The Journal of Nutrition, Health and Aging 28 (2024) 100253

Contents lists available at ScienceDirect

The Journal of Nutrition, Health and Aging

journal homepage: www.elsevier.com/locate/jnha

Original Article

What is the additive value of nutritional deficiency to VA-FI in the risk assessment for heart failure patients?

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ARTICLE INFO

Keywords:
Heart failure
Frailty index
Malnutrition
All-cause mortality

ABSTRACT

Objectives: To assess the impact of adding the Prognostic Nutritional Index (PNI) to the U.S. Veterans Health Administration frailty index (VA-FI) for the prediction of time-to-death and other clinical outcomes in Veterans hospitalized with Heart Failure.

Methods: A retrospective cohort study of veterans hospitalized for heart failure (HF) from October 2015 to October 2018. Veterans ≥50 years with albumin and lymphocyte counts, needed to calculate the PNI, in the year prior to hospitalization were included. We defined malnutrition as PNI ≤43.6, based on the Youden index. VA-FI was calculated from the year prior to the hospitalization and identified three groups: robust (≤0.1), prefrail (0.1−0.2), and frail (>0.2). Malnutrition was added to the VA-FI (VA-FI-Nutrition) as a 32nd deficit with the total number of deficits divided by 32. Frailty levels used the same cut-offs as the VA-FI. We compared categories based on VA-FI to those based on VA-FI-Nutrition and estimated the hazard ratio (HR) for post-discharge all-cause mortality over the study period as the primary outcome and other adverse events as secondary outcomes among patients with reduced or preserved ejection fraction in each VA-FI and VA-FI-Nutrition frailty groups.

Results: We identified 37,601 Veterans hospitalized for HF (mean age: 73.4 ± 10.3 years, BMI: 31.3 ± 7.4 kg/m^2). In general, VA-FI-Nutrition reclassified 1959 (18.6%) Veterans to a higher frailty level. The VA-FI identified 1,880 (5%) as robust, 8,644 (23%) as prefrail, and 27,077 (72%) as frail. The VA-FI-Nutrition reclassified 382 (20.3%) from robust to prefrail and 1577 (18.2%) from prefrail to frail creating the modified-prefrail and modified-frail categories based on the VA-FI-Nutrition. We observed shorter time-to-death among Veterans reclassified to a higher frailty status vs. those who remained in their original group (Median of 2.8 years (IQR:0.5,6.8) in modified-prefrail vs. 6.3 (IQR:1.8,6.8) years in robust, and 2.2 (IQR:0.7,5.7) years in modified-frail vs. 3.9 (IQR:1.4,6.8) years in prefrail). The adjusted HR in the reclassified groups was also significantly higher in the VA-FI-Nutrition frailty categories with a 38% increase in overall all-cause mortality among modified-prefrail and a 50% increase among modified-frails. Similar trends of increasing adverse events were also observed among reclassified groups for other clinical outcomes.

Abbreviations: HF, Heart failure; VA, Veterans affairs; FI, Frailty index; EMR, Electronic medical record; EF, Ejection fraction; PNI, Prognostic nutritional index; ED, Emergency department; UC, Urgent care; LOS, Length of stay; VA-FI, Veterans health administration frailty index; HFrEF, Heart failure with reduced ejection fraction; HFpEF, Heart failure with preserved ejection fraction; COPD, Chronic obstructive pulmonary disease.

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http://doi.org/10.1016/j.jnha.2024.100253
Received 16 February 2024; Received in revised form 19 April 2024; Accepted 20 April 2024
Available online xxx

Conclusion: Adding PNI to VA-FI provides a more accurate and comprehensive assessment among Veterans hospitalized for HF. Clinicians should consider adding a specific nutrition algorithm to automated frailty tools to improve the validity of risk prediction in patients hospitalized with HF.

Clinical Perspective

What is new?

VA-FI-Nutrition, a frailty index based on the accumulation of 31 deficits with the addition of malnutrition, leads to a more accurate assessment of mortality based on hazard ratios in patients hospitalized for HF exacerbations.

What are the clinical implications?

Adding malnutrition to frailty screening can help to determine which patients hospitalized for HF exacerbations are at higher risk for adverse outcomes. Utilizing this screening tool early on during hospital admissions may help identify patients who need either earlier interventions or changes in medical management to prevent worse outcomes and prolonged hospitalizations.

1. Introduction

The prevalence of heart failure (HF), a leading cause of chronic morbidity and death in the United States, has been consistently rising, estimated to increase from 5.8 million people in 2012 to almost 8.5 million by 2030 [1,2]. The lifetime risk of HF is notably high, ranging from 20–45% for individuals aged 45 and older [3]. Older adults with HF often have additional medical conditions, elevating their risk for unfavorable outcomes, including mortality. Specifically, 50% of Medicare beneficiaries do not survive three years after hospitalization due to HF [4], and the median survival time for hospitalized HF patients is 2.4 years [5].

Frailty serves as a measure to comprehend the intricate interplay of these outcomes in a patient's clinical journey. It is characterized by an overall decline in physiological reserve and an increased susceptibility to stressors, functioning as a prognostic marker for HF patients [6,7]. Malnutrition, a crucial component of frailty, results from an imbalance between catabolism and anabolism [8,9], and is closely linked to adverse outcomes in patients with chronic HF [10]. Both frailty and malnutrition are prevalent clinical phenomena in HF, with the same proportion of 45% and are associated with a heightened risk of mortality [11–14].

To enhance the identification of frail individuals, electronic medical record (EMR)-based frailty measures, such as the Veterans Affairs Frailty Index (VA-FI), have been developed [15]. The VA-FI, an automated electronic frailty index derived from a large healthcare system, has demonstrated a robust association with mortality and cardiovascular outcomes [16]. The prognostic nutritional index (PNI), an established assessment of nutritional status based on lab results, including albumin and serum lymphocyte counts, has proven to be a superior marker of nutritional status in HF patients [17].

