion and exclusion criteria. The ethics committee approved the current study.

Assessment of Variables

First data were collected from patients diagnosed with ADHF through their medical forms. Data including age (years), gender (male/female), systolic and diastolic blood pressure (mmHg), heart rate (beats/min), left ventricular ejection fraction (LVEF) (%), smoking status (current/former or never smokers), history of chronic diseases (ischemic heart disease, diabetes mellitus, hypertension, kidney diseases, chronic obstructive pulmonary disease), laboratory data (hemoglobin (g/dL), sodium (mEq/L), potassium (mEq/L), blood urea nitrogen (mg/dL), and creatinine (mg/dL)), and pre-admission medication history (beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), diuretics, mineralocorticoid receptor antagonists, digoxin, and nitrates) were gathered. Body mass index (BMI) was also calculated using the formula: weight/height^2 (kg/m^2).

The following formulae were used to calculate shock *indices for each patient*: SI (heart rate/systolic blood pressure), MSI (heart rate/MAP), ASI (age × SI), and AMSI (age × MSI).

Statistical Analysis

Continuous and categorical data are presented as mean ± standard deviation and counts (percent), respectively. To compare numerical and nominal variables, *t*-test and chi-square tests were used, respectively.

Receiver operating characteristic (ROC) curves were used to determine the optimal cut-off points for SI, MSI, ASI, and AMSI. To demonstrate the sensitivity and specificity for each feasible cut-off point, ROC curves are drawn as a graphical method. The *x*-axis represents 1 – specificity (false positive) and *y*-axis represents sensitivity (true positive). After determining the cut-off point for each index, patients were divided into groups according to their calculated indices.

Multiple logistic regression analysis was utilized to assess the relation of SI, ASI, MSI, and AMSI with in-hospital mortality through both univariate and multivariate models. Variables with significant differences according to SI, ASI,

MSI, and AMSI groups were considered as confounding variables and inserted in multivariate regression model. We assessed the goodness of fit for multivariate regression models with Hosmer–Lemeshow test. Sensitivity analyses with cross-validation and bootstrap methods were performed to assess the robustness of the outcomes. Using two-tailed test, *P* values of less than .05 were considered significant, and all statistical analyses were performed using Statistical Package for Social Sciences (SPSS Inc., version 22.0, Chicago, Ill, USA).

RESULTS

A total of 3652 adult patients, contained 2287 (62.6%) men, with total mean age of age of 70.12 ±12.56 years were enrolled in this study. The area under curve (AUC) resulted from ROC curve analysis for SI, ASI, MSI, and AMSI were 0.668 (95% CI: 0.632-0.705, $P < .001$), 0.684 (95% CI: 0.648-0.720, $P < .001$), 0.640 (95% CI: 0.601-0.628, $P < .001$), and 0.659 (95% CI: 0.622-0.696, $P < .001$) (Figure 1A, B, C, and D).

The optimal cut-off values of SI, ASI, MSI, and AMSI to predict the in-hospital mortality were 0.71 (sensitivity: 63%, specificity: 60%), 50.5 (sensitivity 65%, specificity: 60%), 0.94 (sensitivity: 60%, specificity: 60%), and 66.7 (sensitivity: 62%, specificity: 60%), respectively.

Mean SI, ASI, MSI, and AMSI were 0.71 ± 0.24, 49.92 ± 18.71, 0.94 ± 0.28, and 65.93 ± 22.84, respectively. With an exception of MSI, all other indices differed significantly according to gender (SI: male: 0.72 ± 0.24, female: 0.70 ± 0.24, $P = .043$, ASI: male: 49.05 ± 18.41, female: 51.38 ± 19.13, $P < .001$, MSI: male: 0.94 ± 0.28, female: 0.93 ± 0.27, $P = .277$, AMSI: male: 64.51 ± 22.89, female: 68.29 ± 22.57, $P < .001$).

The results of Hosmer–Lemeshow test were in favor of acceptable goodness of fit in multivariate regression models. Also, the sensitivity analyses results were in favor of the robustness of our findings. In our study, patients who fell into a group with SI greater than or equal to 0.71 were mainly men with faster heart rates, higher levels of potassium, and suffer more from severe left ventricular dysfunction (LVEF < 30%) than the other group (65.0% vs. 60.9%, $P = .011$, 101.65 ± 22.21 beats/min vs. 79.36 ± 13.93 beats/min, $P < .001$, 4.54 ± 0.69 mEq/L vs. 4.47 ± 0.63 mEq/L, $P = .005$, 65.1% vs. 55.3%, $P < .001$, respectively) (Table 1).

