Heart Sci J 2020; 1(4): 25-30

Contents list available at www.heartscience.ub.ac.id

Heart Science Journal

Journal Homepage : www.heartscience.ub.ac.id

Original Article

Validation of Saiful Anwar Clinical Congestion Score in Comparison with NT-proBNP for Prediction of Short-term Outcome in Acute Heart Failure with Reduced Ejection Fraction

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ARTICLE INFO

Keywords:
Acute Heart Failure;
Reduced Ejection Fraction;
Clinical Score;
NT-proBNP;
Mortality;
Rehospitalization

ABSTRACT

Background: Risk stratification of acute heart failure (AHF) patients during hospital admission utilizing clinical scores emerges as an alternative to standard natriuretic peptide measurement. The development of Saiful Anwar clinical congestion score (SACS) as a multivariable predictive model for prediction of short-term outcome in AHF with reduced ejection fraction (AHF-rEF) requires validation in comparison to NT-proBNP.

Objective : To validate prognostic value of SACS compare with NT-proBNP in AHF-rEF

Method: This single-center, prospective cohort study was held in dr. Saiful Anwar General Hospital during January 2019 to June 2020. From total 89 AHF-rEF patients who admitted to emergency department, were assigned to SACS prospective questionnaire fulfillment and NT-proBNP measurement during first 12-hours since admission. Patients were divided into two groups based on SACS score and NT-proBNP value during admission. 90-days follow up was performed after index hospitalization with outcome of interest i.e all-cause mortality (ACM) and HF-related rehospitalization (HFR).

Discussion : NT-proBNP level >5180 pg/mL at admission was recognized as an independent predictor for short-term outcome in AHF; which is similar with the cut-off point expressed in our study [6]. In our study, performance of SACS ≥6 has shown fair discriminative ability with sensitivity 71% and specificity 78% for prediction of 90-days ACM, almost similar to the result found in standard biomarker NT-proBNP ≥5000 pg/mL (sensitivity 71% and specificity 80%). Additive value of NT-proBNP significantly increase the discriminative ability of SACS with sensitivity 86% and specificity 81% for predict 90-days ACM

Results : ACM and HFR rate in this study were 16.8% and 22.5%, respectively. SACS ≥6 demonstrated higher ACM and HFR rate during 90-days follow-up compared to SACS <6 (p=0.000; p=0.000, respectively). Performance of SACS ≥6 on admission showed good discriminative power for predicting 90-days ACM and HFR (AUC 0.841, p=0.000; AUC 0.788, p=0.000, respectively) compared to NT-proBNP ≥5000pg/mL (AUC 0.812, p=0.000; AUC 0.819, p=0.000, respectively). Additive value of NT-proBNP ≥5000pg/mL on top of SACS ≥6 increases discriminative power for predicting 90-days ACM and HFR after index hospitalization (AUC 0.836, p=0.000; AUC 0.90, p=0.000, respectively).

Conclusion: SACS has demonstrated prognostic value compared to NT-proBNP for prediction of 90-days ACM and HFR after index hospitalization in AHF-rEF patients

1. Introduction

Heart failure (HF) is a global pandemic that affected more than 37.7 million world population.[1] Prevalence of HF in Southeast Asia was reported to be 6.7% in Malaysia, 4.5% in Singapore, and 0.3% in Indonesia.[2] Data from the local registry in dr. Saiful Anwar General Hospital Malang in 2016-2017 demonstrated that 64.5% of patients hospitalized for acute worsening of HF had left ventricular ejection fraction (LVEF) < 40%, with a higher incidence of in-hospital mortality. Despite advances in the diagnosis and treatment of HF, the mortality and rehospitalization rates remain unacceptably high globally.A previous local study revealed 30-day all-cause mortality of 12.9% and 30-day HF-related rehospitalization of 20,9% in acute heart failure patients hospitalized in Malang.3 30-day HF-related rehospitalization of 20,9% in acute heart failure patients hospitalized in Malang.[3]

Acute heart failure (AHF) refers to the rapid onset or worsening of signs and/or symptoms of HF, which is a life-threatening

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https://doi.org/10.21776/ub.hsj.2020.001.04.06
Received 9 November 2020; Received in revised form 30 November 2020; Accepted 15 December 2020
Available online 25 December 2020

condition requiring urgent evaluation and treatment, typically leading to hospital admission.[4] Timely and precise risk stratification of HF patients is essential in terms of providing personalized care, especially in AHF hospitalization. In order to achieve those goals, evaluation of risk profile should be performed at two critical turning points i.e: (1) at the time of hospital admission; and (2) at the time of discharge. As a result, several predictive scores have been developed and validated in AHF.[5] However, not all of these prognostic models have prognostic value either during admission or at the time of discharge, to predict future clinical outcomes.