Given the association of malnutrition and adverse outcomes in patients with HF, the objective of this study is to evaluate the impact of adding a marker of nutritional deficiency, using the PNI, to the VA-FI. Specifically, we sought to evaluate if these changes are associated with clinical outcomes.

2. Methods

We used the Corporate Data Warehouse (CDW) data that captures electronic medical record data for veterans admitted to all VHA facilities. The study protocol was approved by the Research & Development Committee of the Michael E. DeBakey VA Medical Center and Baylor College of Medicine Institutional Review Board (IRB# H-464220).

2.1. Study design

We conducted a retrospective cohort study of veterans aged 50 or older, hospitalized with a principal diagnosis of HF from October 2015 to 2018. The International Classification of Diseases (ICD10) hospital discharge codes were used to identify patients with a principal diagnosis of HF *(I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43.x, I50.x, P29.0*) [18,19]. We included veterans who had available laboratory data including albumin and lymphocyte counts measured in an outpatient clinic visit prior to inpatient admission.

2.2. Malnutrition assessment

The most recent albumin and lymphocyte count, at least 72 h prior to index inpatient admission were used to calculate PNI. Based on medical team consensus, 72 h was used as the cut-off point to avoid labs that would represent the acute condition. PNI was calculated using the following formula: PNI = 10 x serum albumin (g/dL) + 0.005 x total lymphocyte count (mm^3) [20]. The original cut-off points for nutritional status classification are as follows: Normal (PNI $>$ 38), moderate (PNI 35–38), and severe (PNI $<$ 35) malnourishment [21]. For our study, malnutrition was defined as PNI $\leq$43.6, based on the Youden index (R-package, 'CutPointR), Supplementary Table 1. The Youden index is used to interpret and evaluate biomarkers. It also measures the overall diagnostic effectiveness as a function of sensitivity and specificity, i.e., area under the curve [22,23]. The normal range of albumin was also defined as 3.4−5 g/dl [24] while this range for lymphocyte count was 0.9–5.1 K/uL [25].

2.3. Frailty assessment

The validated 31-deficit VA-FI was used to assess frailty based on an accumulation of deficits model [16]. VA-FI includes domains related to chronic health conditions, mental health, cognition, function, and geriatric syndromes. Two of the deficits, failure to thrive and weight loss, are related to nutritional status. All deficits were curated from ICD9/10 and CPT codes, as appropriate. VA-FI was calculated using data from the year prior to hospitalization and identified three groups: robust ($\leq$0.1), prefrail (0.1−0.2), and frail ($>$0.2) [26].

Frailty Assessment with PNI as a nutritional index: After calculating the PNI, we added the PNI indicator (PNI $\leq$43.6) as the 32nd deficit and scaled the result to 0–1 by dividing to 32 to create VA-FI-Nutrition. We created three VA-FI-Nutrition classes (robust, pre-frail and frail) using the same cut-off points as used by VA-FI. The VA-FI is a normalized value and the cut-off points do not change based on the numbers of deficits.

Reclassified Frailty Groups: To understand the impact of adding PNI as an additional deficit to VA-FI, we created a three-by-three table. Rows were presented as frailty categories based on VA-FI; and columns based on VA-FI nutrition. We hypothesized that the addition of malnutrition as a deficit may recategorize a veteran from a lower frailty group (original frailty group defined by the row) to a higher frailty group (noted in the columns) (Fig. 1). Two new groups emerged: modified-prefrail (M-PF) and modified-frail (M-F). M-PF represents a group of Veterans who were originally classified as robust by VA-FI and subsequently reclassified as pre-frail by VA-FI Nutrition. M-F represents those Veterans who were originally classified as pre-frail by VA-FI and reclassified as frail by VA-FI Nutrition.

