Diagnostic Performance of INA-FRAIL and Study of Osteoporotic Fractures (SOF) Index Compared to Cardiovascular Health Study (CHS) in Diagnosing Frailty Syndrome in Elderly Patients with Heart Failure

Eka Ginanjar[1], Aulia Rizka[2], Aulia Malik Ayub[3], Ikhwan Rinaldi[4], Rino Alvani Gani[5], Cosphiadi Irawan[4], Noto Dwimartutie[2]*

[1]Division of Cardiovascular, Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[2]Division of Geriatric, Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[3]Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[4]Division Hematology and Medical Oncology, Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[5]Division of Hepatobilliary, Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

Corresponding Author:
Eka Ginajar, MD.. PhD. Division of Cardiology, Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia - Cipto Mangunkusumo Hospital. Jl. Diponegoro no. 71, Jakarta 10430, Indonesia. Email: ekaginanjar.md@gmail.com.

ABSTRACT

Background: *There is currently no gold standard for assessing frailty syndrome in the elderly population with heart failure. The Cardiovascular Health Study (CHS) is a reference standard for evaluating frailty in elderly individuals with heart failure. Still, it requires a dynamometer and a spacious space, rendering it impractical in daily practice. The INA-FRAIL and Study of Osteoporotic Fractures (SOF) Index can often be easy to use; however, it has not been evaluated for diagnostic performance on elderly patients with heart failure in Indonesia. This study aimed to assess the diagnostic performance of INA-FRAIL and SOF-Index in diagnosing frailty in elderly patients with heart failure.* ***Methods:*** *This cross-sectional study evaluated the diagnostic performances of INA-FRAIL and SOF-Index compared to CHS as the gold standard in this study. The population was heart failure patients aged > 60 at Cipto Mangunkusumo Hospital.* ***Results:*** *Analysis from 81 samples shows the prevalence of frailty based on CHS (35.5%), INA-FRAIL (23.5%), and SOF-Index (8,6%). Diagnostic performance analysis of INA-FRAIL showed a sensitivity of 55,17% (95% CI 35.69–73.55), specificity 94.23% (95% CI 84.05– 98.79), and AUC 0.805 (95% CI 0.698–0.912). Diagnostic performance analysis of SOF showed 20,69% sensitivity (95% CI 7.99 – 39.72), 98.08% specificity (95% CI 89.74 – 99.95), and AUC 0.719 (95% CI 0.595 – 0.843).* ***Conclusion:*** *INA-FRAIL and SOF-Index had a significant association with CHS. The cut-off point of INA-FRAIL ≥1 showed the highest sensitivity, while INA-FRAIL ≥2 showed the highest Youden index. The cut-off point of SOF ≥1 showed the highest sensitivity and the highest Youden index.*

Keywords: *frailty, heart failure, CHS, SOF-Index, INA-FRAIL*

INTRODUCTION

Heart failure is a global pandemic with an estimated 64.3 million people affected in 2017.[1] The prevalence of heart failure increases with age, reaching 18% at ≥60 years and twofold every decade thereafter. Heart failure is the main cause of death, morbidity, and hospitalization among the elderly. Furthermore, before managing heart failure in this population, multimorbidity, polypharmacy, cognitive impairment, and frailty should be considered. A comprehensive assessment of geriatric syndromes is key in determining prognosis, patient-centered management, and improving overall clinical outcomes in the elderly with heart failure.[2–4]

Frailty is defined as a condition characterized by an increased individual's susceptibility to stress, followed by a decline in the body's physiological functions as a process of aging. It is considered one of the geriatric syndromes.[5,6] The prevalence of frailty in heart failure is 44.5%. Frailty and heart failure have a bidirectional connection; elderly people with heart failure are more likely to develop frailty, and vice versa. This is believed to be linked to inflammatory processes, metabolic abnormalities, and hormonal imbalances. It is reported that the elderly with frailty and heart failure have a worse prognosis, including increased risk of mortality, hospitalization rates, disability, risk of falls, decreased quality of life, and cognitive decline.[4,7]

Although screening and diagnosis of frailty are important to prevent complications, the topic of frailty in Indonesia has received insufficient attention for several reasons, including the lack of government support in developing healthcare policies and databases, resulting in frailty screening and diagnosis being frequently underestimated.[8] Previous research has shown that some instruments, such as the Tilburg-Frailty Indicator (TFI), Fried frailty phenotype, Frailty Index-40 (FI-40), FRAIL questionnaire, Edmonton Frail Scale (EFS), and Survey of Health, Ageing, and Retirement in Europe (SHARE), can be utilized to screen and diagnose frailty in the Indonesian population.[8–12] In addition, several instruments have also been modified and adapted, such as the Indonesian validated FRAIL Scale (INA-FRAIL) and the Tilburg Frailty Indicator-Indonesia version.[8,12]

Frailty can be diagnosed using phenotype models such as INA-FRAIL, Cardiovascular Health Study (CHS), and the Study of Osteoporotic Fractures (SOF) index.[12–14] There is currently no gold standard for assessing frailty in the elderly population with heart failure.[15,16] The CHS is considered a reference standard in numerous studies and has been used to diagnose frailty in elderly patients with heart failure. However, it requires a dynamometer and spacious room, making it inapplicable in everyday practice.[15–17] INA-FRAIL and SOF Index, on the other hand, are reasonably simple to use but have not been studied for diagnostic performance in elderly patients with heart failure in Indonesia. Thus, this study aims to assess the diagnostic performance of INA-FRAIL and SOF-Index in diagnosing frailty in elderly patients with heart failure.