N-Terminal Pro-B-Type Natriuretic Peptide (NT-proBNP) is widely known as a standard biomarker, accepted by many current guidelines, for its diagnostic and prognostic value in AHF evaluation. ICON study demonstrated that NT-proBNP >5180 pg/mL during admission is an independent predictor for 76-day mortality and rehospitalization in AHF.[6] However, NT-proBNP itself is not widely implemented in daily clinical practice. REPORT-HF registry revealed that natriuretic peptide measurement for AHF in many countries only accounts for <80% of the population, even in some regions such as Southeast Asia, its utilization only accounts for <30% of the total population.[7] In Indonesia, the implementation of the natriuretic peptide is difficult contemplating the archipelagic characteristic, which relates to robust availability. Thus, clinical scores emerge as an alternative to consider.

A number of validated clinical scores such as Lucas score, Rohde score, Larissa score, ELAN-HF score, and EVEREST score had already been developed to predict clinical outcome in AHF patients in Europe.[8] However, in the Asian population, particularly in Indonesia, the development of new evidence-based clinical scores considering the heterogeneity of demographic characteristics (race, age, comorbidities) should be taken into account. Saiful Anwar clinical congestion score (SACS) is a multivariable predictive model which has been formerly calculated using clinical and laboratory data analysis to add prognostic value for prediction of short-term clinical outcome in AHF with reduced ejection fraction (AHF-rEF) patients who being hospitalized in dr. Saiful Anwar General Hospital Malang. This study is aimed to validate whether the SACS will accurately predict short-term outcomes in AHF-rEF in comparison to NT-proBNP as a standard biomarker.

2. Method

2.1. Study population

This is a single-center prospective cohort study. We enrolled 127 patients with AHF-rEF who admitted to emergency department during January 2019 to June 2020 in dr. Saiful Anwar General Hospital, Malang – Indonesia. The study design and primary results have been reported elsewhere in detail. In brief, patients were included if they were aged > 40 years and diagnosed with AHF-rEF (LVEF ≤ 40%) within 12-hours of their first evaluation by clinicians. Only the first hospitalization during the study period was registered and the AHF diagnosis was made based on 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. Exclusion criteria were: 1) pregnancy; 2) LVEF >40%; 3) isolated RV failure; 4) acute coronary syndrome; 5) aborted cardiac arrest; 6) on mechanical ventilation; 7) cardiac tamponade; 8) congenital heart disease; 9) on mechanical/bioprosthetic valve; 10) left atrial myxoma; 11) left atrial thrombus; 12) pulmonary vein thrombus; 13) on cardiac resynchronization therapy; 14) patients who discharge without ACE inhibitors/ARB and β-blockers; 15) sepsis; 16) pulmonary embolism during one month before admission; 17) pulmonary hypertension except for LV dysfunction; 18) acute exacerbation of COPD; 19) pneumothorax; 20) CKD on routine dialysis; 21) history of stroke, clinical signs of a stroke or TIA; 22) malignancy; 23) terminal medical conditions; 24) unwillingness to sign research informed consent. We collected clinical assessment, laboratory blood test, chest X-ray, electrocardiography, and echocardiography. We used SACS as a result of a prior derivation study (as shown in Table 1, Supplementary Table A and B). In this study, the evaluation of the patients included SACS prospective questionnaire fulfillment and NT-proBNP measurement during the first 12-hours of admission. Patients were divided into two groups based on SACS during admission. All patients were treated using standard HF therapy (diuretic, ACE inhibitor / ARB, and β-blocker). During 90-days follow up after discharge, 38 patients were further excluded (29 patients demonstrated poor adherence to standard medical treatment and 10 patients were lost to follow-up). The study complied with the 1975 Declaration of Helsinki and an Institutional Review Board or Local Ethical Committee approval was obtained in each participating subject.

2.2. Outcomes

The outcome of interest was defined as all-cause mortality (ACM) and HF-related rehospitalization (HFR) within 90-days after the index hospitalization. The first event of readmission or death after discharge and in-hospital mortality were regarded as the outcome date.

2.5. Statistical analysis

Categorical variables are expressed as numbers and percentages. Continuous variables are shown as mean and standard deviation. The comparison among groups and baseline characteristics were analyzed using Chi-squared test and independent T-test. Study variables were transformed for further analysis, if necessary. The predictive value of SACS was tested using univariate and multivariate logistic regression from a prior derivation study. The cut-off point of SACS (≥6) and NT-proBNP (≥5000 pg/mL) for 90-days all-cause mortality (ACM) and HF-related rehospitalization (HFR) was determined using the ROC curve based on the previous derivation set. Analysis of the discriminatory ability of both SACS and NT-proBNP was performed using the ROC curve to determine sensitivity and specificity. Kaplan-Meier curves were used for survival analysis and hazard ratio measurement for both outcomes, and log-rank tests were performed to assess differences in survival curves. The Hosmer-Lemeshow test was used to estimate the model calibration. Complete case analysis was employed for missing data. All statistical analyses were performed with SPSS software Version 22. A two-sided p-value <0.05 was considered statistically

Table 1. Final score sheet of Saiful Anwar clinical congestion score (with a total score of 10).