Calculating ASI and categorizing patients into 2 groups according to cut-off point indicated 1498 (41%) patients with ASI of higher than 50.5. Older patients with higher heart rates as well as having higher potassium and blood urea nitrogen levels were most frequently observed in this group (76.04 ± 9.64 years vs. 65.99 ± 12.70 years,

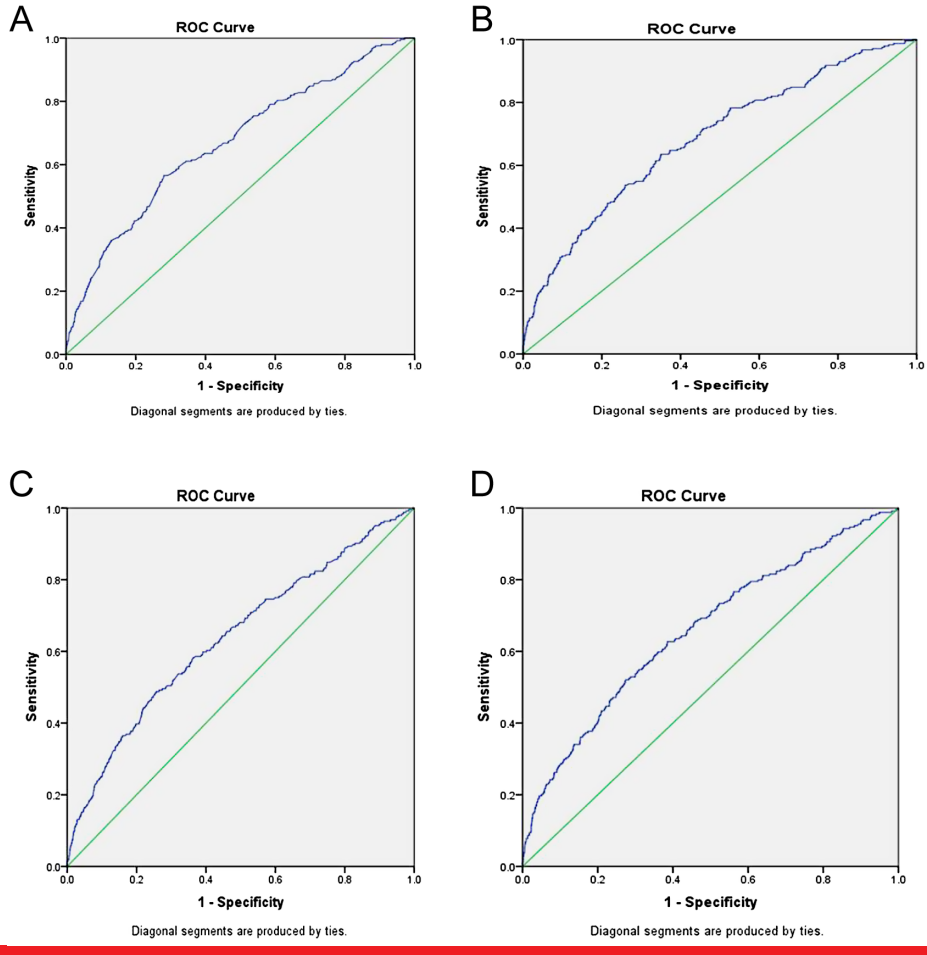

Figure 1. Receiver operating characteristic curve analysis of the study based on shock index (A), age shock index (B), modified shock index (C), and age modified shock index (D).

Table 1. General and Laboratory Characteristics and Drug History of the Study Population According to Shock Index and Age Shock Index Cut-Off Points

