

ORIGINAL RESEARCH PAPER

The Metabolic Vulnerability Index

A Novel Marker for Mortality Prediction in Heart Failure

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ABSTRACT

BACKGROUND Inflammation and protein energy malnutrition are associated with heart failure (HF) mortality. The metabolic vulnerability index (MVX) is derived from markers of inflammation and malnutrition and measured by nuclear magnetic resonance spectroscopy. MVX has not been examined in HF.

OBJECTIVES The authors sought to examine the prognostic value of MVX in patients with HF.

METHODS We prospectively assembled a population-based cohort of patients with HF from 2003 to 2012 and measured MVX scores with a nuclear magnetic resonance scan from plasma collected at enrollment. Patients were divided into 4 MVX score groups and followed until March 31, 2021.

RESULTS We studied 1,382 patients (median age: 78 years; 48% women). The median MVX score was 64.6. Patients with higher MVX were older, more likely to be male, have atrial fibrillation, have higher New York Heart Association class, and have HF duration of >18 months. Higher MVX was associated with mortality independent of Meta-analysis Global Group in Chronic Heart Failure score, ejection fraction, and other prognostic biomarkers. Compared to those with the lowest MVX, the HRs for MVX groups 2, 3, and 4 were 1.2 (95% CI: 0.9-1.4), 1.6 (95% CI: 1.3-2.0), and 1.8 (95% CI: 1.4-2.2), respectively ($P_{\text{trend}} < 0.001$). Measures of model improvement document the added value of MVX in HF for classifying the risk of death beyond the Meta-analysis Global Group in Chronic Heart Failure score and other biomarkers.

CONCLUSIONS In this HF community cohort, MVX was strongly associated with mortality independently of established clinical factors and improved mortality risk classification beyond clinically validated markers. These data underscore the potential of MVX to stratify risk in HF. (J Am Coll Cardiol HF 2023;■:■-■) Published by Elsevier on behalf of the American College of Cardiology Foundation.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

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**ABBREVIATIONS
AND ACRONYMS****BMI** = body mass index**CRP** = C-reactive protein**HF** = heart failure**IVX** = inflammation
vulnerability index**MMX** = metabolic malnutrition
index**MVX** = metabolic vulnerability
index**MAGGIC** = Meta-Analysis
Global Group in Chronic
Heart Failure**NMR** = nuclear magnetic
resonance**NT-proBNP** = N-terminal pro-
B-type natriuretic peptide**S-HDLp** = small high-density
lipoprotein particles

The “cytokine hypothesis,” formulated almost 2 decades ago, proposes that heart failure (HF) progresses as a result of the overexpression of inflammatory molecules, eg, cytokines, which reflect systemic inflammation and are often associated with protein energy malnutrition.¹ Consistent with this hypothesis, several published studies of individual markers of inflammation have reported prognostic associations in HF.²⁻⁴ Further, studies have suggested an association between inflammation and wasting syndromes related to malnutrition, such as cachexia and sarcopenia, and HF prognosis.^{5,6} However, these studies mostly investigated one single marker at a time, and their clinical utility in routine practice has not been fully delineated.^{3,4} It stands to reason that precision phenotyping could improve our understanding of the prognostic

role of inflammation and malnutrition in HF, thereby augmenting the information provided by clinical risk scores, which most often focus on short-term mortality and/or only consider clinical characteristics.⁷⁻⁹ Within this context, we hypothesized that a multi-marker, reflecting inflammation and wasting syndromes associated with malnutrition (which we refer to as “metabolic malnutrition”) would improve mortality risk stratification in HF.¹⁰

Nuclear magnetic resonance (NMR) spectroscopy can generate targeted high-throughput metabolomics data suitable for epidemiologic research. The metabolic vulnerability index (MVX), a novel NMR multi-marker developed for mortality risk stratification, comprises biomarkers of systemic inflammation and metabolic malnutrition.¹⁰ To date, the prognostic value of the MVX has not been evaluated in patients with HF. Therefore, we aim to report the distribution of MVX scores in an HF community cohort as well as the association of MVX with clinical characteristics and with death (**Central Illustration**). We further examined the incremental clinical value of MVX beyond an established mortality risk score and other biomarkers of risk.

METHODS

PATIENT POPULATION. Our HF community cohort is derived from the record linkage system of the Rochester Epidemiology Project, an optimal setting to conduct population research because it captures nearly all clinical diagnoses, procedures, results, and outcomes in its catchment area.^{11,12} Our approach to identify cases, assemble the cohort, and

collect data was previously published.^{13,14} In brief, potential patients with HF were identified with natural language processing of electronic medical record text.¹⁵ We identified patients who were ≥ 20 years old and resided in Olmsted, Dodge, and Fillmore Counties in Minnesota. This approach yielded 100% sensitivity compared with billing data, a reference method for case finding.¹⁵ Research nurses reviewed and validated HF diagnosis with Framingham criteria.¹⁶ Patients were approached in the hospital or after an outpatient encounter to provide written consent to participate in the study, including a blood draw, between September 2, 2003, and June 16, 2012. The Mayo Clinic and Olmsted Medical Center Institutional Review Boards approved of this study.