	Description	Value
Orthopnea (at admission)	No breathlessness during supine position	0
	Requires more than 1 pillow to avoid breathlessness or respiratory distress	1
Paroxysmal Nocturnal Dyspnea (at admission)	Never awakened with severe breathlessness during sleep	0
	Often awakened with severe breathlessness during sleep and is relieved by sitting upright	2
Rales (at admission)	No rales	0
	Bibasilar rales	1
	Rales at ≤ 50% bilateral of the lung	2
Shock (at admission)	SBP > 90 mmHg with no sign of peripheral hypoperfusion	0
	SBP < 90 mmHg with a sign of peripheral hypoperfusion	2
Hyponatremia (at admission)	Serum sodium level > 120 mmol/L	0
	Serum sodium level < 120 mmol/L	1
Increased serum creatinine (at admission)	Serum creatinine level < 1,6 mg/dL	0
	Serum creatinine level > 1,6 mg/dL	1
Tachycardia (at admission)	Heart rate < 110 bpm	0
	Heart rate > 110 bpm	1

Variable		SACS ≥6 (n=23)	SACS <6 (n=66)	P-value
Demographic Characteristics				
Age (year) (mean ± SD)		59 ± 10	59 ± 11	0,21
Sex	Female (n, %)	10 (43,3%)	28 (43%)	0,65
	Male (n, %)	13 (56,7%)	38 (57%)	
Comorbidities				
Hypertension (n, %)		12 (52,2%)	34 (51,5%)	0,36
Diabetes mellitus (n, %)		12 (52,2%)	35 (53%)	0,37
Cigarette smoking (n, %)		12 (52,2%)	35 (53%)	0,37
Atrial fibrillation (n, %)		4 (17,4%)	11 (16,8%)	0,64
Sedentary lifestyle (n, %)		13 (56,6%)	37 (56,1%)	0,38
History of MI (n, %)		9 (39,1%)	26 (39,4%)	0,79
History of prior PCI (n, %)		4 (17,4%)	12 (18,1%)	0,36
History of heart failure (n, %)		13 (56,5%)	37 (56,1%)	0,46
History of stroke / TIA (n, %)		1 (4,3%)	3 (4,5%)	0,77
History of CKD (n, %)		1 (4,3%)	3 (4,5%)	0,77
History of COPD (n, %)		1 (4,3%)	3 (4,5%)	0,77
History of PAD (n, %)		1 (4,3%)	3 (4,5%)	0,77
History of alcohol abuse (n, %)		1 (4,3%)	3 (4,5%)	0,77
Prior history of HF hospitalization (n, %)		13 (56,5%)	37 (56,1%)	0,46
History of anti-hypertensive medication (n,%)		11 (47,8%)	31 (47%)	0,38
Clinical Assessment				
Dyspnea on exertion (n, %)		22 (95,6%)	63 (95,4%)	0,74
Paroxysmal nocturnal dyspnea (n, %)		23 (100%)	60 (91%)	0,01
Orthopnea (n, %)		23 (100%)	61 (92,4%)	0,02
Palpitation (n, %)		23 (100%)	61 (92,4%)	0,02
Fatigue (n, %)		22 (95,6%)	63 (95,4%)	0,74
Lower extremity edema (n, %)		21 (91,3%)	60 (91%)	0,54
Diaphoresis (n, %)		8 (34,8%)	23 (34,9%)	0,82
Increased body weight (n, %)		12 (52,2%)	34 (51,5%)	0,36
NYHA	Class I (n, %)	0	0	-
	Class II (n, %)	0	0	-
	Class III (n, %)	8 (34,3%)	23 (34,8%)	0,37
	Class IV (n, %)	15 (65,7%)	43 (65,2%)	0,28
Forrester	Dry Warm (n, %)	0	0	-
	Dry Cold (n, %)	0	0	-
	Wet Warm (n, %)	18 (78,2%)	56 (84,3%)	0,06
	Wet Cold (n, %)	5 (21,8%)	10 (15,7%)	0,03
SBP < 90 mmHg (n, %)		6 (26,1%)	10 (15,7%)	<0,001
SBP > 140 mmHg (n, %)		10 (43,3%)	28 (43%)	0,65
HR > 100 bpm (n, %)		10 (43,3%)	21 (31,8%)	<0,001
Peripheral hypoperfusion (n, %)		6 (26,1%)	10 (15,7%)	<0,001
JVP > 9 mmHg (n, %)		14 (60,8%)	40 (60,7%)	0,86
Murmur (n, %)		8 (34,3%)	23 (34,8%)	0,37
S3/S4 Gallop (n, %)		3 (13,3%)	9 (13,6%)	0,64
Rales (n, %)		23 (100%)	62 (94%)	0,005
Wheezing(n, %)		1 (4,3%)	3 (4,5%)	0,77
Pleural effusion(n, %)		5 (21,7%)	14 (21,2%)	0,36
Hepatomegaly(n, %)		12 (52,2%)	35 (53%)	0,37
Hepatojugular reflux (n, %)		12 (52,2%)	35 (53%)	0,37
Ascites (n, %)		3 (13,3%)	9 (13,6%)	0,64
Laboratory Parameter				
Haemoglobin (g/dL) (mean ± SD)		14 ± 8	14 ± 7	0,12
Serum creatinine(mg/dL) (mean ± SD)		1,6 ± 1,0	1,5 ± 0,7	0,04
AST (U/L) (mean ± SD)		44 ± 28	45 ± 32	0,34
ALT (U/L) (mean ± SD)		39 ± 19	39 ± 21	0,37
Total cholesterol(mg/dL) (mean ± SD)		141 ± 43	141 ± 42	0,78
LDL (mg/dL) (mean ± SD)		92 ± 35	93 ± 34	0,45
HDL (mg/dL) (mean ± SD)		34 ± 15	35 ± 14	0,79
Triglyceride(mg/dL) (mean ± SD)		111 ± 54	110 ± 53	0,96
Fasting blood glucose (g/dL) (mean ± SD)		102 ± 28	101 ± 27	0,78
HbA1c (%) (mean ± SD)		5,9 ± 1,9	6 ± 2,1	0,56
Lactic acid(mmol/L) (mean ± SD)		2,4 ± 1,1	2,1 ± 1,2	0,03
NT-proBNP at admission(pg/mL) (mean ± SD)		6732 ± 912	3845 ± 426	<0,001
Potassium(mmol/L) (mean ± SD)		4 ± 1,1	4 ± 0,9	0,34
Sodium(mmol/L) (mean ± SD)		119 ± 3	125 ± 3	0,01
pH (mean ± SD)		7,3 ± 0,3	7,32 ± 0,4	0,56
pCO2 (mmHg) (mean ± SD)		75 ± 23	76 ± 24	0,44
HCO3 (mmol/L) (mean ± SD)		19 ± 5,1	19 ± 5,0	0,82
Base excess(mmol/L) (mean ± SD)		-7 ± 5	-7 ± 6	0,94
Echocardiography Parameter				
LVEF (%) (mean ± SD)		33,6 ± 6,4	36,4 ± 6,7	0,005
TAPSE (cm) (mean ± SD)		1,6 ± 0,6	1,6 ± 0,8	0,38
IVC (cm) (mean ± SD)		2,1 ± 0,6	2,1 ± 0,5	0,36
PCWP (mmHg) (mean ± SD)		22,2 ± 4,2	21,6 ± 4,3	0,45