Variables		Total (n=3652)	Shock Index Cut-Off <0.71 (n=2101)	Shock Index Cut-Off ≥0.71 (n=1551)	P	Age Shock Index Cut-Off <50.5 (n=2154)	Age Shock Index Cut-Off ≥50.5 (n=1498)	P
Age(years)		70.12 ± 12.56	71.05 ± 11.74	68.84 ± 13.48	<.001	65.99 ± 12.70	76.04 ± 9.64	<.001
Males (%)		2287 (62.6)	1279 (60.9)	1008 (65.0)	.011	1387 (64.4)	900 (60.1)	.008
BMI (kg/m^2)		26.46 ± 3.73	26.62 ± 3.44	26.26 ± 4.09	.004	26.69 ± 3.79	26.14 ± 3.62	<.001
Ischemic heart disease (%)		3010 (82.4)	1746 (83.1)	1264 (81.5)	.207	1784 (82.8)	1226 (81.8)	.444
Diabetes mellitus (%)		1729 (47.3)	1044 (49.7)	685 (44.2)	.001	1054 (48.9)	675 (45.1)	.021
Hypertension (%)		2415 (66.1)	1521 (72.4)	894 (57.6)	<.001	1473 (68.4)	942 (62.9)	.001
Kidney diseases (%)		1005 (27.5)	567 (27.0)	438 (28.2)	.402	553 (25.7)	452 (30.2)	.003
COPD (%)		533 (14.6)	279 (13.3)	254 (16.4)	.009	287 (13.3)	246 (16.4)	.009
Smoking status (%)		611 (16.7)	337 (16.0)	274 (17.7)	.193	417 (19.4)	194 (13.0)	<.001
Heart rate (beats per minute)		88.83 ± 21.04	79.36 ± 13.93	101.65 ± 22.21	<.001	81.03 ± 15.65	100.05 ± 22.66	<.001
Systolic blood pressure (mm Hg)		129.78 ± 28.12	141.75 ± 26.56	113.57 ± 21.20	<.001	139.21 ± 28.16	116.22 ± 21.817	<.001
Diastolic blood pressure (mm Hg)		80.79 ± 16.13	84.79 ± 15.68	75.38 ± 15.12	<.001	84.16 ± 16.05	75.95 ± 14.97	<.001
Left ventricular ejection fraction (%)	<30	2170 (59.4)	1161 (55.3)	1009 (65.1)	<.001	1264 (58.7)	906 (60.5)	.556
	30-39	729 (20.0)	464 (22.1)	265 (17.1)		446 (20.7)	283 (18.9)	
	40-49	352 (9.6)	232 (11.0)	120 (7.7)		205 (9.5)	147 (9.8)	
	≥50	401 (11.0)	244 (11.6)	157 (10.1)		239 (11.1)	162 (10.8)	
Hemoglobin (g/dL)		13.19 ± 2.26	13.22 ± 2.24	13.17 ± 2.29	.501	13.27 ± 2.24	13.09 ± 2.30	.017
Sodium (mEq/L)		138.71 ± 4.95	139.09 ± 4.69	138.18 ± 5.24	<.001	139.02 ± 4.73	138.26 ± 5.22	<.001
Potassium (mEq/L)		4.50 ± 0.65	4.47 ± 0.63	4.54 ± 69	.005	4.46 ± 0.61	4.56 ± 0.71	<.001
Blood urea nitrogen (mg/dL)		28.86 ± 15.50	28.32 ± 15.40	29.59 ± 15.60	.015	27.36 ± 14.85	31.00 ± 16.15	<.001
Creatinine (mg/dL)		1.74 ± 0.70	1.58 ± 0.98	1.55 ± 0.77	.442	1.55 ± 0.96	1.60 ± 0.79	.107
Drug history	Beta blockers (%)	2754 (75.4)	1631 (77.6)	1123 (72.4)	<.001	1667 (77.4)	1087 (72.6)	.001
	ACEIs/ARBs (%)	2698 (73.9)	1584 (75.4)	1114 (71.8)	.015	1599 (74.2)	1099 (73.4)	.556
	Diuretics (%)	1800 (49.3)	1002 (47.7)	798 (51.5)	.025	1042 (48.4)	758 (50.6)	.186
	Mineralocorticoid receptor antagonists (%)	945 (25.9)	504 (24.0)	441 (28.4)	.002	573 (26.6)	372 (24.8)	.230
	Digoxin (%)	995 (27.2)	537 (25.6)	458 (29.5)	.008	572 (26.6)	423 (28.2)	.261
	Nitrates (%)	1623 (44.4)	970 (46.2)	653 (42.1)	.014	950 (44.1)	673 (44.9)	.623

BMI, body mass index; COPD, chronic obstructive pulmonary disease; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers.

$P < .001$, 100.05 ± 22.66 beats/min vs. 81.03 ± 15.65 beats/min, $P < .001$, 4.56 ± 0.71 mEq/L vs. 4.46 ± 0.61 mEq/L, $P < .001$, 31.00 ± 16.15 mg/dL vs. 27.36 ± 14.85 mg/dL, $P < .001$, respectively) (Table 1).