DATA COLLECTION. Clinical information from inpatient and outpatient records from all providers in the Rochester Epidemiology Project¹⁷ were collected by nurse abstractors. Clinical information included cardiovascular risk factors (eg, smoking status, hypertension, hyperlipidemia, and diabetes), comorbid conditions included in the Charlson comorbidity index, and laboratory values.¹⁷ N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels were measured using a multiplex immunoassay (Meso Scale Diagnostics). Left ventricular ejection fraction was obtained from the closest available echocardiogram value within 6 months before or 2 months after the date of enrollment. Body mass index (BMI) was calculated using weight (in kilograms) from the last outpatient before enrollment divided by their earliest recorded adult height (in meters) squared. Electronic retrieval of international classification of disease codes from inpatient and outpatient encounters was used to ascertain chronic conditions identified as a public health priority by the U.S. Department of Health and Human Services.^{18,19} The MAGGIC (Meta-analysis Global Group in Chronic HF) score was calculated using sex; age; ejection fraction; systolic blood pressure; BMI; creatinine; NYHA functional class; smoking status; diabetes; chronic obstructive pulmonary disease; HF diagnosis at >18 months ago; and use of beta blockers, angiotensin-converting enzyme inhibitors, and/or angiotensin receptor blockers.⁸

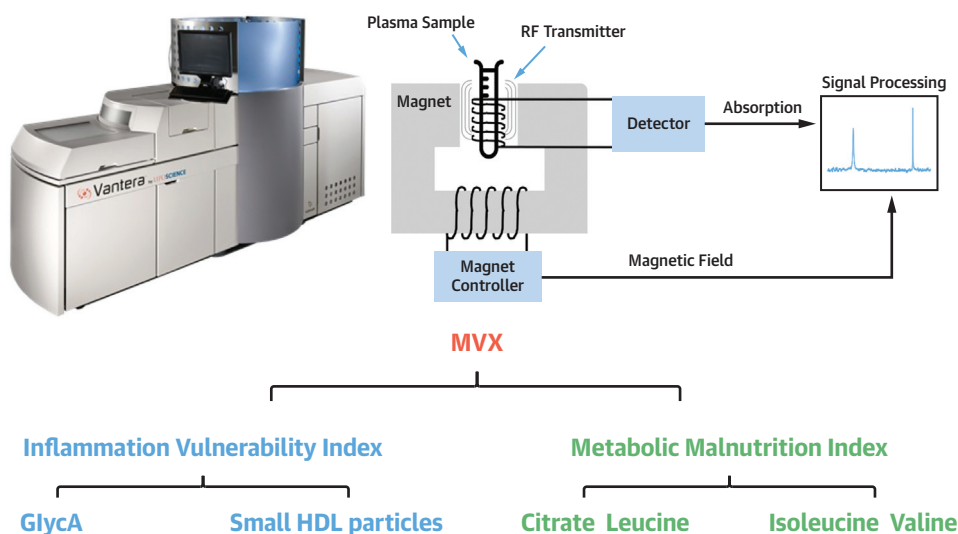
ASCERTAINMENT OF DEATH. Patients were followed through March 31, 2021 using data from the Rochester Epidemiology Project, which obtains death date information from participating health care providers, the State of Minnesota death certificates, and linkage to the National Death Index. Information on cause of death is ascertained from Minnesota death

CENTRAL ILLUSTRATION Study Design to Determine the Prognostic Value of the Metabolic Vulnerability Index in Heart Failure

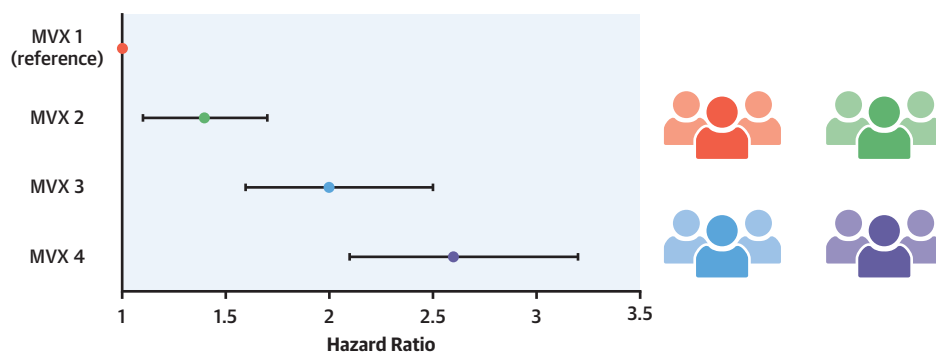
1,382 HF Patients From a Population-Based Electronic Medical Record Linkage System



Metabolic Vulnerability Index (MVX) Calculated by Nuclear Magnetic Resonance Spectroscopy



Survival by MVX Groups Adjusted for MAGGIC Score



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MVX group 1: ≤ 50 (n = 171); MVX group 2: (50-60] (n = 339); MVX group 3: (60-70] (n = 445); MVX group 4: > 70 (n = 427). Image created with BioRender.com. Est. = established; HDL = high-density lipoprotein; HF = heart failure; MAGGIC = Meta-analysis Global Group in chronic heart failure. MVX = metabolic vulnerability index; RF = radiofrequency.

certificates and the National Death Index. We considered all-cause death and cardiovascular death. The latter was defined by using the underlying cause of death classified by ICD-10 codes 100-78. Patients alive at the end of follow-up were censored on March 31, 2021 or the date of last known health care contact, whichever was earlier.

