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Modifiable Risk Factor Burden Among 3 Different Age Groups with Heart Failure

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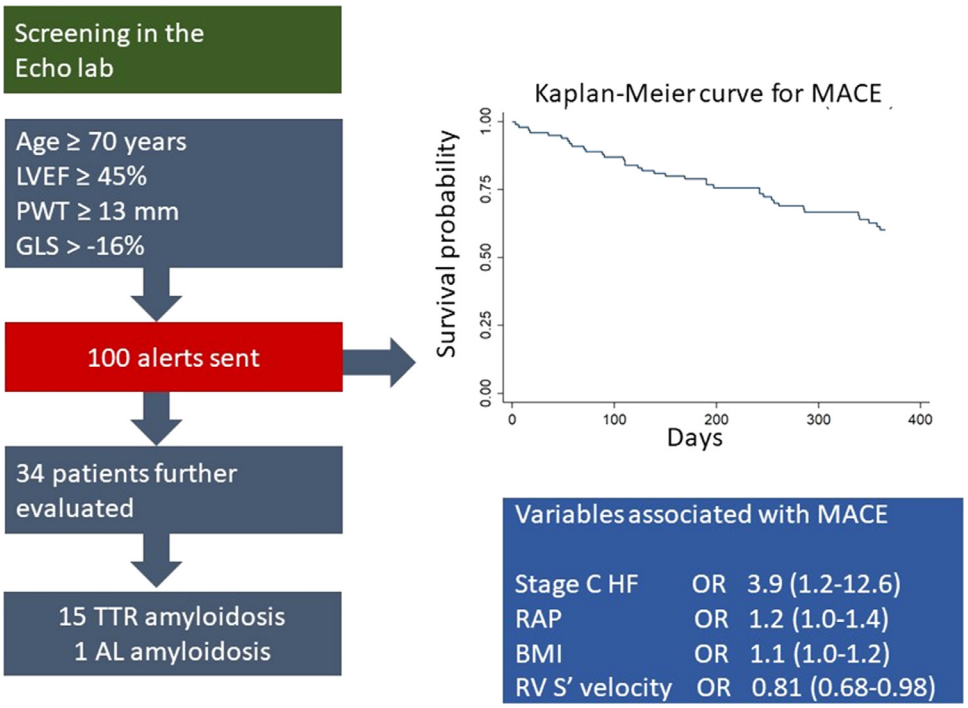

Figure 1. Echocardiographic screening for left ventricular hypertrophy-low longitudinal strain phenotype in elderly patients with preserved or mid-range ejection fraction. BMI = body mass index; GLS = global longitudinal strain; HF = heart failure; LVEF = left ventricular ejection fraction; MACE = major adverse cardiovascular events; PWT = posterior wall thickness; RAP = right atrial pressure; RV = right ventricle.

associated with MACE: ACC/AHA stage C heart failure with odds ratio (OR) of 3.9 (1.2 to 12.6), right atrial pressure with OR of 1.2 (1.0 to 1.4), body mass index with OR of 1.1 (1.0 to 1.2), and right ventricular S' velocity with OR of 0.81 (0.68 to 0.98).

This is a single center, real world echocardiographic screening study with obvious limitations. Although only one third of patients underwent further evaluation for cardiac amyloidosis based on treating team decision, the overall prevalence of cardiac amyloidosis in the study was high. This highlights the need for practitioner education in best practices in recognizing and diagnosing cardiac amyloidosis.[2]

In conclusion, echocardiographic screening for left ventricular hypertrophy-low longitudinal strain phenotype in elderly patients with preserved or mid-range ejection fraction identified a cohort with a high risk of short-term major cardiovascular events. Despite incomplete screening, this cohort carried a high prevalence of cardiac amyloidosis.

Conflict of Interest

None of the authors have any financial or other relations that could lead to a conflict of interest. The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this study.

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Modifiable Risk Factor Burden Among 3 Different Age Groups with Heart Failure

Up to 1 in 5 individuals may develop heart failure (HF) during their lifetimes.[1] Although most individuals who are diagnosed with HF are older adults, an increasing proportion of younger patients are being diagnosed in recent years.[2] These adverse patterns may be a reflection of rising cardiometabolic health burden and obesity in the US and worldwide.[3] Few data exist regarding outcomes of HF in young adults, largely due to limited longitudinal follow-up data. Consequently, we aimed to describe the long-term mortality of young patients diagnosed with HF and assess the relative prognostic value of common comorbidities across age groups.