Table 2. Baseline characteristics of the study population based on SACS stratification at admission

3. Results

3.1. Baseline characteristic

The baseline characteristics of the study population stratified by SACS are presented in Table 2. There were no significant differences in demographic characteristics and comorbidities between SACS ≥6 group and SACS <6 group. Patients with SACS ≥6 were predominantly males; more often presented with PND, orthopnea, palpitation, SBP < 90mmHg, HR >100 bpm, cold and clammy acrals, rales, and Forrester wet cold classification (all p-value > 0.05). Additionally, they had a worse renal function, more severe lactic acidosis, higher admission NT-proBNP, lower value of sodium, and lower LVEF compared to the patients with SACS <6 on admission. Regarding medical therapy during the index hospitalization, both groups revealed no significant difference (all p-value > 0.05). Length of hospital stay among both groups was noted to be significantly not different (p=0.36). All patients were discharged with no clinical congestion. All patients obtained standard heart failure therapy (ACE inhibitor / ARB, β-blocker, and/or mineralocorticoid receptor antagonist). The medical therapy regimen among both groups at the time of discharge was not significantly different. The adherence and compliance of routine drug consumption after index hospitalization were measured using Morisky Medication Adherence Scale-8 (MMAS-8) whenever patients or their families were contacted. During 90-days follow up after discharge, 89 patients revealed a score >6 which was considered as good adherence.