MVX MEASUREMENT. NMR LipoProfile analyses of frozen EDTA plasma collected from community patients with HF at the time of enrollment were performed on the high-throughput 400-MHz Vantera clinical analyzer platform at the National Heart, Lung, and Blood Institute Lipoprotein Metabolism Laboratory using the LP4 algorithm (LabCorp), and sex-specific MVX scores were calculated using the MVX software algorithm.²⁰ Development of the MVX algorithm and the association of MVX scores with mortality in subjects at high risk of cardiovascular disease has been previously reported.¹⁰ A brief description of the analytes that make up the MVX scores are as follows. GlycA and small high-density lipoprotein particles (S-HDLp), measured by the NMR LipoProfile (LabCorp) scan, were associated with an increased risk of mortality in the CATHGEN (Catheterization Genetics) cohort.^{21,22} GlycA arises from the glycan residues of several acute-phase glycoproteins and reflects systemic inflammation.²³ S-HDLp mediates protective functions of anti-inflammatory and immune response proteins.^{24,25} GlycA and S-HDLp were combined into an inflammation vulnerability index (IVX).¹⁰ Further analysis in the CATHGEN and Intermountain Heart studies found 4 malnutrition metabolites that are associated with mortality, including citrate and the branched-chain amino acids—valine, leucine, and isoleucine—which were further combined into a score termed the metabolic malnutrition index (MMX).¹⁰ The MMX and IVX were combined as a composite score called the MVX (metabolic vulnerability index). MVX, IVX, and MMX scores, as well as the analytes that are used to generate the scores, are stable for up to 12 years in EDTA plasma samples when frozen at <-70 °C for up to 12 years. MVX scores are dimensionless, ranging from 1 to 100, with a higher score indicating greater metabolic vulnerability.

STATISTICAL ANALYSIS. Baseline characteristics and individual MVX components are reported as frequency (percentage) for categorical variables, and continuous variables are reported as median (IQR). NT-proBNP values were log₂ transformed for analyses. Continuous variables and categorical variables were compared across MVX groups using Kruskal-Wallis and chi-square tests, respectively.

Median follow-up time was calculated using the reverse Kaplan-Meier method.²⁶ Survival by MVX group was estimated by the Kaplan-Meier method and compared across groups by the log-rank test. Multiple imputations by chain equations was performed to account for missing clinical data used to calculate MAGGIC scores, including BMI (2.8%), NYHA functional class (0.4%), HF duration (0.1%), and ejection fraction (1.8%).²⁷

Multivariable Cox proportional hazard regression was used to examine the association between MVX group and mortality adjusted for age and sex, MAGGIC score, NT-proBNP (log transformed) and hemoglobin. Analysis for cardiovascular death was conducted using Fine-Gray competing risk models. Sensitivity analysis was conducted using complete cases only. Additional stratified analyses were performed by ejection fraction group and MAGGIC score subgroups based on published cutpoints⁸; the 2 highest groups were combined, and the 2 lowest groups were combined because of low sample sizes. Wald tests for trend were performed by assigning mid-points of the 4 MVX groups (1-4) to assess the linearly increasing trend of the HR across MVX groups. To assess the linear association between MVX and mortality, we evaluated the *P* value for nonlinearity based on the likelihood ratio test between a model with and without restricted cubic splines.^{28,29} The number of knots was determined based on the Akaike information criterion.

Several measures of model improvement, including the Uno C-statistic,³⁰ net reclassification improvement, integrated discrimination improvement, and their corresponding 95% CIs were calculated to estimate the incremental prognostic value of MVX group beyond the MAGGIC score and other biomarkers of risk in HF for mortality risk prediction at 3 years because the MAGGIC score is designed to estimate mortality at 3 years.

Analyses were performed using RStudio version 1.3.1093 with a 2-sided *P* value of <0.05 considered statistically significant.

RESULTS

CLINICAL CHARACTERISTICS AND MVX. The cohort included 1,389 patients, 7 of whom did not have sufficient plasma volume, leaving 1,382 patients for analysis. Median age was 78 (IQR: 68-84) years, and 51.7% were male (Table 1). Key cardiometabolic risk factors were highly prevalent, including hypertension, hyperlipidemia, and diabetes. The median MAGGIC score was 26 (IQR:22-30), most patients were in NYHA functional class III or IV, 72% of patients