A total of 1546 (42.3%) patients showed MSI values of higher than 0.94. These patients had higher heart rates with higher percentages of LVEF <30% and higher blood urea nitrogen levels with increased rates of digoxin consumption compared to patients with MSI of less than 0.94 (101.85 ± 22.07 beats/min vs. 79.26 ± 13.93 beats/min, $P < .001$, 63.8% vs. 56.2%, $P < .001$, 29.75 ± 15.84 mg/dL vs. 28.20 ± 15.21 mg/dL, $P = 0.003$, 29.7% vs. 25.5%, $P = .004$, respectively) (Table 2).

Data of categorization of patients according to AMSI cut-off value are provided in Table 2. Compared to patients with AMSI of less than 66.7, individuals with AMSI of ≥ 66.7 had higher average age and heart rate means, and both potassium and blood urea nitrogen levels were higher in their laboratory tests (76.46 ± 9.33 years vs. 65.62 ± 12.61, $P < .001$, 100.30 ± 22.48 beats/min vs. 80.69 ± 15.45 beats/min, $P < .001$, 4.56 ± 0.71 mEq/L vs. 4.46 ± 0.61 mEq/L, $P < .001$, 31.01 ± 15.97 mg/dL vs. 27.33 ± 14.97, $P < .001$, respectively).

A total of 244 (6.7%) patients died during their hospitalizations. Our data analysis revealed death was significantly more prevalent in patients who had higher values of all SI derivative indices than pre-defined cut-off points (Table 3).

We provided univariate and multivariate adjusted odds ratio (OR) according to SI, ASI, MSI, and AMSI in Table 4. Individuals with higher SI derivative indices had higher in-hospital death risk in univariate model. After adjustment of all potential confounders (age (except for ASI and AMSI), sex,

Table 2. General and Laboratory Characteristics and Drug History of the Study Population According to Modified Shock Index and Age-Modified Shock Index Cut-Off Points