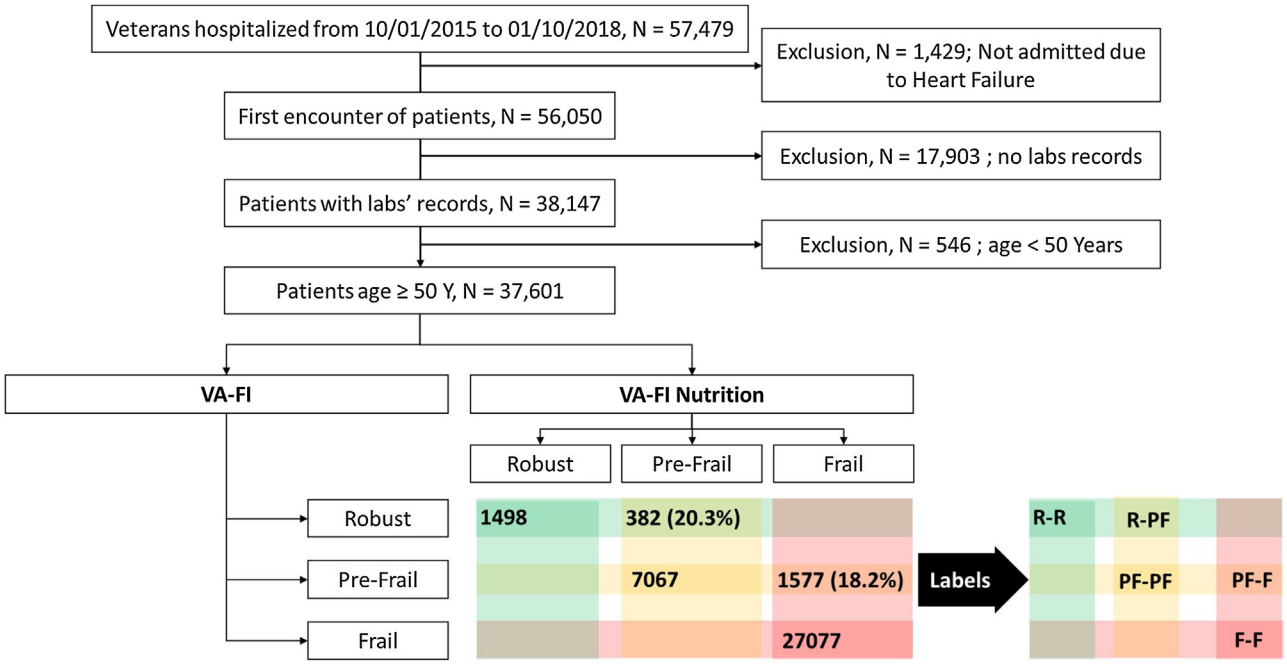

Fig. 1. Study cohort diagram. Using the final cohort, we demonstrate the interplay of VA-FI and VA-FI-Nutrition and how adding nutritional deficit to the frailty index may reclassify frailty status.
(R-R = Robust-Robust, R-PF = Robust- Prefrail, PF-PF = Prefrail-Prefrail, PF-F = Prefrail-Frail, F-F = Frail-Frail).

2.4. Outcomes

The primary outcome of interest was post-discharge all-cause mortality over the study period. The time-to-death was measured by subtracting the date of death from the date of hospital discharge. The follow-up period was until March 22, 2021.

The secondary outcomes were inpatient death, 1-year mortality, 1-year emergency department (ED) or urgent care (UC) visits post-discharge within VA facilities, prolonged length of stay (LOS), and 1-year rehospitalization. The inpatient death was defined as all-cause mortality that took place during the hospitalization, between admission and discharge datetime. 1-year mortality was defined as all-cause mortality happened between discharge datetime and a year after the index date of discharge. 1-year emergency department (ED) or urgent care (UC) visits post-discharge within VA facilities was defined as ED or UC encounter due to any reason between discharge time till one year after the index date of discharge. Prolonged length of stay (LOS) was defined as LOS greater than six days, and 1-year rehospitalization was defined as hospital readmission due to any reason between discharge time till one year after the index date of discharge).

The different causes of re-hospitalization were extracted from the primary diagnosis mentioned in the discharge summary of hospitalization and based on the consensus by our clinical experts the most common diagnosis was known to be Cardiovascular and Respiratory diseases, each containing different conditions. The most common conditions forming cardiovascular disorders were congestive heart failure, hypertensive heart disease, myocardial infarction, and arrhythmia, and for respiratory disorders, the most common conditions were chronic obstructive pulmonary disease (COPD), pneumonia, acute and chronic respiratory failure, and pleural effusion. The data of the main reasons for EC and UC visits were extracted from the chief complaints of participants during their outpatient encounters or the principal cause of visit noted by the caregiver. The most prevalent complaints or causes of visits were related to cardiovascular diseases (chest pain, dyspnea, congestive heart failure, syncope and collapse, and hypotension) or respiratory diseases (COPD exacerbation, acute bronchitis, pneumonia, cough, hemoptysis, hypoxemia).

2.5. Variables

We extracted data on age, sex, race, ethnicity, BMI, EF and the most recent albumin and lymphocyte count from Veterans' structured EMR at the time of VA-FI and PNI calculation and we excluded any laboratory data during acute visits. We considered race as three groups of black, white, and other. For ethnicity, we divided participants in two groups of Hispanic or non-Hispanic. Using the cut-off point of 30, we considered those with BMI $\geq$ 30 as obese [27]. EF was based on the last report of 2D-echocardiography by cardiologist.

2.6. Statistical analysis

For demographic variables and baseline characteristics, we estimated mean and standard deviation for continuous variables and count and percentage for categorical variables. We used chi-square analyses for categorical values. We compared the similarities between malnutrition and the other deficits of VA-FI using the Jaccard-Needham Index (JNI). JNI measures the similarity between two sets of data with values ranging from zero to one, with one representing the dataset that is most similar [28].

Kaplan-Meier estimators were used to examine the association between reclassified frailty groups by VA-FI-nutrition compared to frailty groups by VA-FI and all-cause mortality. We estimated the hazard ratio (HR) and 95% confidence intervals of all-cause mortality over the study period for Veterans who were recategorized to a higher frailty status by VA-FI-nutrition compared to those who remained in the same group. For secondary outcomes, the odds ratio was determined with logistical regression. Models were adjusted for available baseline parameters: sex, race, ethnicity, age, BMI, and left ventricular ejection fraction (LVEF).

We performed a subgroup analysis by stratifying the population based on LVEF levels: heart failure reduced EF (HFrEF), which is defined as LVEF less than 40% and heart failure with preserved ejection fraction (HFpEF) defined as LVEF greater than 50%. For all variables, a P value $<$0.05 was considered as statistically significant.

3. Results

3.1. Patient characteristics

We identified 37061 veterans who met the study criteria. (Mean age: 73.4 ± 10.3 years; BMI: 31.3 ± 7.4 kg/m^2; male 99.2%; white 70.8%). 41% of Veterans were in the age group of 65 to 75 years. 51% of Veterans were classified as obese. The demographics and disease-related characteristics of individuals included in the study are shown in Table 1. Using the PNI, 51% of HF Veterans were identified to have nutritional deficiency. The prevalence of abnormal albumin (28.6%) or abnormal lymphocyte count (26.5%) was lower than the prevalence of abnormal PNI (51.9%). The VA-FI identified 1,880 (5%) as robust, 8,644 (23%) as prefrail, and 27,077 (72%) as frail while VA-FI-Nutrition classified 1,498 (4%) as robust, 7,449 (20%) as prefrail, and 28,654 (76%) as frail (Fig. 1).

The percentage of Veterans with hypoalbuminemia was significantly higher in modified-prefrail (41.9%) compared to robust (10.2%). The percentage of Veterans with lymphopenia was also significantly higher in modified-prefrail (34.8%) compared to robust (11.4%). The same trend was observed for modified-frail for albumin (45.0%) and lymphocyte count (35.8%) when compared to prefrail for abnormal albumin (14.8%) and lymphocyte counts (16.6%). Notably, all Veterans in the modified-prefrail and modified-frail categories had an abnormal PNI, while the proportion of Veterans with an abnormal PNI was lower in the robust (16.4%), prefrail (27.3%), and frail (56.9%) categories. Based on the measurement of similarity, JNI and PNI had a low association with the VA-FI deficits of weight loss and failure to thrive (0.07 and 0.03, respectively).