TABLE 1 Baseline Characteristics by MVX Group

	Total (N = 1,382)	MVX Group 1 (n = 171)	MVX Group 2 (n = 339)	MVX Group 3 (n = 445)	MVX Group 4 (n = 427)	P Value
Age, y	78 (68-84)	72 (61-82)	77 (67-84)	79 (69-85)	79 (70-85)	<0.001
Men	715 (52)	74 (43)	162 (48)	226 (51)	253 (59)	<0.001
Cardiovascular risk factors						
Hypertension	1,261 (91)	154 (90)	316 (93)	414 (93)	377 (88)	0.038
Current smoker	144 (10)	21 (12)	34 (10)	46 (10)	43 (10)	0.800
Diabetes mellitus	493 (36)	51 (30)	132 (39)	165 (37)	145 (34)	0.200
Hyperlipidemia	1,171 (85)	149 (87)	306 (90)	373 (84)	343 (80)	0.001
Body mass index, kg/m ²	28 (25-34)	30 (27-34)	29 (25-34)	28 (24-33)	28 (24-32)	<0.001
Medical history						
Myocardial infarction	391 (28)	34 (20)	96 (28)	133 (30)	128 (30)	0.068
Chronic obstructive pulmonary disease	395 (29)	41 (24)	94 (28)	130 (29)	130 (30)	0.400
Atrial fibrillation	493 (36)	34 (20)	120 (35)	162 (36)	177 (41)	<0.001
HF characteristics						
HF duration >18 months	495 (36)	51 (30)	108 (32)	148 (33)	188 (44)	<0.001
Ejection fraction, %	54 (35-63)	55 (31-65)	55 (36-65)	50 (35-62)	54 (35-62)	0.110
NYHA functional class						<0.001
I or II	426 (31)	66 (39)	133 (39)	124 (28)	103 (24)	
III or IV	950 (69)	103 (61)	205 (61)	320 (72)	322 (76)	
MAGGIC score	26 (22-30)	23 (18-27)	25 (22-29)	26 (22-30)	27 (23-30)	<0.001
Charlson comorbidity index	7 (5-9)	5 (4-7)	6 (5-8)	7 (5-9)	7 (5-9)	<0.001
Laboratory values						
eGFR, mL/min	53 (40-68)	59 (50-70)	57 (44-70)	53 (41-68)	48 (33-60)	<0.001
NT-proBNP, pg/mL	8,896 (4,205-16,301)	2,891 (812-6,758)	6,208 (3,355-11,202)	10,094 (5,464-16,996)	13,889 (7,768-21,824)	<0.001
Hemoglobin, g/dL	12 (11-14)	13 (12-15)	13 (12-14)	12 (11-14)	12 (10-13)	<0.001
MVX components						
GlycA, μ mol/L	453 (391-537)	389 (349-427)	419 (384-472)	475 (419-559)	505 (423-606)	<0.001
S-HDLp, μ mol/L	8.8 (5.3-11.9)	13.7 (11.5-15.7)	11.5 (9.5-13.5)	8.4 (6.1-10.4)	4.6 (2.4-7.0)	<0.001
Leucine, μ mol/L	141 (115-170)	161 (142-186)	147 (128-174)	145 (122-174)	116 (95-144)	<0.001
Isoleucine, μ mol/L	61 (48-74)	65 (55-79)	65 (53-77)	61 (50-74)	55 (42-68)	<0.001
Valine, μ mol/L	208 (173-246)	244 (218-271)	221 (191-257)	212 (181-245)	172 (146-206)	<0.001
Citrate, μ mol/L	121 (97-149)	111 (96-129)	121 (100-144)	123 (97-151)	127 (97-167)	<0.001

Values are median (IQR) or n (%). MVX group 1: ≤ 50 ; MVX group 2: (50-60]; MVX group 3: (60-70]; MVX group 4: >70 . **Bold** values indicate statistical significance.

eGFR = estimated glomerular filtration rate; HF = heart failure; MAGGIC = Meta-analysis Global Group in Chronic Heart Failure; MVX = metabolic vulnerability index; NT-proBNP = N-terminal pro-B-type natriuretic peptide; S-HDLp = small high-density lipoprotein particles.

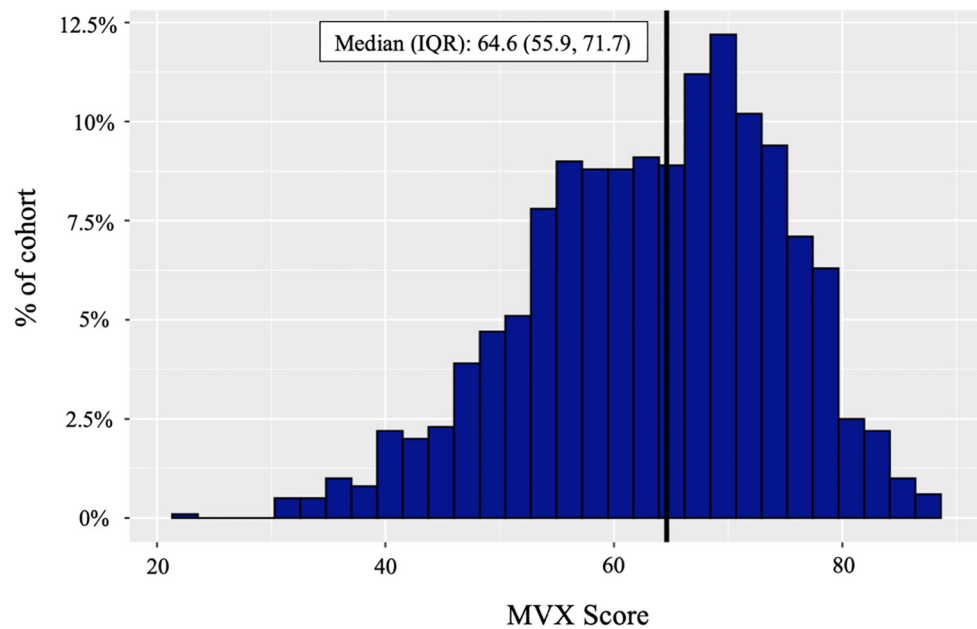
were recruited in hospital, and patients presenting with preserved ejection fraction ($\geq 50\%$) made up 55.7% of the cohort.

MVX scores were normally distributed in the entire cohort with a median of 64.6 (IQR: 55.9-71.7) (Figure 1). The relationship between MVX and mortality was linear (P value of nonlinearity = 0.60) (Figure 2), and we divided the cohort into groups using MVX increments of 10 (group 1: ≤ 50 ; group 2: >50 and ≤ 60 ; group 3: >60 and ≤ 70 ; group 4: >70) for ease of clinical interpretation.