3.2. Performance of the SACS as Predictor of Short-term Clinical Outcome

During 90-days follow-up after discharge, among 89 patients with adequate adherence to standard medical treatment, the clinical outcome measures were observed in 15 patients (16,8%) for all-cause mortality and 20 patients (22.5%) for HF-related rehospitalization, respectively (as shown in Table 3). Fig. 1 and Fig. 2 revealed the Kaplan-Meier survival curves for both clinical outcomes stratified by each SACS. The curves are separated and trends consistent. The log-rank test for both outcomes produced a p-value of <0.001, indicating statistically significant differences in survival curves for both outcomes. Similarly, patients with SACS ≥6 had a significantly worse prognosis compared to those with SACS < 6 in both clinical outcomes measured (p =0.000 and p=0.000, respectively).

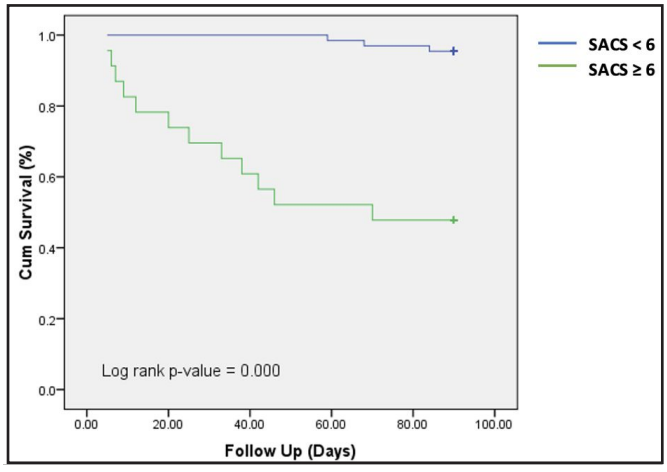

Figure 1. Kaplan-Meier survival analysis demonstrated higher cumulative 90-days all-cause mortality in SACS ≥ 6 (green line) compared to SACS < 6 (blue line) (HR 95% CI 9.08; log-rank p value = 0.000)

Table 3. Distribution of clinical outcomes during 90-days follow up

Symptoms	SACS ≥6 (n=23)	SACS <6 (n=66)	HR (CI 95%)	P value
90-days all-cause mortality (n,%)	12 (52.2%)	3 (4.5%)	9.08 (6.27 – 14.39)	0.000
In-hospital mortality (n,%)	7 (30.4%)	0 (0%)		
Post discharge mortality (n,%)	5 (21.8%)	3 (4.5%)		
90-days HF-rehospitalization (n,%)	16 (69.6%)	4 (6.1%)	11.5 (5.52 – 16.03)	0.000
Combined 90-days ACM and HFR (n,%)	5 (21.8%)	1 (1.5%)	-	0.000

Note; HF= Heart Failure; SACS= Simple Acute Coronary Syndrome; ACM= Arrhythmogenic cardiomyopathy;

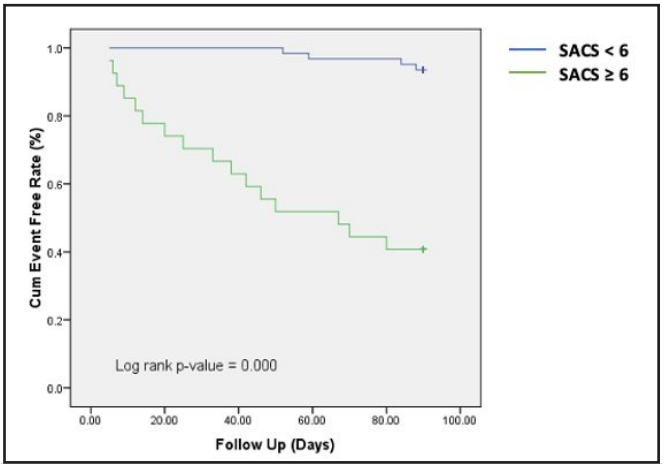

Figure 2. Kaplan-Meier survival analysis revealed higher cumulative for 90-days HF-rehospitalization free rate in SACS < 6 (blue line) compared to SACS ≥ 6 (green line) (HR 95% CI 11.5; log-rank p value = 0.000)

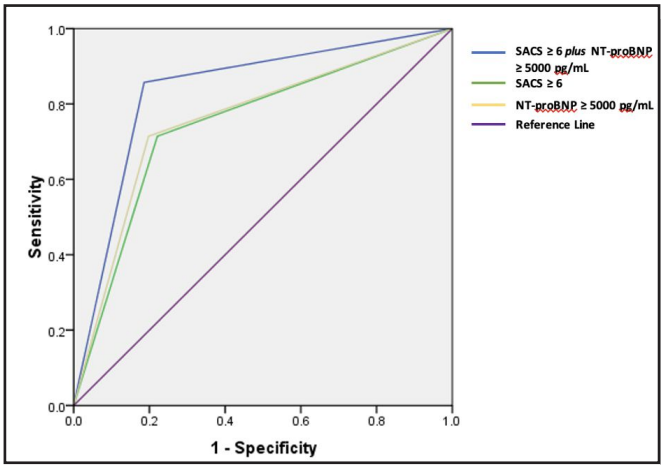

Figure 3. Comparison of performance and discriminative ability by using ROC curve among NT-proBNP ≥5000 pg/mL at admission (yellow line), SACS ≥6 at admission (green line), and both combination (blue line) for prediction of 90-days all-cause mortality