Variables		Total (n = 3652)	Modified Shock Index Cut-Off		P	Age-Modified Shock Index Cut-Off		P
			<0.94 (n = 2106)	≥ 0.94 (n = 1546)		<66.7 (n = 2137)	≥66.7 (n = 1515)	
Age (years)		70.12 ± 12.56	70.72 ± 11.99	69.29 ± 13.25	.001	65.62 ± 12.61	76.46 ± 9.33	<.001
Males (%)		2287 (62.6)	1311 (62.3)	976 (63.1)	.587	1402 (65.6)	885 (58.4)	<.001
BMI (kg/m^2)		26.46 ± 3.73	26.62 ± 3.67	26.25 ± 3.81	.002	26.64 ± 3.78	26.21 ± 3.66	.001
Ischemic heart disease (%)		3010 (82.4)	1758 (83.5)	1252 (81.0)	.051	1777 (83.2)	1233 (81.4)	.167
Diabetes mellitus (%)		1729 (47.3)	1038 (49.3)	691 (44.7)	.006	1043 (48.8)	686 (45.3)	.035
Hypertension (%)		2415 (66.1)	1514 (71.9)	901 (58.3)	<.001	1448 (67.8)	967 (63.8)	.013
Kidney diseases (%)		1005 (27.5)	570 (27.1)	435 (28.1)	.474	551 (25.8)	454 (30.0)	.005
COPD (%)		533 (14.6)	282 (13.4)	251 (16.2)	.016	282 (13.2)	251 (16.6)	.004
Smoking status (%)		611 (16.7)	341 (16.2)	270 (17.5)	.309	416 (19.5)	195 (12.9)	<.001
Heart rate (beats per minute)		88.83 ± 21.04	79.26 ± 13.93	101.85 ± 22.07	<.001	80.69 ± 15.45	100.30 ± 22.48	<.001
Systolic blood pressure (mm Hg)		129.78 ± 28.12	140.46 ± 27.52	115.23 ± 21.66	<.001	137.23 ± 28.63	119.27 ± 23.69	<.001
Diastolic blood pressure (mm Hg)		80.79 ± 16.13	86.38 ± 15.50	73.18 ± 13.67	<.001	85.09 ± 16.12	74.74 ± 14.07	<.001
Left ventricular ejection fraction (%)	<30	2170 (59.4)	1183 (56.2)	987 (63.8)	<.001	1267 (59.3)	903 (59.6)	.813
	30-39	729 (20.0)	456 (21.7)	273 (17.7)		434 (20.3)	295 (19.5)	
	40-49	352 (9.6)	231 (11.0)	121 (7.8)		199 (9.3)	153 (10.1)	
	≥50	401 (11.0)	236 (11.2)	165 (10.7)		237 (11.1)	164 (10.8)	
Hemoglobin (g/dL)		13.19 ± 2.26	13.21 ± 2.22	13.17 ± 2.32	.581	13.28 ± 2.24	13.08 ± 2.29	.008
Sodium (mEq/L)		138.71 ± 4.95	138.99 ± 4.74	138.32 ± 5.20	<.001	138.92 ± 4.69	138.40 ± 5.29	.002
Potassium (mEq/L)		4.50 ± 0.65	4.48 ± 0.63	4.53 ± 0.69	.009	4.46 ± 0.61	4.56 ± 0.71	<.001
Blood urea nitrogen (mg/dL)		28.86 ± 15.50	28.20 ± 15.21	29.75 ± 15.84	.003	27.33 ± 14.97	31.01 ± 15.97	<.001
Creatinine (mg/dL)		1.74 ± 0.70	1.58 ± 0.98	1.55 ± 0.76	.307	1.55 ± 0.96	1.59 ± 0.79	.177
Drug history	Beta blockers (%)	2754 (75.4)	1636 (77.7)	1118 (72.3)	<.001	1648 (77.1)	1106 (73)	.004
	ACEIs/ARBs (%)	2698 (73.9)	1596 (75.8)	1102 (71.3)	.002	1583 (74.1)	1115 (73.6)	.746
	Diuretics (%)	1800 (49.3)	1003 (47.6)	797 (51.6)	.019	1050 (49.1)	750 (49.5)	.825
	Mineralocorticoid receptor antagonists (%)	945 (25.9)	521 (24.7)	424 (27.4)	.067	574 (26.9)	371 (24.5)	.107
	Digoxin (%)	995 (27.2)	536 (25.5)	459 (29.7)	.004	572 (26.8)	423 (27.9)	.440
	Nitrates (%)	1623 (44.4)	962 (45.7)	661 (42.8)	.079	927 (43.4)	696 (45.9)	.125

BMI, body mass index; COPD, chronic obstructive pulmonary disease; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers.

BMI, ischemic heart disease, diabetes mellitus, hypertension, kidney diseases, COPD, smoking, LVEF, hemoglobin, sodium, potassium, blood urea nitrogen, creatinine, and pre-admission drug consumption (beta-blockers, ACEIs, ARBs, diuretics, mineralocorticoid receptor antagonists, digoxin, and nitrates), this increased mortality risk remained significant in a way that participants with higher SI (≥0.71), ASI (≥50.5), MSI (≥0.94), and AMSI (≥66.7) had 2.59 (95% CI: 1.94-3.46, $P < .001$), 2.61 (95% CI: 1.95-3.48, $P < .001$), 2.14 (95% CI: 1.61-2.84, $P < .001$), and 2.28 (95% CI: 1.72-3.03, $P < .001$) times higher likelihood of in-hospital mortality rather than patients in the other SI, ASI, MSI, and AMSI categories, respectively.

Table 3. Distribution of In-Hospital Mortality of Study Population According to Shock Index, Age Shock Index, Modified Shock Index, and Age-Modified Shock Index Cut Off-Points

Variable	Total (n = 3652)	Shock Index Cut-Off		P	Age Shock Index Cut-Off		P	Modified Shock Index Cut-Off		P	Age-Modified Shock Index Cut-Off		P
		<0.71 (n = 2101)	≥0.71 (n = 1551)		<50.5 (n = 2154)	≥50.5 (n = 1498)		< 0.94 (n = 2106)	≥0.94 (n = 1546)		<66.7 (n = 2137)	≥ 66.7 (n = 1515)	
Mortality (%)	244 (6.7)	89 (4.2)	155 (10)	<.001	85 (3.9)	159 (10.6)	<.001	97 (4.6)	147 (9.5)	<.001	91 (4.3)	153 (10.1)	<.001