The National Health and Nutrition Examination Survey (NHANES) is a stratified, multistage probability sample representative of the civilian non-institutionalized US population, described in detail elsewhere.[4] We analyzed data of participants aged ≥18 years with self-reported HF enrolled in 6 cycles of NHANES from January 1, 1999, to December 31, 2010. These data were linked with National Death Index data

provided by the Centers for Disease Control and Prevention to obtain data regarding long-term mortality.[5] We summarized baseline characteristics of adults with HF by age group (younger: 18-54 years, middle-aged: 55-65 years and older: >65 years) at study entry. The primary outcome of interest was all-cause mortality in follow-up. We used multivariable Cox proportional hazards models to examine the association between traditional risk factors (age, gender, presence of hypertension, diabetes, obesity, smoking status, and estimated glomerular filtration rate) and mortality. We performed age-pooled analyses to examine multiplicative interaction terms between age as a linear and categorical variable with each risk factor. We then used age-stratified Cox proportional hazards models to evaluate age-specific associations of each risk factor with mortality. We further compared the accuracy of these traditional risk factors in predicting mortality in each age group using Harrel's C-statistic. The proportionality assumption was met for all models using Schoenfeld residuals. We considered a two-sided p-value below 0.05 to be statistically significant.

Overall, 1,071 individuals with HF were followed for 6.7±4.3 years. Younger patients with HF were more often Black, had better kidney function, and had higher rates of diabetes, obesity, and smoking than middle-age and older adults (Table 1). The median (IQR) age at death was 55 (50-60) years for young, 69 (65-71) years for middle-aged, and 83 (79-86) years for older adults. Age modified the association of obesity and diabetes on subsequent risk of mortality such that diabetes was associated with higher mortality risk in younger (adjusted hazard ratio [HR] 2.11; 95% confidence interval [CI]: 1.04-4.31) and middle-aged adults (adjusted HR 2.18; 95% CI: 1.34-3.57) as compared with older adults (adjusted HR 1.27; 95% CI: 1.04-1.55); P-interaction<0.05.

Table 1
Baseline characteristics and risk associations with mortality among young, middle-aged, and older adults with heart failure

	Ages (Years)			
Baseline characteristics	18-54 (n=154)	55-65 (n=190)	>65 (n=727)	p-value
Age, median (IQR) (Years)	48 (42, 51)	61 (59, 63)	78 (72, 81)	<0.01
Men	84 (54.5%)	116 (61.1%)	386 (53.1%)	0.15
Non-Hispanic White	61 (39.6%)	70 (36.8%)	495 (68.1%)	<0.01
Non-Hispanic Black	61 (39.6%)	66 (34.7%)	106 (14.6%)	
Mexican American	18 (11.7%)	35 (18.4%)	77 (10.6%)	
Other	6 (3.9%)	5 (2.6%)	16 (2.2%)	
Other Hispanic	8 (5.2%)	14 (7.4%)	33 (4.5%)	
Estimated glomerular filtration rate (ml/min/1.73m^2)	97.1 (78.5,119.7)	84.2(67.8,99.6)	63.6(47.5,81.2)	<0.01
Hypertension	118 (80.8%)	159 (85.0%)	580 (84.3%)	0.53
Diabetes Mellitus	51 (35.4%)	100 (55.9%)	299 (47.7%)	<0.01
Hemoglobin (mg/dl)	14.1 (13.1, 15.2)	14.1 (12.9, 15.1)	13.5 (12.4, 14.7)	<0.01
Total leukocyte count (cells/mm$^{3)}$	7.5 (6, 9.1)	7.3 (5.9, 9.2)	7.2 (5.9, 8.6)	0.57
Dyslipidemia	101 (66.4%)	143 (76.1%)	458 (65.1%)	0.018
Smoker	103 (66.9%)	135 (71.1%)	400 (55.2%)	<0.01
Previous Stroke	22 (14.3%)	32 (16.9%)	170 (23.5%)	0.012
Coronary Artery Disease	24 (15.6%)	42 (22.1%)	114 (15.7%)	0.100
Obesity	70 (54.7%)	86 (55.5%)	286 (46.1%)	0.040
Heart Rate (bpm)	72 (62, 84)	70 (62, 82)	70 (62, 78)	0.57
Body Mass Index (kg/m^2)	30.2 (26.1, 38.8)	31.7(26.6,38.8)	28.3(25.2,32.4)	<0.01
Serum Creatinine (mg/dl)	.85 (.7, 1.02)	.92 (.8, 1.1)	1.11 (.9, 1.49)	<0.01
Glycosylated Hemoglobin (%)	5.5 (5.2, 6)	6.1 (5.6, 7.1)	5.8 (5.5, 6.5)	<0.01
Age Diagnosed with Heart Failure	41 (28, 47)	54 (50, 58)	69 (61, 77)	<0.01
Died	48 (31.2%)	89 (46.8%)	530 (72.9%)	<0.01
Time to Death (years)	8.58(5.66, 12.16)	7.58(5.42, 10.13)	5.5 (2.42, 8.42)	<0.01
Prognostic Associations with Mortality Presented as Hazard Ratios (95% Confidence Intervals)	Younger: 18-54 years (n=154)	Middle-aged: 55-65 years (n=190)	Older: >65 years (n=727)	Overall Cohort
Age (per increase in 1 year)	1.01 (0.95 - 1.07)	1.07 (0.97 - 1.20)	1.09 (1.07 - 1.11)	1.05 (1.04 - 1.06)
Women	0.94 (0.48 - 1.84)	1.42 (0.89 - 2.28)	0.78 (0.63 - 0.96)	0.88 (0.74 – 1.05)
Hypertension	0.87(0.37- 2.01)	1.32 (0.68 - 2.56)	0.99 (0.78 - 1.27)	0.99 (0.81 - 1.23)
Diabetes Mellitus	2.11 (1.04 - 4.31)	2.18 (1.34 - 3.57)	1.27 (1.04 - 1.55)	1.29 (1.09 – 1.54)
Smoker	2.04 (0.93- 4.47)	0.94 (0.56 - 1.59)	1.10 (0.90 - 1.34)	1.14(0.72 – 1.81)
Obesity	2.07 (1.02 - 4.22)	0.61 (0.37 - 1.01)	1.03 (0.85 - 1.26)	1.00 (0.84 - 1.19)
Estimated glomerular filtration rate (per increase by 1 ml/min/1.73m^2)	0.98(0.97 - 0.99)	0.99(0.98 - 1.01)	0.99 (0.98 - 0.99)	0.99(0.989 - 0.99)
Harrell's C-statistic for model	0.71(0.63 - 0.77)	0.67 (0.61 - 0.73)	0.66 (0.63 - 0.69)	0.69(0.67 - 0.71)