3.3. Performance of the SACS in Comparison to NT-proBNP as Predictor of Short-term Clinical Outcome

We also elucidated the predictive value of SACS ≥6 as compared to NT-proBNP ≥5000 pg/mL, in which cut-off of both variables were determined during prior derivation study. Goodness of fit study using ROC curve were performed. Discriminative ability was noted to be fair for NT-proBNP ≥5000 pg/mL (sensitivity 71.4% and specificity 80.2%; AUC 0.758 [95% 0.612 – 0.905]; p=0.002) and also for SACS ≥6 (sensitivity 71.4% and specificity 77.9%; AUC 0.747 [95% 0.60 – 0.893]; p=0.003) for prediction of 90-days all-cause mortality (as shown in Fig. 3). Addition of NT-proBNP ≥5000 pg/mL to SACS ≥ 6 was found to increase discriminative ability of the score to predict 90-days all-cause mortality (sensitivity 85.7% and specificity 81.4%; AUC 0.836 [95% 0.719 – 0.952]; p=0.000). The Hosmer-Lemeshow test revealed a good calibration (observed versus predicted outcomes) regarding NT-proBNP ≥5000 pg/mL and SACS ≥6 for 90-days all-cause mortality (p=0.86 and p=0.75, respectively).

Discriminative ability was found to be good for NT-proBNP ≥ 5000 pg/mL (sensitivity 80% and specificity 83.8%; AUC 0.819 [95% 0.707 – 0.931]; p=0.000) and was fair for SACS ≥6 (sensitivity 75% and specificity 82.5%; AUC 0.788 [95% 0.667 – 0.908]; p=0.000) for prediction of 90-days HF-related rehospitalization (as shown in Fig. 4). Addition of NT-proBNP ≥5000 pg/mL to SACS ≥6 was found to increase discriminative ability of the score to predict 90-days HF-related rehospitalization (sensitivity 90% and specificity 90%; AUC 0.90 [95% 0.815 – 0.985]; p=0.000). The Hosmer-Lemeshow test also revealed a good calibration (observed versus predicted outcomes) regarding NT-proBNP ≥5000 pg/mL and SACS ≥6 for 90-days HF-related rehospitalization (p=0.86 and p=0.82, respectively).

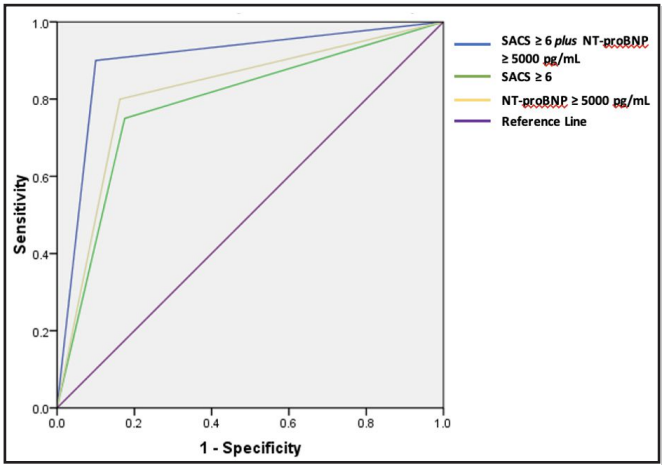

Figure 4. Comparison of performance and discriminative ability by using ROC curve among NT-proBNP ≥5000 pg/mL at admission (yellow line), SACS ≥6 at admission (green line), and both combination (blue line) for prediction of 90-days HF-related rehospitalization

Performance of SACS ≥6 among 38 patients with poor adherence to standard medical treatment during 90-days follow up was found to be less sensitive for prediction of all-cause mortality (sensitivity 66.7% and specificity 81.2%; AUC 0.740 [95%CI 0.50 – 0.98]; p=0.046) and HF-related rehospitalization (sensitivity 70% and specificity 85.7%; AUC 0.779 [95%CI 0.59 – 0.96]; p=0.010) as compared to SACS <6 (as shown in Fig. 5).