METHODS

The study was a cross-sectional study aimed to assess the diagnostic performance of INA-FRAIL and SOF-Index, using CHS as the gold standard. The research population included heart failure patients over the age of 60. The sample was collected from December 2023 to August 2024 at *Poliklinik Jantung Terpadu* (PJT) and the Geriatric Outpatient Clinic at Cipto Mangunkusumo Hospital (RSCM) in Jakarta, Indonesia.

Study Population

The study participants were the elderly over the age of 60 who had been diagnosed with heart failure based on medical records, clinical signs, and symptoms. This study's population includes elderly people over 60 years old who have heart failure with NYHA functional class I-III.

Data Collection

The sampling method used in this study was the consecutive method. Patients aged over 60 years from the PJT and geriatric outpatient clinic in RSCM were assessed for eligibility criteria. Patients who met the eligibility criteria and agreed to informed consent were included. Data collection included sociodemographic

information, comorbid diseases and medication history, anthropometric and nutritional status, as well as the examination of CHS, INA-FRAIL, and SOF index.

For frailty assessment with CHS, subjects underwent interviews with respective questionnaires, performed a walking speed test with a distance of 4.75 m, and assessed hand grip strength by holding or squeezing the hand dynamometer measuring tool at the angle of the elbow and knee by making a 90 ° angle for 3-5 seconds. Measurements were repeated three times, and the highest value was obtained. For frailty assessment with INA-FRAIL, patients underwent an interview with respective questionnaires consisting of five questions. For frailty assessment with the SOF-index, the patient underwent an interview with a respective questionnaire consisting of two questions and a 5-time ability test to get up from a chair without hand assistance. There was a 5-minute rest period between the walking speed, handgrip strength, and chair stand tests.

Data Analysis

The data were analyzed using IBM SPSS for Windows version 25. We assessed the normality of all quantitative variables using the Kolmogorov-Smirnov test. Quantitative variables were presented as median with interquartile range (non-normal distribution) or mean value with standard deviation (normal distribution data). The qualitative variables were reported as percentages. In this study, we analyzed the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and likelihood ratio (LR) of the INA-FRAIL and SOF index using 2x2 tables. The receiver operating characteristic (ROC) analysis for INA-FRAIL and SOF index towards CHS was performed to obtain the new cut-off point and the Area Under Curve (AUC). According to Hosmer and Lemeshow's rule of thumb, the AUC is considered good if it is > 0.7.[18]

Ethical Clearance

This study was approved by the institutional review board of the Faculty of Medicine, Universitas Indonesia, with the number KET-99/UN2.F1/ETIK/PPM.00.02/2024. The informed consent was obtained after the patients had received the information about the study.

RESULTS

Screening for inclusion and exclusion criteria was carried out on 126 heart failure patients aged ≥60 years who came to PJT and Geriatric Outpatient Clinic RSCM in the period May 2024 to June 2024. We excluded 45 patients due to several conditions, including having NYHA IV classification, limited physical mobility, and refusal to participate. Hence, 81 patients were included in this study. The flow diagram of the screening process is depicted in **Figure 1.**

The demographic characteristics in this study revealed a median age of 68 years (64-74 years old), with the majority of subjects (53.1%) being male. The NYHA classification class II had the highest proportion (46.9%), followed by NYHA I (30.9%) and NYHA III (22.2%). The median ejection fraction was 57% (46%-62.3%), with 64.2% of subjects having heart failure preserved ejection fraction (HFpEF). The causes of heart failure were coronary heart disease (85.2%), cardiomyopathy (7.4%), heart valve disease (3.7%), and arrhythmia (3.7%). The mean body mass index (BMI) was 26.59, with 38.3% of participants classified as Obesity Class I. The MNA-Short Form score had a median of 12. It is shown that 34.6% were classified as at risk of malnutrition, while 9.9% were classified as malnourished. A total of 95.1% of subjects received polypharmacy treatment for several comorbidities, including diabetes

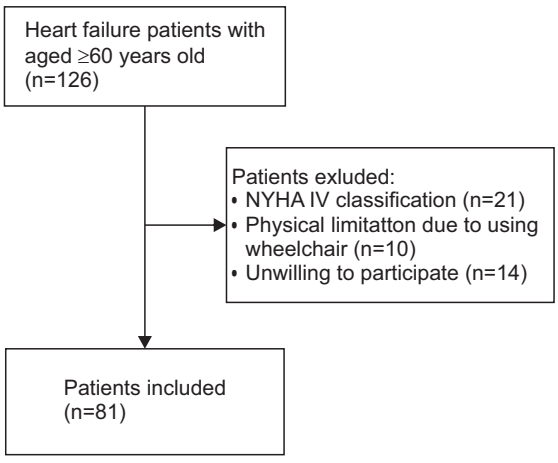

Figure 1. The flow diagram of the subject screening process

mellitus (59.3%), hypertension (85.2%), and coronary heart disease (64.2%). **Table 1** shows the baseline characteristics of this study.

The frailty diagnosis proportion using CHS was 35.5%, INA-FRAIL was 23.5%, and SOF was 8.6%. According to the CHS, 45 (55.6%) of the participants were classified as pre-frail, and 7 (8.6%) were classified as fit/robust. According to the INA-FRAIL assessment, 38 subjects (46.9%) were classified as pre-frail, while 24 (29.6%) were classified as fit/robust. Meanwhile, using the SOF index, 19 subjects (23.5%) were classified as pre-frail, and 55 (67.9%) were classified as robust/fit (**Table 2**).