3.2. Outcomes

Primary outcome: Over a median follow up of 439 days (IQR 156 to 866), 73% of Veterans (27,671 individuals) died. Among all groups of frailty, time-to-death was shortest in the frail population (Median of 2.0 years, IQR, 0.6–5.0), followed by the modified-frail group (Median of 2.2 years, IQR, 0.7, 5.7), modified-prefrail group (Median of 2.8 years, IQR, 0.5, 6.8), prefrail group (Median of 3.9 years, IQR, 1.4, 6.8) and the robust population had the longest value (Median of 6.3 years, IQR 1.8,6.8)

Table 1
Patient demographics, nutritional indices, and disease-related outcomes compared between different various groups of original frailty status and regrouped ones.

	Robust-Robust	Robust-Prefrail	Prefrail-Prefrail	Prefrail-Frail	Frail-Frail
Demographics					
N	1,498	382	7,067	1,577	27,077
Age, M(SD)	67.8(10.2)	71.6(11.2)	71.6(10.4)	73.6(10.5)	74.8(10.2)
Age, 50–65, N (%)	637(42.5)	113(29.6)	1,821(25.8)	291(18.5)	4,028(14.9)
Age, 65−75, N (%)	530(35.4)	137(35.9)	2,889(40.9)	664(42.1)	10,698(39.5)
Age, 75+, N (%)	331(22.1)	132(34.6)	2,357(33.4)	622(39.4)	12,351(45.6)
Sex, Male	1,454(97.1)	374(97.9)	6,903(97.7)	1,547(98.1)	26,516(97.9)
Race					
White	865(57.7)	219(57.3)	4,627(65.5)	987(62.6)	19,545(72.2)
Black	527(35.2)	135(35.3)	1,936(27.4)	479(30.4)	5,794(21.4)
Others	106(7.1)	028(7.3)	504(7.1)	111(7.0)	1,738(6.4)
Ethnicity-Hispanic	070(4.7)	009(2.4)	339(4.8)	070(4.4)	1,593(5.9)
BMI, M(SD)	29.7(7.9)	28.7(8.4)	30.4(7.8)	29.5(7.7)	30.4(7.7)
BMI ≥ 30, N (%)	614(41.0)	135(35.3)	3,222(45.6)	643(40.8)	12,339(45.6)
EF Status					
HFrEF, N (%)	546(36.4)	135(35.3)	2,893(40.9)	656(41.6)	11,983(44.3)
HFmrEF, N (%)	057(3.8)	014(3.7)	450(6.4)	105(6.7)	2,103(7.8)
HFpEF, N (%)	225(15.0)	066(17.3)	1,740(24.6)	481(30.5)	10,085(37.2)
Labs					
ALB, M(IQR)	3.9(3.7, 4.1)	3.4(3.2, 3.6)	3.8(3.6, 4.1)	3.4(3.1, 3.6)	3.6(3.3, 3.9)
Hypoalbuminemia, N (%)	153.0(10.2)	160.0(41.9)	1048.0(14.8)	710.0(45.0)	8679.0(32.1)
LYF, M(IQR)	1.7(1.3, 2.2)	1.1(0.9, 1.4)	1.6(1.2, 2.0)	1.1(0.9, 1.4)	1.3(0.9, 1.8)
Lymphopenia, N (%)	171.0(11.4)	133.0(34.8)	1175.0(16.6)	565.0(35.8)	7909.0(29.2)
PNI, M(IQR)	47.5(44.9, 51.0)	40.5(37.9, 42.2)	46.5(43.2, 50.0)	40.1(37.5, 42.1)	42.8(38.6, 46.9)
PNI < 43.85, N (%)	246.0(16.4)	382.0(100.0)	1931.0(27.3)	1577.0(100.0)	15397.0(56.9)
Conditions					
Dementia, N (%)	23(1.5)	10(2.6)	326(4.6)	105(6.7)	6787(25.1)
Cancer, N (%)	74(4.9)	35(9.2)	837(11.8)	266(16.9)	6931(25.6)
Cerebrovascular accident, N (%)	18(1.2)	10(2.6)	435(6.2)	125(7.9)	6161(22.8)
Outcomes					
Inpatient Death, N (%)	24.0(1.6)	12.0(3.1)	122.0(1.7)	34.0(2.2)	854.0(3.2)
Death-1-year, N (%)	264.0(17.6)	113.0(29.6)	1447.0(20.5)	497.0(31.5)	9380.0(34.6)
Prolonged LOS, N (%)	333.0(22.2)	107.0(28.0)	1607.0(22.7)	456.0(28.9)	7591.0(28.0)
Time-to-Death, year, M(IQR)	6.3(1.8, 6.8)	2.8(0.5, 6.8)	3.9(1.4, 6.8)	2.2(0.7, 5.7)	2.0(0.6, 5.0)
ED and UC visits, N (%)	890(59.4)	239(62.6)	4,534(64.2)	1,049(66.5)	19,780(73.1)
Rehospitalization, N (%)	522(34.8)	156(40.8)	2,864(40.5)	725(46.0)	13,578(50.1)
Causes of ED and UC visits					
Cardiovascular Complaints, N (%)	354(39.8)	90(37.7)	1,693(37.3)	386(36.8)	6,972(35.2)
Respiratory Complaints, N (%)	80(9.0)	24(10.0)	419(9.2)	96(9.2)	1,882(9.5)
Causes of Rehospitalization					
Cardiovascular Diagnosis, N (%)	334(64.0)	98(62.8)	1,725(60.2)	386(53.2)	7,356(54.2)
Respiratory Diagnosis, N (%)	31(5.9)	12(7.7)	232(8.1)	66(9.1)	1,145(8.4)

HFrEF = Heart Failure with reduced Ejection Fraction (LVEF < 40%).
HFmrEF = Heart Failure with Mid-Range Ejection Fraction (LVEF = 40–49%).
HFpEF = Heart Failure with preserved Ejection Fraction (LVEF > 50%).
ED = Emergency Department, UC = Urgent Care, LOS = Length of Stay.