In univariable analyses, compared to the lowest MVX group, higher MVX was associated with older age, male sex, higher NYHA functional class, higher MAGGIC score, higher Charlson comorbidity index, higher NT-proBNP level, higher prevalence of atrial fibrillation, HF duration of >18 months, lower BMI,

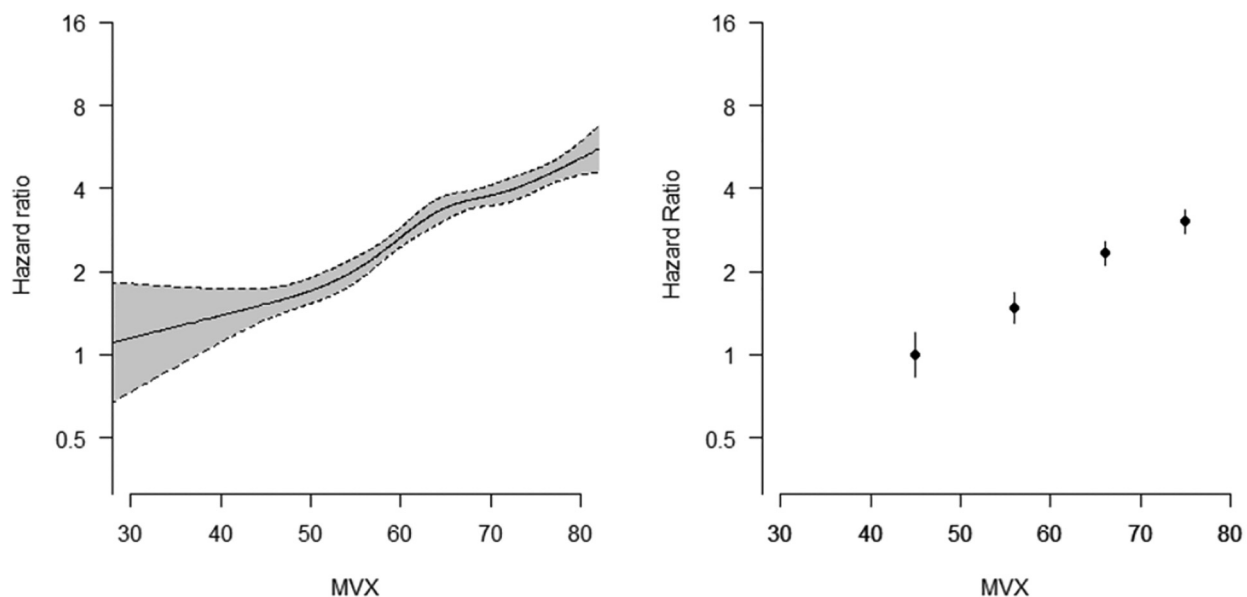
lower hemoglobin and estimated glomerular filtration rate, and a lower prevalence of hypertension and hyperlipidemia. In multivariable analyses, age, sex, NYHA functional class, atrial fibrillation, and HF duration remained independently associated with higher MVX ($P < 0.05$). Notably, we did not detect an association between MVX and ejection fraction modeled continuously or categorically.

MVX AND MORTALITY. Over a median follow-up of 13.9 (IQR: 11.5-15.4) years, 1,158 patients died, equating to a 5-year all-cause mortality rate of 51.8% (95% CI: 49.1-54.4). This corresponds to 14.5 (95% CI: 13.6-15.3) deaths per 100 patient-years. Mortality also varied by MVX group with a graded positive association between MVX group and mortality ($P_{\text{trend}} < 0.001$). The 5-year mortality rate in MVX group 1 was 23.5% (95% CI: 16.8-29.6), compared to 69.0%

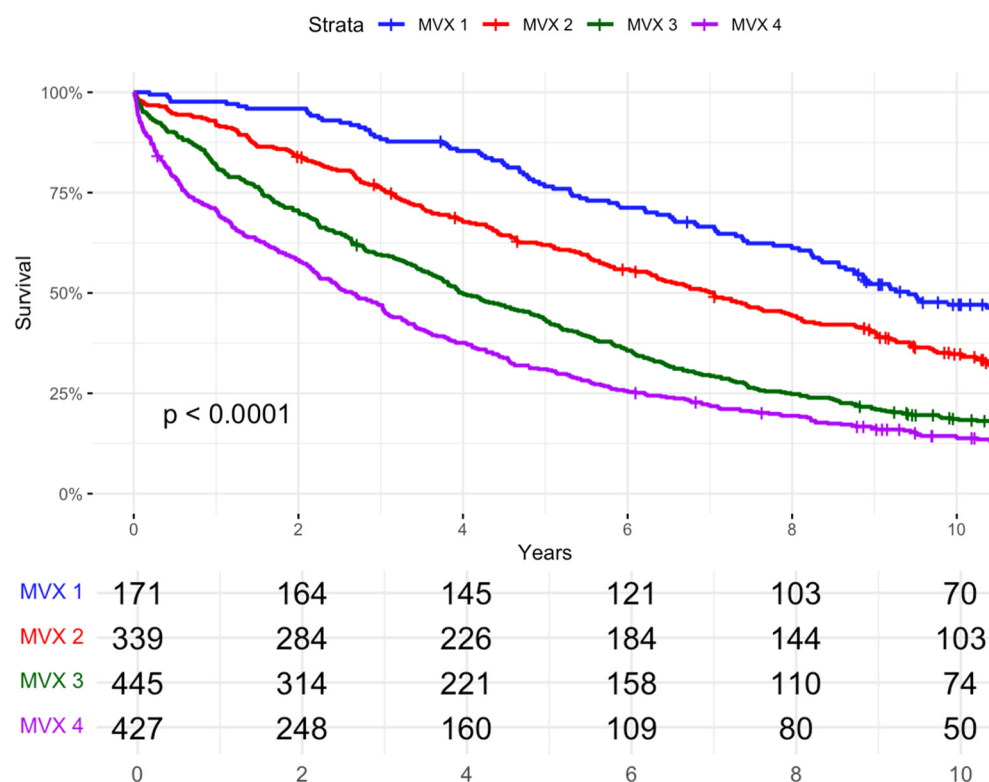
FIGURE 1 Distribution of Metabolic Vulnerability Index Scores Among 1,382 Community-Dwelling Persons With Heart Failure