Data are presented as count (percentage) and median (interquartile range), as appropriate. Models were adjusted for age, gender, history of smoking, presence of diabetes, hypertension, obesity, and estimated glomerular filtration rate.

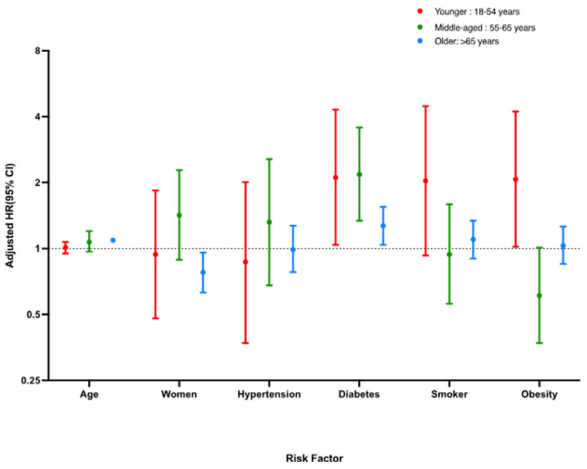

Figure 1. Prognostic associations of risk factors with mortality among younger, middle-aged, and older adults with heart failure. Age significantly modified the association of obesity and diabetes on subsequent risk of mortality (p-interaction<0.05 for both).

Similarly, obesity was associated with higher risk of mortality in younger (adjusted HR 2.07; 95% CI: 1.02-4.22) compared with middle-aged (adjusted HR 0.61; 95% CI: 0.37- 1.01) and older adults (adjusted HR 1.03; 95% CI: 0.85-1.26); p-interaction<0.05; Figure 1. All other risk factors showed similar prognostic associations with mortality across the age ranges. Age as a continuous function did not modify the association of risk factors with long-term mortality. Predictive accuracy of multivariable models declined with increasing age, with a Harrel's C- statistic (95% CI) of 0.71(0.63-0.77) in young, 0.67 (0.61 - 0.73) in middle-aged, and 0.66 (0.63-0.69) in older adults.

In this longitudinal analysis of adults in NHANES, we found cardiometabolic risk factors, including obesity and diabetes, appear more closely linked with mortality in younger adults with HF compared with older age groups. Furthermore, models including these established, modifiable risk factors were more accurate and discriminative of subsequent mortality in younger individuals.

In recent years, the incidence of HF and case mortality rates have remained large stable in older adults.[6] However, prevalence of HF has consistently been rising, potentially due to the increase in the overall population and expansion in the burden of cardiometabolic risk factors in younger adults.[7] Our study highlights that core risk factors, including ones that are modifiable, discriminate most deaths among young patients with HF and represent a key opportunity for early intervention. Our data are consistent with previous studies that have shown higher population attributable risk for traditional risk factors among young individuals for the development of HF.[3] This study extends these findings and points toward higher predictive ability of these risk factors for mortality in young patients with HF, and may inform population-level targeted efforts to slow disease progression and prevent premature mortality at an earlier time-point.

Our study has certain limitations. As an administrative and self-reported dataset, NHANES is susceptible to miscoding and responder bias. Cause-specific deaths were not available for analysis. Further, to allow for longitudinal follow-up, the baseline cohort was enrolled in 1999-2010, and standard of care has evolved since then. Lastly, data regarding background therapy and ejection fraction were not available (Figure 1).

Cardiometabolic risk factors are more common, carry greater prognostic association, and when combined with other traditional risk factors, more accurately forecast future mortality in younger adults compared with middle-aged or older adults with HF.

Disclosures

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Dr. Vaduganathan has received research grant support or served on advisory boards for American Regent, Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, Boehringer Ingelheim, Cytokinetics, Lexicon Pharmaceuticals, Relypsa, and Roche Diagnostics, speaker engagements with Novartis and Roche Diagnostics, and participates on clinical endpoint committees for studies sponsored by Galmed and Novartis.

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