The percentage of each cause of rehospitalization or ED and UC visits is calculated by dividing the number of each condition in different groups of original frailty status and regrouped ones to the total number of rehospitalization or ED and UC visits in each group.

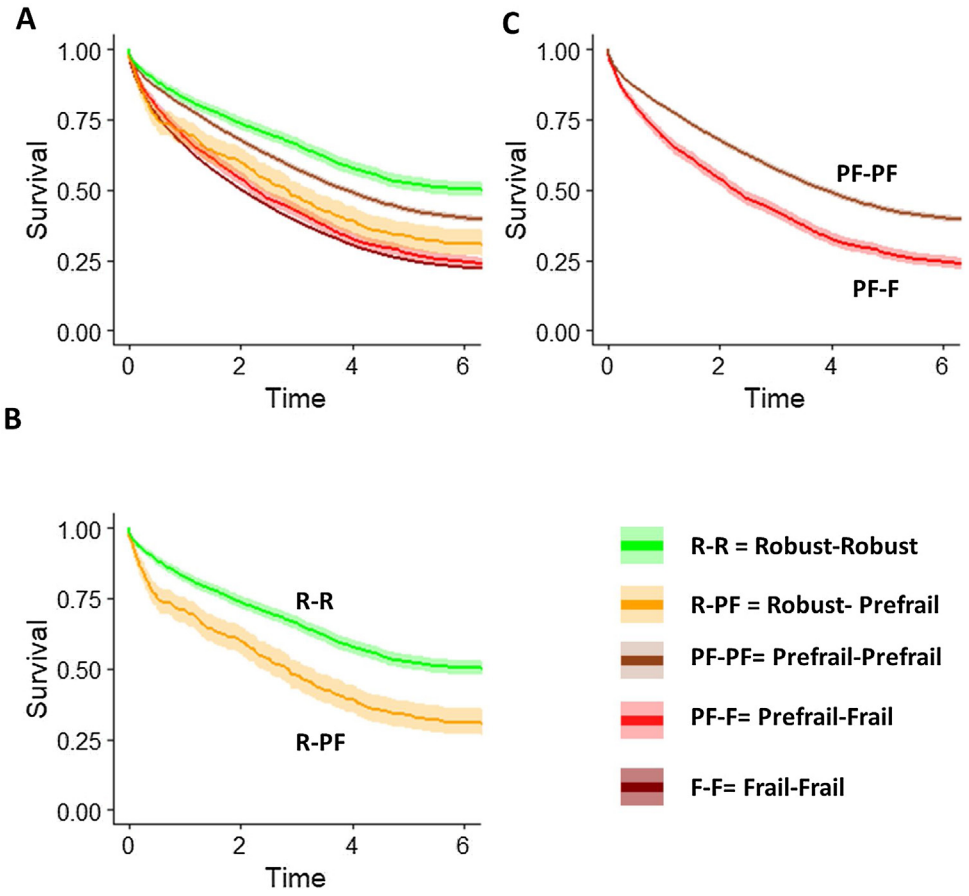

Fig. 2. Kaplan-Meier curve demonstrating the comparisons of survival rate among reclassified frailty groups by VA-FI-nutrition and frailty groups by VA-FI.

(Fig. 2). As demonstrated in Table 2, the adjusted HR (aHR) for all-cause mortality during the study period in modified-prefrail group was 38% higher compared to robust (aHR, 1.38, 95% CI, 1.14, 1.66). On a similar trend, the aHR of all-cause mortality in modified-frail was 50% higher compared to prefrail (aHR, 1.50, 95% CI, 1.39, 1.61).

Inpatient Death Rate: In general, we observed 2.8% rate of inpatient death with the highest rate in frail population (3.2%), followed by modified-prefrail (3.1%) and modified-frail (2.2%), while the prefrail (1.7%) and robust (1.6%) groups had the lowest rates. The aOR of inpatient death between modified-prefrail vs. robust (aOR, 0.90, 95% CI: 0.25, 3.27) and modified-frail vs. prefrail (aOR, 1.36, 95% CI: 0.86, 2.15) were not significantly different.

1-year All-Cause Mortality: The overall prevalence of 1-year all-cause mortality was 31.5% with the highest prevalence in the frail (34.6%) group, followed by modified-frail (31.5%) and modified-prefrail (29.6%) groups. The robust group had the lowest all-cause mortality rate (17.6%). The risk of 1-year all-cause mortality was 64% higher in modified-prefrail compared to robust (aOR, 1.64, 95% CI: 1.15, 2.34) and 66% higher in modified-frail compared to prefrail (aOR, 1.66, 95% CI: 1.44, 1.91) group.

Prolonged Length of Stay: Prolonged LOS was observed in 27.2% of Veterans and with those in the frail (28.0%), modified-frail (28.9%), and modified-prefrail (28.0%) groups having the highest rate of prolonged LOS when compared to robust (22.2%) and prefrail (22.7%). The prolonged LOS was not significantly different between modified-prefrail vs. robust (aOR, 1.38, 95% CI: 0.97, 1.98), but it was significantly 44% higher in modified-frail compared to prefrail (aOR, 1.44, 95% CI: 1.25, 1.67).

Emergency Department or Urgent Care Visits: Generally, 71.4% of Veterans returned to ED or UC in 1 year. The highest prevalence was observed in the frail (73.1%) group, followed by modified-frail (66.5%),

Table 2
Comparing the odds ratio between the regrouped frailty status by frailty index with nutrition and the frailty index without nutrition.