Table 1. Baseline characteristics of the patients

Characteristic	Subject (N=81)
Age (median, Q1-Q3), years	68 (64-74)
Gender, n (%)	
Male	43 (53.1)
Female	38 (46.9)
Education level, n (%)	
Unschooled	1 (1.2)
Elementary-Middle	13 (16.0)
High school	35 (43.2)
Bachelor-Diploma	32 (39.5)
Marital status, n (%)	
Single	1 (1.2)
Married	65 (80.2)
Divorced	4 (4.9)
Widowhood	17 (56.7)
Income, n (%)	
< Rp 1.500.000,00	49 (60.5)
Rp 1.500.000,00-Rp 2.500.000,00	1 (1.2)
Rp 2.500.000,00 – Rp 3.500.000,00	22 (27.2)
> Rp 3.500.000,00	9 (11.1)
NYHA classification, n (%)	
Class I	25 (30.9)
Class II	38 (46.9)
Class III	18 (22.2)
Ejection fraction (Median, Q1-Q3)	57 (46-62.3)
HF classification, n (%)	
HFpEF	52 (64.2)
HFmrEF	15 (18.5)
HFrEF	14 (17.3)
HF etiology, n (%)	
Coronary heart disease	69 (85.2)
Cardiomyopathy	6 (7.4)
Valve disease	3 (3.7)
Arrhythmia	3 (3.7)
BMI (mean ± SD)	26.60 ± 4.53
Nutritional status, n (%)	
Underweight	2 (2.5)
Normal	17 (21)
Overweight	11 (13.6)
Obesity Class I	31 (38.3)
Obesity Class II	20 (24.7)
MNA-short form (Median, Q1-Q3)	12 (10-13
MNA-short form classification, n (%)	
Normal	45 (55.6)
Risk of malnutrition	28 (34.6)
Malnutrition	8 (9.9)
Polypharmacy, n (%)	
Yes	77 (95.1)
No	4 (4.9)

Comorbidities, n (%)	
Diabetes	48 (59.3)
Hypertension	69 (85.2)
Thyroid disease	0 (0.0)
Chronic liver disease	0 (0.0)
Kidney disease	16 (19.8)
Neoplasm	0 (0.0)
Hematology disorder	1 (1.2)
AIDS	0 (0.0)
Osteoarthritis	29 (35.8)
Autoimmune disease	0 (0.0)
Coronary heart disease	52 (64.2)

NYHA: New York Heart Association, HF: Heart Failure, HFpEF: Heart Failure preserved Ejection Fraction, HFmrEF: Heart Failure with mid-range or mildly reduced Ejection Fraction, HFrEF: Heart Failure reduced Ejection Fraction, BMI: Body Mass Index, AIDS: Acquired Immunodeficiency syndrome

Table 2. Characteristics of Frailty Syndrome

Frailty Syndrome	CHS (n = 81)	INA-FRAIL (n = 81)	SOF Index (n=81)
Frail	29 (35.8)	19 (23.5)	7 (8.6)
Pre-frail	45 (55.6)	38 (46.9)	19 (23.5)
Fit/Robust	7 (8.6)	24 (29.6)	55 (67.9)

According to the CHS component, the majority of subjects had low hand grip strength (79%) and low physical activity (53.1%). Weight loss was observed in only four subjects (4.9%), with the median anaerobic capacity being 140 kcal/mol.

In the INA-FRAIL instrument, it showed that 34 subjects (42%) had poor resistance, 26 subjects (32.1%) had less activity, 45 subjects (55.6%) had more than 5 comorbidities, 11 subjects (13.6%) had poor ambulation, and 7 subjects (8.6%) experienced weight loss.

The SOF Index questionnaire revealed that 8 subjects (9.9%) experienced weight loss, 9 subjects (11.1%) were unable to perform chain stands, and 17 subjects (21%) had low energy levels. The description of each component of the instrument is presented in **Table 3**.

Table 3. Components of CHS, INA-FRAIL, and SOF Index

CHS Component	Subjects (N=81)
Weight loss, n (%)	4 (4,9)
Low hand-grip strength, n (%)	64 (79,0)
Fatigue, n (%)	19 (23,5)
Slow walking speed, n (%)	34 (42,0)
Low physical activity, n (%)	43 (53,1)
Anaerobic capacity (kcal), median (RIK)	140 (0 – 655)
INA-FRAIL Component	Subject (N = 81)
Resistance, n (%)	34 (42.0)
Less activity, n (%)	26 (32.1)
Comorbidities ≥ 5 illnesses, n (%)	45 (55.6)
Poor walking effort, n (%)	11 (13.6)
Weight loss, n (%)	7 (8.6)
SOF Index Component	Subject (N = 81)
Weight loss, n (%)	8 (9.9)
Chair stands, n (%)	9 (11.1)
Low energy level, n (%)	17 (21.0)

We performed a diagnostic performance analysis on the INA-FRAIL instrument and discovered that the results of the ROC analysis score showed an AUC of 0.805 (95% CI 0.698 – 0.912) (**Table 4**). The diagnostic accuracy analysis of INA-FRAIL for CHS showed a sensitivity of 55.17% (95% CI 35.69 - 73.55) and a specificity of 94.23% (95% CI 84.05 - 98.79). The result of PPV and NPV showed 84.21% (95% CI 62.89 – 94.38) and 79.03% (95% CI 71.45 - 85.02), respectively, with +LR 9.56 (95% CI 3.04 - 30.09) and -LR was 0.48 (95% CI 0.32 - 0.72).