(95% CI: 64.3-73.1) in MVX group 4 (**Figure 3**). After adjustment for age and sex, patients in MVX group 4 had a nearly 3-fold increase in the risk of death compared to group 1 (HR: 2.8; 95% CI: 2.3-3.4)

(**Table 2**). Adjustment for the MAGGIC score only minimally attenuated this association (HR: 2.5; 95% CI: 2.0-3.1). After sequential adjustment for NT-proBNP and hemoglobin, MVX group 4 remained

FIGURE 2 Association Between MVX and Mortality

Left panel is a cubic spline and **right panel** shows study defined cutpoints. HRs and 95% CIs are shown on both plots. MVX = metabolic vulnerability index.

FIGURE 3 Kaplan-Meier Survival Curves by MVI Group

MVX group 1: ≤ 50 (n = 171); MVX group 2: (50-60] (n = 339); MVX group 3: (60-70] (n = 445); MVX group 4: >70 (n = 427).

MVX = metabolic vulnerability index.

associated with a large increase in the risk of death (HR: 1.8; 95% CI: 1.40-2.2). Results were similar when the follow-up was restricted to 3 or 5 years and when a complete case analysis was carried out. Of the individual MVX components, the inflammation vulnerability index had the highest HR (1.4; 95% CI: 1.3-1.5) per 1 SD (Figure 4).

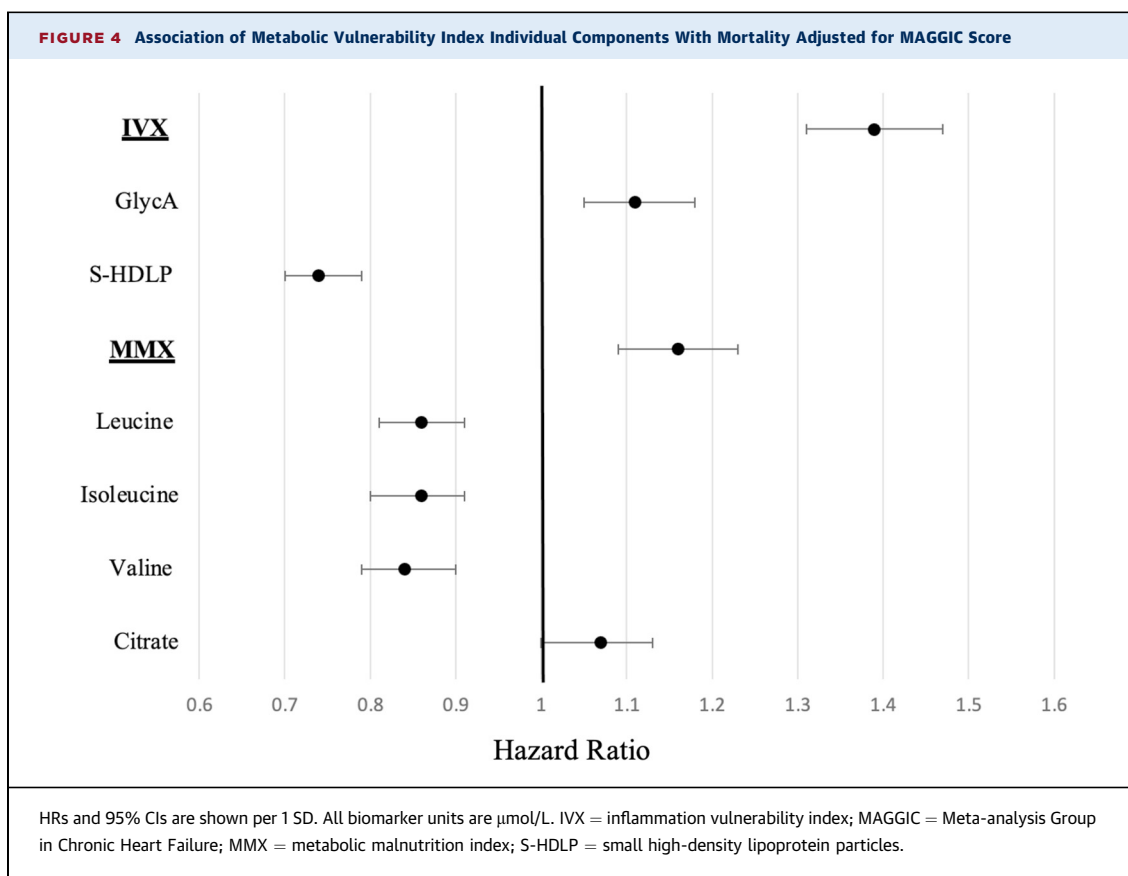
Notably, we observed no significant interaction between ejection fraction and MVX group in survival analyses stratified by ejection fraction group (reduced <50% and preserved $\geq 50\%$). The HR for the association between cardiovascular death (45% of all deaths) and MVX group 4 was 1.6 (95% CI: 1.2-2.1) compared to MVX group 1, similar to the HR of 1.8