	Robust- Prefrail vs. Robust-Robust (Ref)		Prefrail-Frail vs. Prefrail-Prefrail (Ref)	
	Unadjusted OR (95%CI)	Adj OR (95%CI)[†]	Unadjusted OR (95%CI)	Adj OR (95% CI)[†]
Primary outcome				
Overall mortality	2.25(1.77, 2.86)	1.38 (1.14,1.66)	1.06(0.92,1.22)	1.50 (1.39,1.61)
Secondary outcomes				
Inpatient death	1.99(0.99, 4.02)	0.90(0.25, 3.27)	1.43(0.90, 2.26)	1.36(0.86, 2.15)
Death 1 year	1.96(1.52, 2.54)	1.64(1.15, 2.34)	1.71(1.49, 1.96)	1.66(1.44, 1.91)
Prolonged LOS	1.38(1.06, 1.78)	1.38(0.97, 1.98)	1.45(1.26, 1.67)	1.44(1.25, 1.67)
ED/UC 1Y	1.14(0.91, 1.44)	1.30(0.94, 1.79)	1.11(0.99, 1.25)	1.11(0.97, 1.27)
Rehospitalization 1Y	1.29(1.03, 1.62)	1.43(1.05, 1.94)	1.25(1.12, 1.39)	1.27(1.12, 1.44)

LOS = Length of Stay.
ED/UC 1Y = Emergency Department or Urgent Care visits in one year post discharge.
Rehospitalization 1Y = all cause hospitalization in one year post discharge.
[†] Adjusted by Sex, Race, Ethnicity, Age, BMI, & EF.

prefrail (64.2%), modified-prefrail (62.6%), and the lowest proportion was amongst the robust group (59.4%). Two of the most common causes of total ED and UC visits were Cardiovascular (35.8%) and Respiratory complaints (9.4%), respectively. The number and percentages of these two conditions in each group of frailty status is reported in Table 1. The percentage of Cardiovascular complaints among those with ED or UC visits due to any reason was the highest in the robust group (39.8%) and gradually decreased with worsening of frailty status, with the lowest percentage in the frail group (35.2%). The rate of Respiratory complaints among any causes of ED and UC visits was almost similar between different groups, ranging from 9–10%. No significant differences in this regard were observed between modified-prefrail vs. robust (aOR, 1.30, 95% CI: 0.94, 1.79) or modified-frail vs. prefrail (aOR, 1.11, 95% CI: 0.97, 1.27).

1-Year Re-hospitalization: 48.1% of Veterans re-admitted in 1-year. This outcome was most prevalent in the frail group (50.1%), followed by the modified-frail (46.0%), modified-prefrail (40.8%), and prefrail group (40.5%) while the lowest rate was seen in the robust group (34.8%). Among all the reasons of re-hospitalization, Cardiovascular and Respiratory disorders were two of the most commons with 55.5% and 8.4% prevalence, respectfully. The number and percentages of these two conditions in each group of frailty status is reported in Table 1. The percentage of Cardiovascular diagnosis among the total re-hospitalizations was the highest in robust group (64%), followed by modified-prefrail (62.8%), prefrail (60.2%), frail (54.2%), and modified-frail group (53.2%). However, the rate of those with respiratory diagnosis among total re-hospitalizations was the lowest in robust group (5.9%), followed by modified-prefrail (7.7%), prefrail (8.1), frail (8.4%), and modified-frail (9.1%). We observed 43% higher in the odds of re-hospitalization in modified-prefrail vs. robust (aOR, 1.43, 95% CI: 1.05, 1.94) and 27% higher in the odds of re-hospitalization in modified-frail vs. prefrail (aOR, 1.27, 95% CI: 1.12, 1.44).

Stratified Analysis based on LVEF: After stratifying the analysis based on LVEF, as demonstrated in Table 3, we observed a significant increased odds of all-cause mortality over the study period in the subgroups of modified-prefrail and modified-frail among both categories of HFrEF (aOR of modified-prefrail vs. robust, 1.34; 95% CI: 1.05,1.70 ; aOR of modified-frail vs. prefrail, 1.46; 95% CI: 1.32, 1.61) and HFpEF (aOR of modified-prefrail vs. robust, 1.49; 95% CI: 1.06, 2.11; aOR of modified-frail vs. prefrail, 1.46; 95% CI: 1.29, 1.65). The odds of 1-year death was also significantly different across the regrouped Veterans compared to those who remained in their original frailty status in both HFrEF (aOR of modified-prefrail vs. robust, 1.57, 95% CI: 1.01, 2.43; aOR of modified-frail vs. prefrail, 1.57, 95% CI:1.30, 1.90) and HFpEF (aOR of modified-prefrail vs. robust, 2.13, 95% CI: 1.13, 4.02; aOR of modified-frail vs. prefrail, 1.65, 95% CI:1.30, 2.09) categories. No significant difference was observed in the aOR for inpatient death and ED/UC visits in 1-year. The odds of LOS were significantly different in the modified-frail subgroup compared to prefrail in both HFrEF (aOR, 1.47, 95% CI: 1.21, 1.80) and HFpEF (aOR,1.37, 95% CI: 1.09, 1.72) categories. Comparing the modified-prefrail and robust groups, odds of LOS was only significantly higher in the HFpEF category (aOR, 2.29, 95% CI: 1.23, 4.23), but it was not significantly different in HFrEF (aOR, 0.97, 95% CI: 0.60, 1.56). For all 1-year readmissions, only comparisons between modified-frail vs. prefrail in both HFrEF (aOR, 1.34, 95% CI: 1.13, 1.59) and HFpEF (aOR, 1.24, 95% CI: 1.02, 1.52) have shown significant results.