Table 5 shows various cut-offs for sensitivity and specificity of INA-FRAIL towards CHS. With a cut-off of ≥1, INA-FRAIL demonstrated the highest sensitivity (89.7%) and specificity (38.5%). Meanwhile, according to the Youden index, a cut-off ≥ 2 is considered optimal. **Figure 2** depicts the ROC curve for the INA-FRAIL compared to CHS.

In the ROC analysis of the SOF Index score towards CHS, the AUC score was 0.719 (CI 95% 0.595 – 0.843). SOF-Index sensitivity was 20.69% (95% CI 7.99 – 39.72), and specificity was 98.08% (95% CI 89.74 – 99.95), with PPV and NPV were 100% (95% CI 39.76-100) and 77.49% (74.85-79.93), respectively. The result of +LR was 10.76 (95% CI 1.36 – 85.07) and -LR was 0.81% (95% CI 0.67 – 0.98). The ROC curve of SOF-Index towards CHS is presented in **Figure 3**.

Table 4. Diagnostic Accuracy Parameter of INA-FRAIL towards CHS

Parameter	Value	CI 95%
AUC*	0.805	0.698 - 0.912
Sensitivity, %	55.17	35.69 - 73.55
Specificity, %	94.23	84.05 - 98.79
PPV, %	84.21	62.89 - 94.38
NPV, %	79.03	71.45 - 85.02
+LR	9.56	3.04 - 30.09
-LR	0.48	0.32 - 0.72

*p value < 0.05

Table 5. Cut-off of Sensitivity and Specificity of INA-FRAIL towards CHS

Cut-off	Sensitivity, %	Specificity, %
≥1*	89.7	38.5
≥2*	72.4	73.1
≥3*	55.2	94.2
≥4*	31.0	100%
≥5	6.9	100%

*p value < 0.05

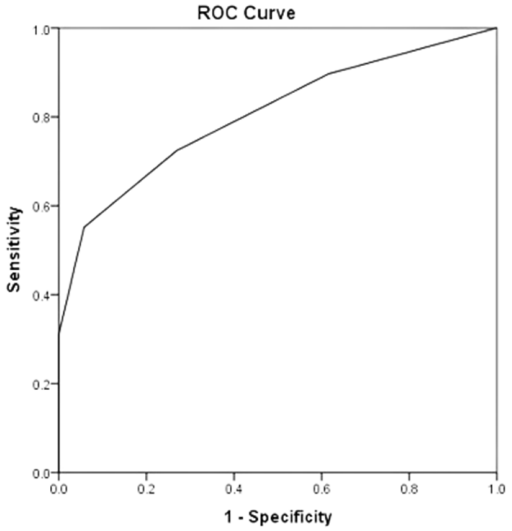

Figure 2. ROC curve INA-FRAIL towards CHS

Table 6. Diagnostic Accuracy Parameter of the SOF Index towards CHS

Parameter	Value	CI 95%
AUC*	0.719	0.595 – 0.843
Sensitivity, %	20.69	7.99 – 39.72
Specificity, %	98.08	89.74 – 99.95
PPV, %	85.71	43.14 – 97.94
NPV, %	68.92	64.72 – 72.83
+LR	10.76	1.36 – 85.07
-LR	0.81	0.67 – 0.98

*p value < 0.05

Table 7. Cut-off of Sensitivity and Specificity of the SOF Index towards CHS

Cut-off	Sensitivity, %	Specificity, %
≥1*	58,6	82,7
≥2*	20,7	98,1
≥3	3,4	100

*p value < 0.05

DISCUSSION

Frailty is becoming a concern among the elderly population that impacts health, energy, and physical abilities by increasing a patient's vulnerability to stressors (e.g., falls, infection) and risk of further decline.[19] Frailty may affect many organ systems, leading to worse clinical

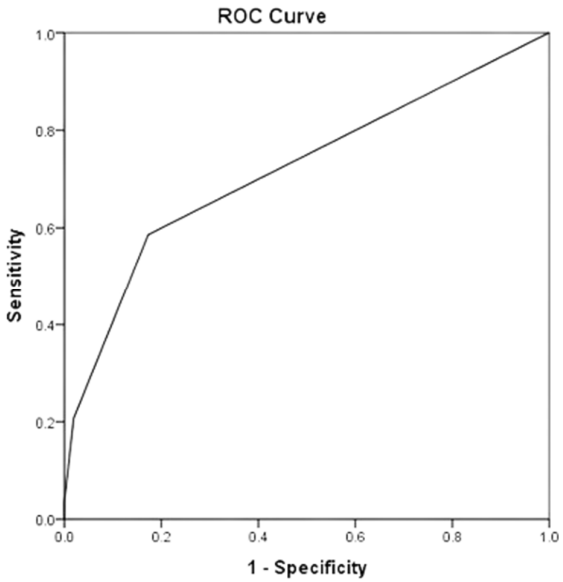

Figure 3. ROC curve SOF Index towards CHS

outcomes. Heart failure symptoms, particularly in the latter stages, can overlap with frailty signs and are often connected.[16] Furthermore, heart failure is considered to be linked to frailty. Although somewhat understood, it is mainly associated with increased inflammation. Inflammation, which leads to tissue damage, is linked to aging and heart failure, resulting in an immunological response.[6] The pro-inflammatory markers (e.g., TNF-α, IL-6, and C-reactive protein), along with hormonal as well as metabolic problems, may lead to anabolic-catabolic imbalance, thus worsening heart failure. Other mechanisms that correlate frailty to heart failure include sarcopenia, a persistent decline in functional ability, and multisystem symptoms such as tiredness and lower tolerance to physiological stresses.[4,6,20] Furthermore, establishing the diagnosis of frailty requires a comprehensive approach to history taking and physical examination, which emphasizes several key elements.[19] Patients suspected of being frail should be evaluated with a valid frailty assessment instrument.[21] Several instruments are most often used to assess frailty, such as the Fried frailty phenotype and the Rockwood frailty index.[22] In Indonesia, several instruments have been adapted and modified to fit the needs of patients, including the Indonesian validated frailty Scale (INA-FRAIL) and the Tilburg Frailty Indicator Indonesian version. In this study, we evaluated the INA-FRAIL and SOF Index scores compared to CHS to examine the frailty in HF patients.