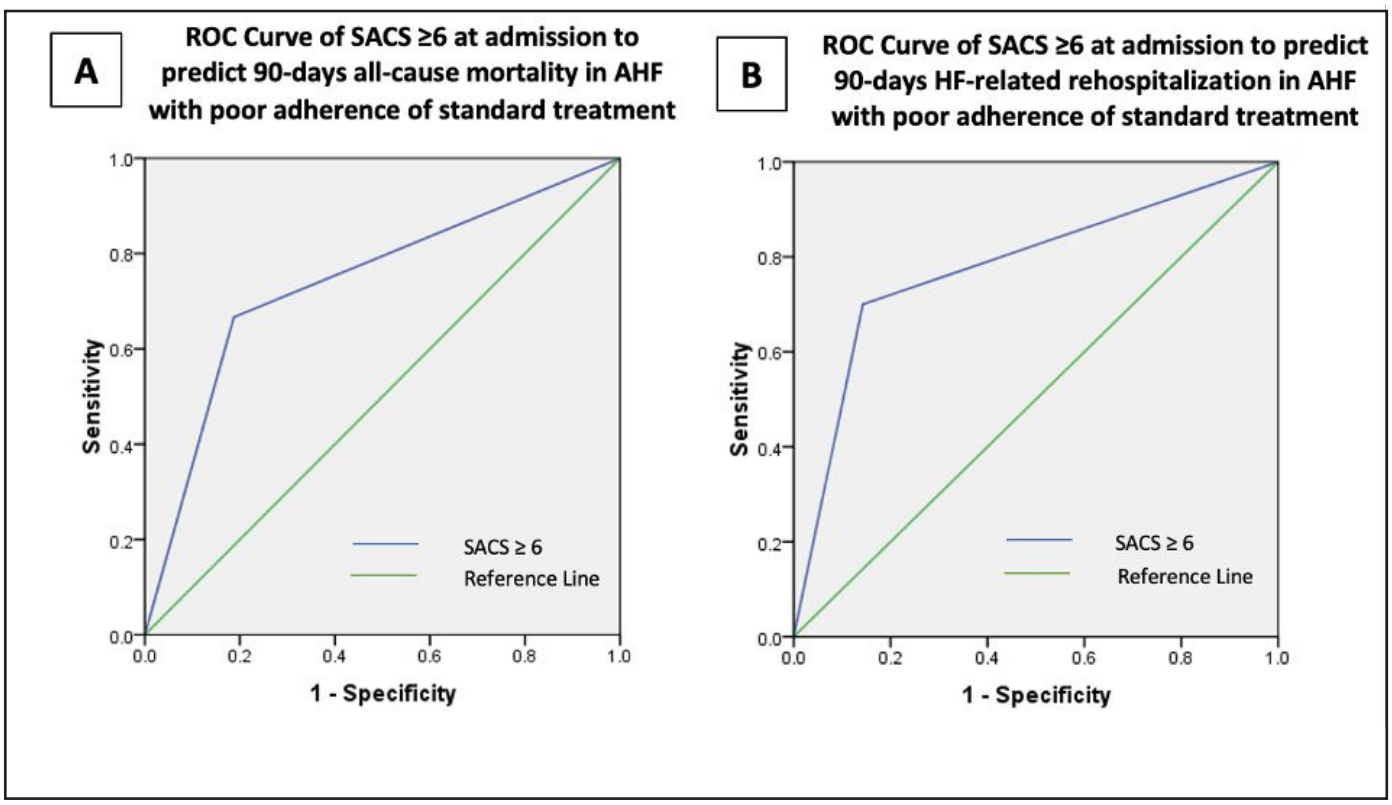

Figure 5. Discriminative ability subanalysis of SACS ≥6 at admission by using ROC curve among patients with poor adherence to standard medical treatment during 90-days follow up for prediction of all-cause mortality (Fig. 5A [AUC 0.74; p=0.046]) and HF-related rehospitalization (Fig. 5B [AUC 0.779; p=0.01])

4. Discussion

In our study, the 90-days ACM rate was 16.8%. It was nearly similar to the previous meta-analysis study which revealed a 90-days ACM in AHF patients of 14.7%.[9] The 90-days HFR rate was 22.5% in our study, which was similar to a previous meta-analysis study which showed a 90-days rehospitalization rate in AHF patients of 22.9%.10 Our study included patients with LVEF ≤40% and excluded patients with isolated RV failure. Right HF secondary to LV dysfunction was included and found in 8.9% of the total study population.

SACS comprises 7 variables (5 clinical variables and 2 laboratory variables) which are easily obtained in our daily clinical practice, at affordable cost and measured at the time of hospital admission. In our study, AHF-rEF patients who admitted with SACS ≥6 revealed a 48% increased risk of ACM and 63% increased risk of HFR compared to SACS <6 during 90-days follow-up.