Table 4. Multiple Logistic Regression Analysis

Models		Shock Index Cut-Off		P	Age Shock Index Cut-Off		P	Modified Shock Index Cut-Off		P	Age-Modified Shock Index Cut-Off		P
		< 0.71 (n = 2101)	≥ 0.71 (n = 1551)		<50.5 (n = 2154)	≥50.5 (n = 1498)		<0.94 (n = 2106)	≥0.94 (n = 1546)		<66.7 (n = 2137)	≥66.7 (n = 1515)	
Univariate analysis	Odd ratio (95% CI)	1.00	2.51 (1.91-3.28)	<.001	1.00	2.89 (2.20-3.79)	<0.001	1.00	2.17 (1.66-2.83)	<.001	1.00	2.52 (1.93-3.30)	<.001
Multivariate analysis*	Odd ratio (95% CI)	1.00	2.59 (1.94-3.46)	<.001	1.00	2.61 (1.95-3.48)	<0.001	1.00	2.14 (1.61-2.84)	<.001	1.00	2.28 (1.72-3.03)	<.001

*Adjusted for age (except for age shock index and age-modified shock index), sex, body mass index, ischemic heart disease, diabetes mellitus, hypertension, kidney diseases, chronic obstructive pulmonary disease, smoking, left ventricular ejection fraction, hemoglobin, sodium, potassium, blood urea nitrogen, creatinine, and drug consumption (beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, mineralocorticoid receptor antagonists, digoxin, and nitrates).

DISCUSSION

We conducted the current study to evaluate the utility of SI, ASI, MSI, and AMSI in predicting in-hospital mortality among Iranian ADHF patients. We found all mentioned indices are quite reliable bedside tools for assessing HF conditions and prioritizing therapeutic interventions. Those with higher SI, ASI, MSI, and AMSI values than optimum cut-off point had more than 2 times increased likelihood of in-hospital mortality during their hospital stay days. Thus, prompt evaluation of ADHF at admission time seems necessary.

There are few studies in the literature assessing the utility of these indices in HF patients. For instance, El-Menyar et al performed a retrospective study from multinational database registry of AHF patients in 7 Middle-East Arab countries (Bahrain, Kuwait, United Arab Emirates, Yemen, Qatar, Oman, and Saudi Arabia) to evaluate predictive values of SI derivatives including SI, ASI, and MSI. They recruited 4818 subjects who suffered from AHF (age: 50 ± 18 years, males: 63%). Mean SI, MSI, and ASI were found to be remarkably higher in deceased subjects in comparison to survivors (SI: 0.93 ± 0.39 vs. 0.74 ± 0.27, MSI: 1.2 ± 0.54 vs. 0.30, ASI: 51 ± 24 vs. 43 ± 17). Also, these indices were higher among those experienced cardiogenic shock (SI: 0.98 ± 0.48 vs. 0.73 ± 0.25, MSI: 1.3 ± 0.6 vs. 0.99 ± 0.3, ASI: 53 ± 29 vs. 42 ± 16). The AUC (standard error (SE)) extracted from ROC curve analysis based on mortality were the followings: SI: 0.70 (0.02), MSI: 0.65 (0.02), and ASI: 0.61 (0.02). The best SI cut-off was found to be 0.9 (sensitivity: 49%, specificity: 79%) for the prediction of in-hospital mortality. After adjustment of potential confounding variables, SI of ≥ 0.9 was associated with 4.55 times (95% CI: 2.90-7.14, $P = .001$) increased likelihood of in-hospital death. They also calculated adjusted OR of 3- and 12-month mortality with similar outcomes (OR: 2.26, 95% CI: 1.49-3.42, $P = .001$ and OR: 1.79, 95% CI: 1.18-2.70, $P = .006$). However, they did not provide any further analyses in terms of MSI or ASI and suggested all SI derivative indices reliably predicted chances of in-hospital mortality at admission, but SI was a better tool due to higher AUC value and easier calculation.[26] On the other hand, Pourafkari and colleagues implemented a retrospective analysis of 554 medical records of AHF patients with a mean age of 77.1 ± 11.4 years to assess predictable value of SI, MSI, and ASI on in-hospital death rate. The AUC ± SE for ASI differed significantly from SI and MSI (ASI: 0.68 ± 0.03, $P = .002$, SI: 0.60 ± 0.06, $P = .086$, MSI: 0.59 ± 0.06, $P = .098$). They found that neither SI nor MSI were distributed significantly between deceased patients and survivors (SI: 0.66 ± 0.25 vs. 0.62 ± 0.18, $P = .480$, MSI: 0.95 ± 0.26 vs. 0.89 ± 0.22, $P = .136$). However, ASI was significantly higher in subjects who died in the hospital. The proposed ASI cut-off point was set to be 50.8 (sensitivity: 46%, specificity: 71%) which was quite similar with our findings. They also followed 323 subjects for a median duration of 17 months and indicated equivalent results in a way that only ASI with a cut-off point of 59.6 (sensitivity: 54%, specificity: 83%) could predict long-term mortality.[27] Another study was done on 112 patients admitted to ED with AHF (age: 74.8 ± 9.4 years, females: 51.7%). Area under the curve resulted from ROC curve analysis was 0.81 ($P < .001$) with