This study involved 81 heart failure patients aged ≥ 60 years who came to the PJT and Geriatric Outpatient Clinic at Cipto Mangunkusumo National General Hospital. We found that the majority of research subjects (53.1%) were men with a median age of 68 years (64-74). Similarly, a previous study by Mehta et al[23] showed that the incidence of heart failure in men was higher than in women in all age groups, especially in the age group over 55 years.

The most common cause of heart failure in this study was coronary heart disease (85.2%). This finding is consistent with prior research conducted in the United States, Eastern Europe, the Middle East, and South Asia.[24] The median EF in this study was 57% (46-62.3), with HFpEF (64.2%) being the highest HF classification. However, this contradicts prior research that linked CHD to HFrEF. Other studies have revealed that CHD is common in people with HFpEF, with a prevalence of 35% to 60%. This could be explained by the greater incidence of epicardial CHD in HFpEF compared to HFrEF. This indicates a stronger association between epicardial CHD and HFpEF. Additionally, 85.2% of those enrolled in this study had hypertension, which is the primary cause of HFpEF. Apart from that, as we demonstrated in our findings, HfpEF is frequently observed in elderly individuals with hypertension and obesity for the reason that it can produce chronic inflammation, which leads to an increase in adipose tissue in the myocardium, culminating in cardiac remodeling. This cardiac remodeling will lead to diastolic dysfunction, which is the cause of HFpEF.[25–27]

The mean BMI among all participants was 26.59 ± 4.53, with 38.3% classified as Obese Class I. Furthermore, the MNA-SF score analysis revealed a median of 12 (10-13), with 34.6% of participants at risk of malnutrition and 9.9% experiencing malnutrition. The risk of malnutrition and the presence of malnutrition in this study are higher than those reported by Sargento et al., who investigated the nutritional condition of elderly individuals with HFrEF.

According to Sargento et al., 20% of patients are at risk of malnutrition, with 7.6% in fact dealing with malnutrition.[28] Zainul et al. also observed that 40.5% of elderly patients with HFpEF were at risk of malnutrition, with 19.3% already suffering from malnutrition.[29]

In this study, 95.1% of participants had polypharmacy. Another study by Unlu et al. observed that 85% of geriatric patients with heart failure received ≥5 medicines upon admission and 95% at discharge.[30] The high rate of polypharmacy in heart failure may be caused by heart failure management guidelines that emphasize the effectiveness of combination medication to improve the survival rate.[31] The significant polypharmacy rate in this study can also be attributed to the high prevalence of comorbidities among the study participants: 85.2% of the study participants had hypertension, 59.3% had diabetes, 19.8% had kidney illness, and 35.8% had osteoarthritis.

The socioeconomic characteristics revealed that most participants had an income of < IDR 1,500,000 (60.5%). Furthermore, 48 of the 81 individuals (59.2%) earned IDR 0 or did not work. This could be due to the research population's age, which has passed the productive age, or to impairment in everyday activities induced by heart failure.

In this study, the CHS instrument had the highest proportion of frailty (35.5%), followed by INA-FRAIL (23.5%) and SOF-Index (8.6%). Compared to the previous study conducted by Seto et al at RSCM, the prevalence of frailty from the CHS and SOF instruments in this study was higher. The disparities in frailty prevalence could be caused by differences in the study population, since the elderly with heart failure individuals involved in this study would tend to have a higher CHS score than the general elderly patient population.[32] Another study by Fajrin et al., who also assessed the diagnostic performance of CHS and FRAIL-Index in geriatric patients undergoing chronic hemodialysis at Cipto Mangunkusumo National General Hospital, found a lower prevalence of frailty for CHS (30.8%) but a higher prevalence for FRAIL Index or untranslated INA-FRAIL (35.2%). The explanation of INA-FRAIL components in the study of Fajrin et al. revealed a higher proportion of weight loss, tiredness, and slow walking pace than in this study. In this study, the most common NYHA functional classifications were class I (30.9%) and class II (46.9%). This demonstrates that the majority of research participants had heart failure with minimal or no symptoms; meanwhile, in Fajrin et al.'s study, participants were patients with chronic kidney disease who received hemodialysis, which can result in a higher INA-FRAIL score.[33]

This study evaluated the diagnostic performance of the INA-FRAIL and SOF-Index instruments in comparison to CHS, the gold standard. At present, no examination has been agreed upon as the gold standard in diagnosing frailty in the elderly population with heart failure; hence, CHS is considered the reference standard in diagnosing frailty in the heart failure population using a phenotypic model, as it is widely used and consists of a clinical subjective and objective component. However, CHS requires a dynamometer to evaluate hand grip strength components and a wider room to analyze walking speed. This limits the application of CHS in outpatient clinics.