TABLE 2 Association Between MVX and Mortality

	MVX Group 1 (n = 171)	MVX Group 2 (n = 339)	MVX Group 3 (n = 445)	MVX Group 4 (n = 427)	P _{trend}
Deaths per 100 patient-years	7.3 (6.0-8.7)	10.8 (9.5-12.1)	17.2 (15.5-18.8)	22.6 (20.3-24.8)	N/A
Univariate HR	1.00 (reference)	1.47 (1.18-1.84)	2.33 (1.89-2.87)	3.03 (2.45-3.74)	<0.001
HR adjusted for age and sex	1.00 (reference)	1.37 (1.10-1.71)	2.19 (1.78-2.71)	2.78 (2.25-3.44)	<0.001
HR adjusted for MAGGIC score	1.00 (reference)	1.31 (1.05-1.63)	2.01 (1.63-2.48)	2.52 (2.03-3.11)	<0.001
HR adjusted for MAGGIC score + NT-proBNP	1.00 (reference)	1.17 (0.93-1.47)	1.64 (1.32-2.05)	1.94 (1.55-2.45)	<0.001
HR adjusted for MAGGIC score + NT-proBNP + hemoglobin	1.00 (reference)	1.15 (0.92-1.44)	1.57 (1.26-1.96)	1.80 (1.39-2.21)	<0.001

Values are HR (95% CI). MVX group 1 is the reference group. MVX group 1: ≤ 50 (n = 171); MVX group 2: (50-60]; MVX group 3: (60-70]; MVX group 4: >70.

N/A = not applicable; other abbreviations as in Table 1.



(95% CI: 1.4-2.2) for all-cause mortality. In survival analyses stratified by MAGGIC score subgroups (Table 3), we observed a positive association between MVX group and increased mortality across all groups. Notably, MVX group 4 HR was highest among patients in the lowest-risk MAGGIC score subgroup (HR: 2.8; 95% CI: 1.5-5.2).

Finally, we evaluated the incremental value of adding MVX group to reference models including MAGGIC score, NT-proBNP, and hemoglobin at 3 years. The Uno C-statistic, net reclassification improvement, and integrated discrimination

improvement indicate that MVX group improves model performance beyond these clinical variables (Table 4).

DISCUSSION

We report that the MVX score is associated with a large increase in the risk of death in a community cohort representing the entire spectrum of the HF syndrome. Patients in the highest MVX group were nearly 3 times more likely to die compared to those in the lowest MVX group, showing a graded positive

TABLE 3 MVX Group Association With Mortality Across MAGGIC Score Subgroups

MAGGIC Score Subgroup	Number of Deaths/Total	Deaths per 100 Patient-Years	MVX Group 2 (n = 339)	MVX Group 3 (n = 445)	MVX Group 4 (n = 427)	P _{trend}
<21	145/267	6.1 (5.1-7.1)	1.30 (0.74-2.31)	2.22 (1.29-3.83)	2.83 (1.54-5.21)	<0.001
[21-25)	243/293	12.7 (11.1-14.3)	1.00 (0.64-1.55)	1.33 (0.86-2.06)	1.33 (1.85-2.09)	0.60
[25-29)	340/378	17.9 (16.0-19.8)	1.28 (0.82-2.00)	1.48 (0.94-2.35)	1.82 (1.13-2.91)	<0.001
≥29	430/444	24.2 (21.9-26.5)	1.12 (0.73-1.71)	1.55 (1.04-2.32)	1.78 (1.18-2.70)	<0.001

Values are HR (95% CI) unless otherwise indicated. MVX group 1 is the reference. Cox models were adjusted for NT-proBNP and hemoglobin. MVX group 1: ≤50 (n = 171). MVX group 2: (50-60); MVX group 3: (60-70); MVX group 4: >70.

Abbreviations as in Table 1.

TABLE 4 Measures of Prognostic Model Improvement

	MAGGIC Score	MAGGIC Score + NT-proBNP	MAGGIC Score + NT-proBNP + Hemoglobin	MAGGIC Score + NT-proBNP + Hemoglobin + MVX Group
Uno's C-statistic (95% CI)	0.61 (0.59-0.64)	0.66 (0.64-0.69)	0.67 (0.65-0.70)	0.69 (0.67-0.71)
P value ^a	N/A	<0.001	0.035	<0.001
IDI, % (95% CI)	N/A	3.6 (2.3-4.8)	1.2 (0.5-2.1)	1.6 (0.7-2.7)
NRI, % (95% CI)	N/A	20 (16-25)	14 (10-20)	18 (11-24)

^aP value indicates whether the C-statistic is significantly increased by adding a new variable to the previous model.

IDI = integrated discrimination improvement; NRI = net reclassification improvement; other abbreviations as in Tables 1 and 2.

association between MVX and mortality. The strong association persisted after adjustment for the MAGGIC score and other biomarkers of risk as well as in stratified analyses. MVX added substantial information on the risk of death in all categories relying on predetermined values of the MAGGIC score. Further, we found evidence that MVX improved the classification of the risk of death at 3 years over the MAGGIC score and validated prognostic biomarkers using 3 distinct measurements of model performance. Our results are consistent with those of the CATHGEN observational cohort; among 1,556 patients with HF in CATHGEN, there was a strong positive association between MVX and mortality: in a model fully adjusted for several clinical factors, the HR for MVX was 1.95 (95% CI: 1.7-2.2) per 1 SD.¹⁰ Collectively, our findings suggest that MVX can provide substantial clinical benefit for mortality risk stratification across the entire spectrum of the HF syndrome because all associations were independent of ejection fraction.