optimal cut-off point of 0.94 (sensitivity: 80%, specificity: 84.7%). About 15.1% of the study population died within 24 hours of admission. They found SI median was significantly higher in non-survivors rather than survivors (1.11 (interquartile range (IQR)): 0.91-1.41 vs. 0.75 (0.56-0.90), $P = .001$) and suggested this bedside index can be a useful tool for triaging AHF patients in ED.[28]

Although evaluation of SI derivatives is less frequently investigated in HF, there are several records that assessed the utility of these indices in acute coronary syndrome (ACS), especially myocardial infarction (MI) patients.[29-32] A study on 24 636 subjects suffered from ACS with optimal SI cut-off point of 0.80 showed patients who had higher values experienced 3.40 times (95% CI: 2.29-5.02, $P < .001$) increased chance of in-hospital death compared to those with lower SI ranges.[33]

Shock index was first proposed by Allgöwer and colleagues for the assessment of hypovolemia in different settings including septic and hemorrhagic shocks.[16] However, the practical utility of this index is not assessed in CVDs until recent years. Despite the unknown exact association of SI in HF, overstimulation of sympathetic autonomic nervous system in ADHF as well as probable relation of SI to alteration in left ventricular stroke volume might play roles in this regard and possibly reflects the interaction between nervous and cardiovascular systems.[34]

Modified shock index was also suggested to be a better bedside tool than SI due to the incorporation of MAP in its measurement. It has been reported MAP could better assess the need for fluid resuscitation and titration of vasopressor agents than systolic blood pressure used in SI calculation.[35]

Heart failure is a disease of older individuals and more than 60% of patients are aged more than 65 years.[36] Also, they mostly used beta-blockers as one of the main medications. Moreover, SI values reduce by increase in age.[27,37] Therefore, usage of newer indices with consideration of age in the calculation of SI derivatives might be reasonable. We found patients with higher ASI values had higher risks of in-hospital death and this index might be a useful tool for triaging older HF individuals. To the best of our knowledge, there is no study in the literature assessing the utility of AMSI in ADHF patients. We figured out this easily measured index reliably predicts mortality during hospitalization in HF patients admitted with decompensated status. However, further studies are required.

We conducted this study for the first time in the literature to assess 4 SI derivatives including SI, ASI, MSI, and AMSI with quite large sample size for in-hospital mortality prediction among ADHF patients. By the way, several limitations are existing. First, the observational design of this study prevents us from finding any cause and effect relation. Also, the current study was performed retrospectively. Therefore, the generalization of our findings should be cautiously done. We tried our best to adjust all potential confounders, but some unmeasured variables including blood indices (platelets, lymphocytes, and neutrophils) might negatively affect our outcomes. We did not perform this study in multiple centers, and a single center was defined for data gathering which might limit extension to other nations. However, better coordination for proper assessment of SI indices might probably cover this limitation.

In conclusion, this study indicated usage of simple bedside tools including SI, ASI, MSI, and AMSI for assessment of in-hospital mortality in ADHF patients, especially in developing countries, might be a useful strategy for prioritizing high-risk patients. Moreover, usages of these aforementioned indices might be helpful in clinical settings to predict long-term complications among ADHF patients to better recognition of those in severe status and implement appropriate health care interventions. These SI derivatives might also have a pivotal role to predict HF complications through their utilization in different computer-based algorithmic models in near future. Further studies are mandatory in this regard.

Ethics Committee Approval: All procedures performed in studies involving human participants were under the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The ethics committee affiliated to Isfahan University of Medical Sciences (IUMS) approved this study (IR.MUI.MED.REC.1399.1138).

Informed Consent: Written informed consent was obtained from the patients. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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