4. Discussion

In a cohort of Veterans admitted with HF, our study demonstrates the value of adding specific biomarkers related to nutrition to the existing frailty index to identify risk of mortality and other important health related outcomes. The nutritional deficiency re-stratified Veterans to a higher frailty class, hence increasing the predictive value of the frailty index. Our data confirmed the high prevalence of both frailty and nutritional deficiencies amongst Veterans with HF in a large prospective national database. We observed higher rates of inpatient deaths, 1-year all-cause mortality, prolonged LOS, ED visits, and hospitalizations, as well as lower median time-to-death in Veterans who were reclassified into a higher frailty group by VA-FI-Nutrition as compared to the Veterans who remained in their original frailty group by both indices. Results were consistent for multiple pre-specified clinical endpoints, independent of age, sex, race, ethnicity, BMI, and EF.

Frailty indices have been previously established for other clinical syndromes benefitting from additional prognostication, including but not limited to pre-operative surgical risk assessment, prediction of institutionalization and functional decline, and differentiating acute vs. chronic

Table 3
Comparing the odds ratio and 95 percentage confidence intervals between the regrouped frailty status by frailty index with nutrition and the frailty index without nutrition for two categories of Heart Failure divided by Ejection Fraction.

	Robust- Prefrail vs. Robust-Robust (Ref)		Prefrail-Frail vs. Prefrail-Prefrail (Ref)	
	Unadjusted OR (95%CI)	Adj OR (95%CI)[†]	Unadjusted OR (95%CI)	Adj OR (95%CI)[†]
Inpatient Death				
HFrEF	0.90(0.19, 4.20)	0.79(0.17, 3.71)	1.48(0.84, 2.63)	1.41(0.80, 2.51)
HFpEF	3.45(0.21, 55.75)	2.83(0.17, 46.02)	1.27(0.53, 3.02)	1.13(0.47, 2.69)
Death 1 Year				
HFrEF	1.71(1.11, 2.62)	1.57(1.01, 2.43)	1.64(1.36, 1.97)	1.57(1.30, 1.90)
HFpEF	2.46(1.32, 4.57)	2.13(1.13, 4.02)	1.77(1.41, 2.23)	1.65(1.30, 2.09)
Prolonged LOS				
HFrEF	0.98(0.61, 1.58)	0.97(0.60, 1.56)	1.48(1.21, 1.80)	1.47(1.21, 1.80)
HFpEF	2.27(1.23, 4.20)	2.29(1.23, 4.23)	1.38(1.09, 1.73)	1.37(1.09, 1.72)
Overall mortality				
HFrEF	1.44(1.14, 1.84)	1.34(1.05, 1.70)	1.50(1.36, 1.65)	1.46(1.32, 1.61)
HFpEF	1.74(1.23, 2.45)	1.49(1.06, 2.11)	1.52(1.35, 1.72)	1.46(1.29, 1.65)
ED/UC 1Y				
HFrEF	1.17(0.79, 1.74)	1.17(0.79, 1.75)	1.13(0.95, 1.35)	1.14(0.95, 1.36)
HFpEF	1.43(0.80, 2.56)	1.50(0.83, 2.68)	1.06(0.86, 1.32)	1.09(0.88, 1.35)
Rehospitalization 1Y				
HFrEF	1.36(0.93, 2.00)	1.38(0.94, 2.03)	1.32(1.12, 1.57)	1.34(1.13, 1.59)
HFpEF	1.44(0.82, 2.53)	1.49(0.85, 2.62)	1.22(1.33, 1.64)	1.24(1.02, 1.52)

HFrEF = Heart Failure with reduced Ejection Fraction (LVEF < 40%), HFpEF = Heart Failure with preserved Ejection Fraction (LVEF > 50%).
ED/UC 1Y = Emergency Department or Urgent Care visits in one year post discharge, LOS = Length of Stay, Rehospitalization 1Y = all cause hospitalization in one year post discharge.
[†] Adjusted by Sex, Race, Ethnicity, Age, BMI, & EF.

conditions. The benefits of frailty indices are that they provide an efficient, automated, and effective tool for data collection that has feasible potential for widespread implementation across an EMR [29–31]. VA-FI is an established frailty assessment that was developed and validated for the general veteran population in assessing the overall impact of frailty [16]. We integrated PNI, a validated nutritional assessment [14]. VA-FI-Nutrition incorporates dynamic lab values into its algorithm, which suggests that patients' frailty statuses are also dynamic and may need to be re-evaluated at subsequent hospitalizations. The trend in VA-FI-nutrition values can guide physicians on how to appropriately titrate medical therapy or provide interventions accordingly. Additional studies are necessary to assess the prognostic utility of VA-FI-Nutrition in an outpatient setting, both before and after hospital admission to see if the index hospitalization also has an impact on the patient's overall frailty status.

The impact of frailty alone assessed by different methods and malnutrition alone on different adverse outcomes of heart failure have been extensively investigated. Sze et al. evaluated the association of both malnutrition and frailty with mortality and showed a strong relationship between these factors and mortality in patients hospitalized with HF [14]. A meta-analysis of 18757 frail patients with chronic HF reported an average of 48% and 40% increase in the hazard ratio of all-cause mortality and hospitalization, respectively [32]. Similarly, another meta-analysis studied the impact of malnutrition on all-cause mortality in patients with HF reported that malnutrition is associated with an increased risk of all-cause mortality, HR of 2.15 ($P < 0.05$) [13]. Furthermore, it is worth mentioning that the overall rate of all-cause mortality was higher in the whole population of our study comparing to the last update by American Heart Association which reported the 5-year mortality of patients with HF to be around 50% [3]. This difference in numbers might be related to the different sample size of our study comparing to the general population, as the poorer health status among Veterans was observed in previous investigations. Agha et al., showed that large differences in sociodemographic status, health status, and subsequent resource use exist between the VA and the general patient population [33]. Also, most of the participants in our study were frail and several studies have demonstrated that patients with HF who are also frail or malnourished are at increased risk of mortality and re-hospitalizations [34–40].