The study divided participants into groups: INA-FRAIL ≥3 (Frail), INA-FRAIL <3 (Fit/Prefrail), as well as CHS ≥3 (Frail) and CHS <3 (Fit/Prefrail). Data analysis between INA-FRAIL and CHS revealed a significant connection (p-value < 0.001) with diagnosis accuracy was 55.17% (95% CI 35.69 - 73.55), specificity 94.23 (95% CI 84.05 - 98.79), PPV 84.21% (95% CI 62.89 - 94.38), NPV 79.03% (CI 95% 71.45 - 85.02), +LR 9.56 (95% CI 3.04 - 30.09), and −LR 0.48 (95% CI 0.32 - 0.72). These findings showed that only 55.17% of all patients classified as frail based on CHS were identified as frail by the INA-FRAIL.

Despite its high specificity, INA-FRAIL with this grouping scheme has a high false negative rate. Therefore, it is considerably too high to be used as the initial examination/screening method. To improve the accuracy of the analysis, sensitivity and specificity tests were performed on several INA-FRAIL score cutoffs. It shows that the INA-FRAIL cut-off ≥1 had the best sensitivity (89.7%) and specificity (38.5%).

However, the Youden index (0.455) was highest at the INA-FRAIL cut-off ≥2. The Youden index is an indicator used to summarize the measurement of the ROC curve. It can measure the effectiveness of diagnostic markers and select the optimal threshold value for the marker (cutoff point). The optimal cutoff value with the Youden index is the cutoff value that provides the best balance between sensitivity and specificity.[34]

The ROC analysis showed an AUC of 0.805 (95% CI 0.698-0.912). This suggests that an overall INA-FRAIL score of 0.455 shows good diagnostic performance for CHS. The INA-FRAIL cut-off value of ≥2 has good sensitivity and specificity (72.4% and 73.1%, respectively). It means that 72.4% of participants who were frail based on CHS were detected as frail using the INA-FRAIL instrument (true positive), but only 26.9% of subjects who were not frail based on CHS were deemed frail (false positive). The INA-FRAIL ≥2 cut-off has a high true positive rate for diagnosing frailty in older patients with heart failure, since most patients with frailty are diagnosed. From a false positive rate perspective, initiating non-invasive therapy, such as medical rehabilitation and nutritional therapy, in patients with INA-FRAIL ≥ 2 is safe and beneficial to patients with frailty and will not pose a risk to patients without frailty. Dong et al. in China conducted another investigation on the diagnostic accuracy of the FRAIL-Index in geriatric patients, using the Fried Frailty Phenotype/CHS as the gold standard, and reported better diagnostic performance than this study. Dong et al. discovered that at the FRAIL-Index cut-off of ≥1, FRAIL-Index exhibited a sensitivity of 97.83% and a specificity of 57.97%. The highest Youden index in Dong et al.'s research was discovered at the FRAIL-Index cut-off ≥2 (72.60), as in this study, with AUC FRAIL-Index 0.91 (95% CI 0.87-0.95).[12] Dong et al. in China conducted another investigation on the diagnostic accuracy of the FRAIL-Index in geriatric patients, using the Fried Frailty Phenotype/CHS as the gold standard, and reported better diagnostic performance than this study. Dong et al. discovered that at the FRAIL-Index cut-off of ≥1, FRAIL-Index exhibited a sensitivity of 97.83% and a specificity of 57.97%. The highest Youden index in Dong et al.'s research was discovered at the FRAIL-Index cut-off ≥2 (72.60), as in this study, with AUC FRAIL-Index 0.91 (95% CI 0.87-0.95).[35] Aprahamian et al.[36] Also conducted similar research in Brazil using the Brazilian language FRAIL-BR or FRAIL-Index. This study reported a similar diagnostic performance to the present study. A FRAIL-BR cut-off of ≥1 resulted in a sensitivity of 85% and a specificity of 37%. The Youden index was also found to be the highest at the cut-off ≥2 with a value of 27%.

The research participants were divided into two groups based on SOF-Index: SOF-Index ≥2 (Frail) and SOF-Index < 2 (Fit/Prefrail). The hypothesis test of the association between SOF-Index and CHS yields a significant relationship with a p-value of 0.004. The SOF-Index diagnostic accuracy analysis revealed the following results: sensitivity 20.69 (95% CI 7.99 - 39.72), specificity 98.08 (95% CI 89.74 - 99.95), PPV 85.71 (95% CI 43.14 - 97.94), NPV 68.92 (95% CI 64.72 - 72.83), +LR 10.76 (95% CI 1.36 - 85.07), and -LR 0.81 (95% CI 0.67 - 0.98).

Similar to INA-FRAIL findings, the SOF-Index's sensitivity with this grouping is still insufficient for use as a screening instrument despite its high specificity. These findings also show that if the SOF-Index yields a negative/robust result, there is only a 68.92% chance that the result is truly negative, and only 20.69% of patients who are positive/frail based on CHS are equally positive/frail based on SOF. The low sensitivity of the SOF-Index can be caused by a high cut-off value, hence, a sensitivity and specificity study was performed at each cut-off value. The SOF-Index cut-off of ≥1 resulted in the highest sensitivity of 58.6% and specificity of 82.7%. The greatest Youden Index (0.413) was obtained at the SOF-Index cut-off of ≥1. Although reducing the cut-off can boost sensitivity, the SOF-Index instrument's greatest sensitivity values are still insufficient to be employed as a screening tool because approximately 41.4% of patients who experience frailty are categorized as not frail. As a result, a significant proportion of frail patients will receive insufficient medical attention. The SOF-

index sensitivity and specificity findings may be explained by SOF Index components that are rare in patients with HF NYHA class I-III. The ROC analysis in this study yielded an AUC of 0.719 (95% confidence interval 0.595 - 0.843), indicating that the SOF-Index has good overall diagnostic accuracy for CHS.