In the HF-rEF subset, congestion is one of the conditions which easily found. The higher the grade of congestion, the worse the clinical and laboratory presentation may we obtain. Multivariate logistic regression analysis of the previous derivation study demonstrated a number of independent predictors of the short-term outcome, which further establish a novel clinical predictive model, known as SACS. Orthopnea and PND were found to be an independent predictor of both short-term clinical outcome. A previous study revealed that persistent orthopnea has been associated with a higher rate of rehospitalization and mortality during 6-months follow up.[11] Supine position results in the shifting of fluid from dependent venous reservoirs around the splanchnic area and in the lower extremities, increasing venous return (about 250 to 500 mL of fluid) to the thoracic compartment. Whereas, PND results as decreased response of respiratory center in the brain and blunted adrenergic activity in myocardium during sleep.[4] Rales indicate fluid overload and in the lower extremities, increasing venous return (about 250 to 500 mL of fluid) to the thoracic compartment. Whereas, PND results in a decreased response of the respiratory center in the brain and blunted adrenergic activity in the myocardium during sleep.[4] Rales indicate fluid overload and was found to be associated with poor outcome, if not immediately treated. Presentation of cardiogenic shock at admission was associated with poor outcome in AHF-rEF, similar to the result of OPTIMIZE-HF.[11]

Hyponatremia in AHF reflected an excessive activation of the renin-angiotensin-aldosterone axis, upregulation of the sympathetic nervous system, and exaggerated vasopressin release.[12] Post hoc analysis of ICON study also reported that hyponatremia at admission was corresponded to the increase NT-proBNP level and was discovered as an independent predictor of 1-year mortality.[6] OPTIMIZE-HF and ESCAPE study demonstrated an increased mortality risk in AHF patients with hyponatremia at admission during 60-180 days follow up.[12] A previous study revealed that increased serum creatinine level on admission was associated with an increase of 12% risk of ACM during 90-days follow up.[13] Tachycardia on admission during the congestion period was associated with poor prognosis as well.[4]

In the ICON study, NT-proBNP level >5180 pg/mL at admission was recognized as an independent predictor for short-term outcome in AHF; which is similar with the cut-off point expressed in our study [6]. In our study, performance of SACS ≥6 has shown fair discriminative ability with sensitivity 71% and specificity 78% for prediction of 90-days ACM, almost similar to the result found in standard biomarker NT-proBNP ≥5000 pg/mL (sensitivity 71% and specificity 80%). Additive value of NT-proBNP significantly increase the discriminative ability of SACS with sensitivity 86% and specificity 81% for predict 90-days ACM. Performance of SACS ≥6 has shown fair discriminative ability with sensitivity 75% and specificity 82% for

prediction of 90-days HFR, a little lower to the result found in standard biomarker NT-proBNP ≥5000 pg/mL (sensitivity 80% and specificity 84%). Additive value of NT-proBNP significantly increase the discriminative ability of SACS to excellent with sensitivity 90% and specificity 90% for predict 90-days HFR.

Our study has several limitations. First, it included a relatively small number of patients thus could not represent the real picture of entire population. Second, has relatively short duration of follow up. Third, it was single-center based study. Fourth, the subset of study population is limited to HF-rEF. Fifth, the precipitating factors of AHF contributing to rehospitalization is difficult to control. Sixth, prognostic evaluation of SACS and NT-proBNP in this study is only limited to the time of admission. Despite these limitations, our study demonstrated certain novelty or strengths. First, the exclusion criteria in our study was strictly defined in order to reduce bias / confounders. Second, all of study population receive disease modifying pharmacological therapy (eg. ACE inhibitors / ARBs and β-blockers) during hospitalization and after discharge. Third, our score was particularly designed for AHF population with adequate adherence to standard medical treatment.

5.Conclusion

Our study elucidated a validation of SACS in a cohort of hospitalized AHF-rEF patients. SACS revealed a good prognostic value when compared to NT-proBNP for prediction of ACM and HFR during 90-days after index hospitalization in AHF-rEF. Additive value of NT-proBNP into SACS demonstrated a higher prognostic value for prediction of ACM and HFR during 90-days after index hospitalization in AHF-rEF, as well. SACS is a simple and very easily calculated risk prediction model, thus can be able to use widely as a risk stratification tool in patients hospitalized for AHF.

6. Declarations

6.1. Ethics Approval and Consent to participate
This study was approved by local Institutional Review Board, and all participants have provided written informed consent prior to involve in the study.

6.2. Consent for publication
Not applicable.

6.3. Availability of data and materials
Data used in our study were presented in the main text.
Supplementary figure can be accessed at: https://-doi.org/10.6084/m9.figshare.13473726

6.4. Competing interests
Not applicable.

6.5. Funding source
Not applicable.

6.6. Authors contributions
Idea/concept: HLA. Design: HLA. Control/supervision: MSR, CT, AAR, NK. Data collection/processing: HLA, MSR. Extraction/Analysis/interpretation: HLA, MSR. Literature review: HLA, MSR. Writing the article: HLA, MSR. Critical review: MSR, CT, AAR, NK. . All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

6.7. Acknowledgements
We thank to Brawijaya Cardiovascular Research Center.

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