While the association between frailty, malnutrition and adverse outcomes in HF has been investigated, the additional value of adding a nutritional index to frailty indices to increase the prognostic capability for HF adverse outcomes is an area of ongoing research. A study by Ju et al. developed a modified electronic frailty model incorporating nutritional indices into a conventional frailty scoring system and found that baseline PNI in the modified electronic frailty index is one of the most predictive variables for the short-term mortality outcomes in HF patients [12]. Mangalesh et al. have also demonstrated that combined nutritional and frailty screening may improve the risk of prognostication in older adults following MI [41]. Furthermore, by Noike et al. found that patients with both frailty and malnutrition have a higher risk of major adverse clinical outcomes after percutaneous coronary intervention than patients with frailty or malnutrition [42]. Our study adds to this emerging literature base in frail older adults with heart disease by focusing specifically on a HF population with longer follow up, diverse end points, and comparing the ratio of each outcome between the modified frailty index and the conventional one.

The incorporation of malnutrition into VA-FI and the subsequent reclassification of patients into higher frailty strata with observed higher mortality rates suggests that nutrition plays a critical role as an additional prognostic factor for hospitalized HF patients. Advanced HF itself is a catabolic condition that can further exacerbate metabolic impairments through upregulation in inflammation, such as hemodynamic dysregulation resulting in tissue hypoxia and cellular apoptosis, chronic volume overload leading to gut ischemia and translocation of the gut microbiome, and activation of neurohormonal pathways, such as the renin-angiotensin-aldosterone system [9,43,44]. Previous studies have also demonstrated the importance of nutritional status as another prognostic marker for patients with HF [10,45]. This is important to consider as nutritional supplementation is an area of investigation to potentially reverse this aspect of frailty [46]. It is also noteworthy that the prevalence of malnutrition, using the PNI, in our study is 51%, which is consistent with a meta-analysis reporting 46% of malnutrition among patients with HF [13]. Given that more than half of this population are facing nutritional deficiencies, malnutrition is a valuable predictor of important adverse outcomes.

HF patients are at particular risk for increased length of stay and hospital readmissions post-discharge [47,48]. Moreover, It has been shown that repeated hospitalization is associated with an increased risk of 30-day and 1-year mortality with rates of 7.4% and 27.3%, respectively [49], and prolonged LOS by itself is associated with increased risk of all types of re-admission and mortality [50]. Additionally, although the overall 30-day readmissions and hospitalizations due to HF have decreased, the overall number of hospital encounters had a 20–30% increase [51,52]. and the patients who are evaluated in ER or UC settings without re-admission also have an increased risk of mortality [52–54]. The increased number of medical encounters that do not lead to hospitalizations could represent patients at a vulnerable time who require closer follow-up or may have required longer stays during their index hospitalization to prevent additional healthcare encounters, given their tenuous clinical status [55]. Identifying these at-risk patients can provide an opportunity for interventions to improve outcomes.

Our subcategory analyses based on EF also demonstrated a significant difference in all-cause mortality over the study period and 1-year-Death for Veterans with both HFpEF and HFrEF across all frailty strata which is supported by previous studies that demonstrated the association between frailty and increased mortality in patients with both HFpEF and HFrEF, instead of HF as the overall clinical syndrome [6,56]. While there are more robust guidelines for HFrEF guideline-directed medical therapy (GDMT), the data for HFpEF GDMT is not as strong, which has resulted in a more limited toolkit of medications and interventions to help increase the quality of life in patients with HFpEF. This is increasingly becoming a dilemma, as the prevalence of frailty is higher in older individuals with HFpEF, as well as a higher symptom burden and decreased quality of life in HFpEF patients compared with HFrEF patients [6].

5. Strengths and limitations

Our study has important strengths. We used a large national database of VA, which provided a variety of participants from geographically diverse backgrounds. Moreover, using structured EMR data of VA gave us the opportunity to extract information from this large cohort. To our knowledge, this is the first study comparing the ratio of different adverse outcomes between modified frailty status based on nutrition and its conventional counterpart. The strength of this study is through the usage of simple factors for evaluating nutrition like albumin and lymphocyte count that help retain maintain as many Veterans as possible in the sample population.

This study has some limitations. Given most participants in this cohort are male, findings from this study may not be generalizable to other populations. The formal gold standard for assessing malnutrition in patients is through body composition assessment through methods such as bioelectrical impedance analysis, dual-energy X-ray absorptiometry, computed tomography, and magnetic resonance imaging. These methods may provide a more accurate assessment of malnutrition but are not feasible to perform for large populations due to availability, accessibility, and requirement of technical expertise to perform. Further, the lack of information about the primary cause of death during hospitalization and follow-up is another limitation of our study and reporting them in addition to focusing specifically on cardiovascular death is warranted in the future investigations.

6. Conclusion

In this study, the VA-FI-Nutrition by utilizing a feasible surrogate malnutrition assessment, identified Veterans with decreased time-to-death and increased risk for multiple adverse outcomes which all have clinical importance in the overall prognosis of HF patients. VA-FI-Nutrition not only has potential in the risk stratification and prognostication of HF patients, but it can also be a standardized, automated metric that can be implemented across an EMR in a healthcare system, such as the VA.

Future directions for the project include the addition of other lab markers to VA-FI-nutrition for increasing the predictive value of the index, the utility of nutritional interventions and physical rehabilitation sessions in these patients and their effects on their frailty status, and the application of VA-FI-nutrition to HFrEF and HFpEF cohorts to assess the impact of guided medical therapy on overall frailty status.

Disclosure

The authors declare no conflicts of interest.

Acknowledgments

Supported by seed funding from Baylor College of Medicine, Houston, Texas, United States, the Center for Innovations in Quality, Effectiveness and Safety (CIN 13–413), Michael E. DeBakey VA Medical Center, Houston, TX, United states, and a national institute of health (NIH), National Heart, Lung, and Blood Institute (BHLBI) K25 funding (#:1K25HL152006-01) to Dr. Razjouyan. Dr. Orkaby is supported by VA CSR&D CDA-2 award IK2-CX001800.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jnha.2024.100253.

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