DETERMINANTS OF MVX IN HF. Patients had a median MVX score of 64.6 and a mean score of 63, notably higher than the mean of 50 reported in the CATHGEN cohort, reflecting differences in study populations.¹⁰ Indeed, patients in CATHGEN were younger, were more likely to be men, and had a lower prevalence of hypertension and diabetes, and only a minority of patients had HF. In the present cohort, higher MVX was associated with older age, male sex, greater HF duration, higher NYHA functional class, and atrial fibrillation, all clinical indicators of more advanced HF.³¹⁻³³ The distribution of MVX did not differ by ejection fraction.

INFLAMMATION AND MALNUTRITION IN PATIENTS WITH HF. Prior studies mainly focused on the association of single markers of inflammation, such as C-reactive protein (CRP), interleukin-6, tumor necrosis factor- α , and galectin-3, with HF severity and prognosis,²⁻⁴ with few studies of S-HDL and GlycA in HF.³⁴⁻³⁷ Reports of an inverse association between

S-HDL and mortality in HF reflected heterogeneous designs with varying population size, endpoint definition, and follow-up duration.³⁴⁻³⁶ Data on GlycA in HF are scarce, with a positive association between elevated GlycA and a composite endpoint of hospital readmission and mortality in nonischemic patients only noted in a small convenience sample of ambulatory patients with chronic HF.³⁷

Studies of malnutrition markers in HF are equally scarce, with limited data on citrate and the branched-chain amino acids (leucine, isoleucine, and valine). In a referral population of 130 patients with acute HF, citrate was positively associated with 3-month mortality (OR: 11.74; 95% CI: 1.44-113.20).³⁸ A study of 41 chronic HF patients found an inverse association between the branched-chain amino acids and NYHA functional class, suggesting an association with worse prognosis.³⁹ However, the patient selection, small sample size, and wide confidence intervals compromise inference and validity.

Composite biomarker indices provide more comprehensive mechanistic “coverage” than an individual biomarker. The Glasgow prognostic score⁴⁰ is a categorical scoring system based on CRP and albumin initially proposed to assess inflammation and malnutrition in cancers. It was recently evaluated in 2 studies of HF. The first study, of 443 patients presenting with chronic stable HF with reduced ejection fraction at a tertiary care center, found increased Glasgow prognostic score to predict mortality at 3 years, independent of age and NT-proBNP.⁴¹ Likewise, in a multicenter sample of 870 patients hospitalized with acute decompensated HF, those with the highest Glasgow prognostic score had a nearly 3-fold increased risk of short-term (18 months) death compared to patients with the lowest scores, independent of clinical risk factors.⁴²

The Glasgow prognostic score relies on a point system categorically integrating 2 variables, each with 2 levels. Conversely, the MVX captures 6 biomarkers as continuous variables, which conceptually

provides more comprehensive metabolic information while allowing for a greater range of values.^{28,43,44} Specifically for inflammation, there is evidence that GlycA and high-sensitivity CRP have distinct inflammation-related metabolic effects,⁴⁵ and several epidemiologic studies reported associations between branched-chain amino acids and cardiovascular risk.^{46,47}

Therefore, our findings provide novel evidence that a composite biomarker index that encompasses comprehensive measures of inflammation and metabolic malnutrition provides important prognostic information in a large community cohort of optimal clinical generalizability.

A key challenge in biomarker research is to identify markers with predictive capabilities that are substantial enough to change clinical practice. We acknowledge the challenge in doing so given controversies surrounding the preferred approach to assess model performance.⁴⁸ These challenges notwithstanding, the substantial incremental value of MVX over the MAGGIC score, a class 2a recommendation in the 2022 HF guidelines,⁴⁹ is particularly notable because it is independent from ejection fraction. These data thus suggest that the MVX score, an NMR-based assessment of inflammation and metabolic malnutrition, may have a broad applicability to stratify risk across the entire spectrum of the HF syndrome.

STUDY LIMITATIONS AND STRENGTHS. Our cohort was predominantly of European ancestry, limiting the generalizability of our findings in other populations and warranting research in a more racially and ethnically diverse population. As in any observational study, we cannot rule out residual confounding. Additionally, more contemporary HF guideline-directed medical therapy was not assessed given the time of the study. Finally, these results require replication in a different cohort.

Our study has several important strengths. We examined the association of MVX and mortality in a population-based cohort that represents the community practice and has strong clinical relevance. Nearly all in-patient and outpatient encounters within the Rochester Epidemiology Project were captured, providing us with a rich clinical data set that enabled comprehensive adjustments for known indicators of risk in HF.

CONCLUSIONS

Among a community cohort of patients with HF, MVX, a novel risk score derived from markers of

inflammation and malnutrition, was associated with a large increase in risk of death independent of established clinical risk factors.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In this HF community cohort, MVX, a composite measure of inflammation and metabolic malnutrition, conferred strong incremental prognostic information over clinically validated biomarkers and the MAGGIC score, adding risk prediction information even among patients considered to be at low risk. Thus, MVX may offer a feasible and scalable method to measure inflammation and metabolic malnutrition, which can improve risk stratification in HF.

TRANSLATIONAL OUTLOOK: Further studies are warranted to define the relationship between MVX and other clinical indicators of inflammation and malnutrition in HF (eg, frailty, sarcopenia, cachexia).

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