Previous research has also identified the SOF Index as an instrument with low sensitivity but high specificity. Shourick et al.[37] Conducted a similar study in which they compared the SOF-Index's diagnosis accuracy to the gold standard CHS in an older population in France. The SOF-Index has a sensitivity of 66.6% (95% CI 57.2-75.2), specificity of 84.2% (95% CI 80.8-87.2), PPV of 47.8% (95% CI 39.8-55.9), and NPV of 92.1% (95% CI 89.3-94.3) at a cut-off SOF-Index of ≥2. A SOF-Index cut-off of ≥1 resulted in a sensitivity of 65.5% (95% CI 60.7-70.1), specificity of 72.6% (95% CI 66.4-78.3), PPV of 80.9% (95% CI 76.3-85.1), and NPV of 54.2% (95% CI 48.5-59.9). Other investigations by Seto et al. compared the diagnosis accuracy of the SOF-Index in the geriatric population at RSCM to the FI-40 gold standard. The diagnostic accuracy analysis using a SOF-Index cut-off ≥2 resulted in a sensitivity of 17.6% and a specificity of 99.5%.[32]

This is the first study to compare the diagnostic performance of INA-FRAIL with the SOF-Index in an elderly population with heart failure. This study also looked at the individuals' clinical characteristics (NYHA classification, ejection fraction, heart failure classification), heart failure etiology, nutritional state, comorbidities, polypharmacy, and socioeconomic level. This research also analyzes each cut-off for each instrument to obtain the cut-off with the best performance. In addition, selection bias in this study was well controlled through consecutive sampling techniques. This study did not blind the examiners, so the examiners will know the INA-FRAIL and SOF scores when examining CHS. However, detection bias is not a problem in this study because the components of each instrument are assessed by the subjects independently or are objective and can be measured.

Considering the high prevalence of frailty in the elderly population with heart failure, the findings in this study can be useful for clinicians to conduct screening for the diagnosis of frailty cases in daily clinical practice. According to this study, the INA-FRAIL instrument can be used in the elderly population with heart failure because it has high sensitivity, while the SOF index instrument is less recommended because of its poor sensitivity.

The limitation of this study is that the proportion of heart failure classifications in subjects was uneven between HFpEF, HFmrEF, and HFrEF. This makes the results of this study more representative of the elderly population with HFpEF, which constitutes 64.2% of study subjects, despite the fact that patients with HFrEF are more likely to experience frailty. As a result, further research involving the balance number in each group of heart failure classification is warranted to validate the findings.

CONCLUSION

In this study, INA-FRAIL and SOF-Index were significantly associated with CHS. The INA-FRAIL cut-off points of ≥1 demonstrated the highest sensitivity, whereas the Youden index yielded the highest value of ≥2. Furthermore, SOF≥1 demonstrates the highest both in sensitivity and the Youden index.

ACKNOWLEDGMENTS

We thank Dr. Cipto Mangunkusumo General Hospital and the Faculty of Medicine Universitas Indonesia, especially those in the Cardiovascular Division and Geriatric Division, Internal Medicine Department, Faculty of Medicine Universitas Indonesia-Cipto Mangunkusumo Hospital.

CONFLICT OF INTEREST

There is no conflict of interest.

FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats AJS. Global burden of heart failure: a comprehensive and updated review of epidemiology. Cardiovasc Res. 2022;118(17):3272–87.
2. Khan H, Kalogeropoulos AP, Georgiopoulou VV, et al. Frailty and risk for heart failure in older adults. Am Heart J. 2013;166(5):10.1016/j.ahj.2013.07.032.
3. Liu E, Lampert BC. Heart failure in older adults: Medical management and advanced therapies. Geriatr Basel Switz. 2022;7(2):36.
4. Butrous H, Hummel SL. Heart failure in older adults. Can J Cardiol. 2016;32(9):1140–7.
5. Jung HW. Frailty as a clinically relevant measure of human aging. Ann Geriatr Med Res. 2021;25(3):139–40.
6. Vitale C, Uchmanowicz I. Frailty in patients with heart failure. Eur Heart J Suppl J Eur Soc Cardiol. 2019;21(Suppl L):L12–16.
7. Goldwater DS, Pinney SP. Frailty in advanced heart failure: A consequence of aging or a separate entity? Clin Med Insights Cardiol. 2015;9(Suppl 2):39–46.
8. Pradana AA, Gobbens RJJ, Susanto H, Rohayati, Siahaan J, Lee SC. Multidimensional frailty assessment: Development and validation of the Tilburg Frailty Indicator-Indonesia version. Geriatr Nur (Lond). 2024;59:614–22.
9. Pradana AA, Chiu HL, Lin CJ, Lee SC. Prevalence of frailty in Indonesia: a systematic review and meta-analysis. BMC Geriatr. 2023;23:778.
10. Euphemia Seto Anggraini W A. Uji diagnostik sistem skor sindrom frailty berdasarkan cardiovascular health study, study of osteoporotic fracture, dan indeks frailty berbasis comprehensive geriatric assessment dibandingkan dengan indeks frailty 40 item pada pasien usia lanjut = Diagnostic test of cardiovascular health study, study of osteoporotic fracture, and frailty index comprehensive geriatric assessment scoring system for the diagnosis of frailty syndrome compared with frailty index 40 items in elderly patients [Internet]. Universitas Indonesia Library. Fakultas Kedokteran Universitas Indonesia; 2014 [cited 2024 Dec 1]. Available from: https://lib.ui.ac.id
11. Setiati S, Laksmi PW, Aryana IGPS, et al. Frailty state among Indonesian elderly: prevalence, associated factors, and frailty state transition. BMC Geriatr. 2019;19(1):182.
12. Dwipa L, Apandi M, Utomo P, et al. Adaptation and validation of the Indonesian version of the FRAIL scale and the SARC-F in older adults. Asian J Gerontol Geriatr. 2021;16:40–7.
13. Ensrud KE, Ewing SK, Taylor BC, et al. Comparison of 2 frailty indexes for prediction of falls, disability, fractures, and death in older women. Arch Intern Med. 2008;168(4):382–9.
14. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146-156.
15. Vitale C, Spoletini I, Rosano GM. Frailty in heart failure: Implications for management. Card Fail Rev. 2018;4(2):104–6.
16. Salmon T, Essa H, Tajik B, Isanejad M, Akpan A, Sankaranarayanan R. The impact of frailty and comorbidities on heart failure outcomes. Card Fail Rev. 2022;8:e07.
17. Danielsen R, Thorgeirsson G, Einarsson H, et al. Prevalence of heart failure in the elderly and future projections: the AGES-Reykjavík study. Scand Cardiovasc J SCJ. 2017;51(4):183–9.
18. Assessing the fit of the model. Applied logistic regression [Internet]. John Wiley & Sons, Ltd; 2013 [cited 2024 Dec 1]. p. 153–225. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/9781118548387.ch5
19. Robert Allison II, Assadzandi S, Adelman M. Frailty: evaluation and management. Am Fam Physician. 2021; 103(4):219–26.
20. Tersalvi G, Gasperetti A, Schiavone M, et al. Acute heart failure in elderly patients: a review of invasive and non-invasive management. J Geriatr Cardiol JGC. 2021;18(7):560–76.
21. Dent E, Martin FC, Bergman H, Woo J, Romero-Ortuno R, Walston JD. Management of frailty: opportunities, challenges, and future directions. Lancet Lond Engl. 2019;394(10206):1376–86.
22. Hoogendijk EO, van Kan GA, Guyonnet S, Vellas B, Cesari M. Components of the frailty phenotype in relation to the frailty index: Results from the toulouse frailty platform. J Am Med Dir Assoc. 2015;16(10):855–9.
23. Mehta PA, Cowie MR. Gender and heart failure: a population perspective. Heart. 2006;92(Suppl 3):iii14–18.
24. Chioncel O, Lainscak M, Seferovic PM, et al. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. Eur J Heart Fail. 2017;19(12):1574–85.
25. Ho JE, Gona P, Pencina MJ, et al. Discriminating clinical features of heart failure with preserved vs. reduced ejection fraction in the community. Eur Heart J. 2012;33(14):1734–1741.
26. Trevisan L, Cautela J, Resseguier N, et al. Prevalence and characteristics of coronary artery disease in heart failure with preserved and mid-range ejection fractions: A systematic angiography approach. Arch Cardiovasc Dis. 2018;111(2):109–18.
27. Golla MSG, Shams P. Heart Failure With Preserved Ejection Fraction (HFpEF). In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Jun 26]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK599960/
28. Sargento L, Satendra M, Almeida I, Sousa C,

Gomes S, Salazar F, et al. Nutritional status of geriatric outpatients with systolic heart failure and its prognostic value regarding death or hospitalization, biomarkers, and quality of life. J Nutr Health Aging. 2013;17(4):300–4.
29. Zainul O, Perry D, Pan M, et al. Malnutrition in heart failure with preserved ejection fraction. J Am Geriatr Soc. 2023;71(11):3367–75.
30. Unlu O, Levitan EB, Reshetnyak E, et al. Polypharmacy in older adults hospitalized for heart failure. Circ Heart Fail. 2020;13(11):e006977.
31. Perreault S, Schnitzer ME, Disso E, Qazi J, Boivin-Proulx LA, Dorais M. Polypharmacy and risk of mortality among patients with heart failure following hospitalization: a nested case-control study. Sci Rep. 2022;12(1):19963.
32. Seto E, Setiati S, Laksmi PW, Tamin TZ. Diagnostic test of a scoring system for frailty syndrome in the elderly according to cardiovascular health study, study of osteoporotic fracture and comprehensive geriatric assessment-based frailty index compared with frailty index 40 items. Acta Medica Indones. 2015;47(3):183–7.
33. Akhmad Fajrin Priadinata A. Performa indeks FRAIL dan indeks cardiovascular health study (CHS) untuk memprediksi status frailty pada pasien dewasa hemodialisis kronik di RSUPN Cipto Mangunkusumo = [Internet]. Universitas Indonesia Library. Fakultas Kedokteran Universitas Indonesia; 2022 [cited 2024 Jun 26]. Available from: https://lib.ui.ac.id
34. Fluss R, Faraggi D, Reiser B. Estimation of the youden index and its associated cut-off point. Biom J. 2005;47(4):458–72.
35. Dong L, Qiao X, Tian X, et al. Cross-cultural adaptation and validation of the FRAIL scale in Chinese community-dwelling older adults. J Am Med Dir Assoc. 2018;19(1):12–17.
36. Aprahamian I, Cezar NO de C, Izbicki R, et al. Screening for frailty with the FRAIL scale: A comparison with the phenotype criteria. J Am Med Dir Assoc. 2017;18(7):592–6.
37. Shourick J, Lucas P, Tavassoli N, et al. Sensitivity, specificity, positive and negative predictive values of a postal mail self-screening tool for frailty in french older adults. J Frailty Aging. 2023;12(3):175–181.