Association of Frailty Status on the Causes and Outcomes of Patients Admitted With Cardiovascular Disease

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Data are limited about the contemporary association between frailty and the causes and outcomes of patients admitted with cardiovascular diseases (CVD). Using the US National Inpatient Sample, CVD admissions of interest (acute myocardial infarction, ischemic stroke, atrial fibrillation (AF), heart failure, pulmonary embolism, cardiac arrest, and hemorrhagic stroke) were stratified by Hospital Frailty Risk Score (HFRS). Logistic regression was used to determine adjusted odds ratios (aORs) and 95% confidence intervals (CIs) of in-hospital mortality among different groups with frailty. The study included 9,317,398 hospitalizations. Of these, 5,573,033 (59.8%) had a low HFRS (<5); 3,422,700 (36.7%) had an intermediate HFRS (5 to 15); and 321,665 (3.5%) had a high HFRS (>15). Ischemic stroke was the most common admission for the groups with high risk (75.4%), whereas acute myocardial infarction was the most common admission for the group with low risk (36.9%). Compared with the group with low risk, patients with high risk had increased mortality across the most CVD admissions, except in patients admitted for cardiac arrest and hemorrhagic stroke (p <0.001). The strongest association with all-cause mortality was shown among patients with high risk admitted for AF (aOR 6.75, 95% CI 6.51 to 7.00, and aOR 17.69, 95% CI 16.08 to 19.45) compared with their counterparts with low risk. In conclusion, patients with CVD admissions have varying frailty risk according to cardiovascular cause of admission, with ischemic stroke being the most common among groups with frailty and high risk. Increased frailty is associated with all-cause mortality in patients with most CVD admissions, except for cardiac arrest and hemorrhagic stroke, with the strongest association seen in patients admitted with AF. **(Am J Cardiol 2023;192:7−15)**

Frailty is defined as an impairment of multiple systems resulting in an increased vulnerability to stress, leading to an increased risk of adverse outcomes such as hospitalizations and mortality, and is strongly associated with age.[1] With the growing numbers of the older population, the proportion living with frailty in society and across healthcare systems is increasing.[2] Similarly, the numbers of patients living with cardiovascular (CV) disease (CVD) are increasing, particularly given an improved survivorship in patients with acute or chronic CVD.[3] The relation between frailty and CVD is bidirectional.[4] CVD is associated with a threefold increase in frailty, and frailty is independently associated with an increased mortality from CVD.[5,6] A recent meta-analysis including 31,343 patients with CVD reported that the prevalence of frailty was 17.9% and was associated with an increased risk of heart failure (HF).[7] Previous studies have attempted to understand the underlying mechanisms linking older age and adverse CVD outcomes, with common mechanisms implicated being inflammation, concomitant risk factors, and co-morbidity burden.[2] However, there are few data investigating whether CVD admissions vary by frailty status and whether frailty is associated with in-hospital outcomes in patients admitted with acute CVD conditions. Knowledge of the specific causes of CVD admissions and their outcomes in relation to frailty status is fundamental in planning healthcare services around the growing needs of the population living with frailty. Therefore, the aim of this study was to describe the prevalence, clinical characteristics, and in-hospital mortality of patients with the CVD admissions of interest based on their frailty status, as measured by the Hospital Frailty Risk Score (HFRS).

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Methods

The National Inpatient Sample (NIS) is the largest available database of US hospitalizations developed for the Healthcare Cost and Utilization Project sponsored by the Agency for Healthcare Research and Quality.[8] The NIS contains anonymized data on diagnoses and procedures from >7 million hospitalizations annually, representing a 20% stratified sample of all discharges from US community hospitals, excluding rehabilitation and long-term acute care hospitals.[8]

The HFRS was developed by Gilbert et al[9] to establish whether older patients at risk of adverse outcomes could be identified using routinely collected healthcare data. Briefly, a cohort of older patients (aged >74 years) hospitalized with diagnoses associated with frailty was identified.[9] The HFRS was then created by grouping the patients identified according to their International Classification of Diseases (ICD) Tenth Revision codes into 3 groups: low risk (HFRS <5), intermediate risk (HFRS 5 to 15), and high risk (HFRS >15).[9] The score was then validated using a local and national United Kingdom cohort.[9] Each component of the HFRS and the associated weighting is outlined in Supplementary Appendix 1.

Using ICD Tenth Revision codes (Supplementary Table 1), all adult discharge records with a principal diagnosis of an acute CVD admission between October 2015 and December 2019 were identified. This sample was further filtered by focusing on the 7 CVD admissions of interest: acute myocardial infarction (AMI), atrial fibrillation/flutter (AF), ischemic stroke, HF, pulmonary embolism (PE), cardiac arrest, and hemorrhagic stroke. The sample was further stratified according to their frailty status measured by the HFRS into 3 groups: low risk (HFRS <5), intermediate risk (HFRS 5 to 15), and high risk (HFRS >15), as defined by Gilbert et al.[9] Cases were excluded owing to missing data for the following variables: age, gender, elective admission, in-hospital mortality, primary expected payer, total charges, and length of stay. These cases accounted for no more than 1.0% of the original dataset. Cases not pertaining to 1 of the 7 diagnoses of interest were also excluded (Supplementary Figure 1). This observational study was appraised according to the Strengthening The Reporting of OBservational Studies in Epidemiology recommendations (Supplementary Appendix 2).

Continuous variables such as age, length of stay, and total charges were summarized using median and interquartile range. Categorical variables were compared using the chi-square test and summarized as percentages (%). Multivariable logistic regression was performed to determine the adjusted odds ratio (aOR) for all-cause mortality. Regression was adjusted for the following variables: age, gender, race, weekend admission, primary expected payer, median household income, bed size of hospital, region of hospital, location/teaching status of hospital, smoking status, previous myocardial infarction, previous percutaneous coronary intervention, previous coronary artery bypass graft, dyslipidemia, and Elixhauser co-morbidities (anemias, coagulopathy, diabetes mellitus, liver disease, metastatic cancer, peripheral vascular disorders, and chronic renal failure). Results were presented as aORs with 95% confidence intervals (CIs). Results were determined significant at the level of $p < 0.05$. All statistical analyses were weighted and performed using SPSS version 27 (IBM Corp, Armonk, New York).[10]

Results

A total of 9,317,398 discharges had 1 of the 7 CVD diagnoses of interest (AMI, ischemic stroke, AF, HF, PE, and hemorrhagic stroke) (Supplementary Figure 1). Overall, 5,573,033 discharges (59.8%) had an HFRS of <5; 3,422,700 (36.7%) had an HFRS of 5 to 15; and 321,665 (3.5%) had an HFRS of >15 (Table 1).

Patients with an HFRS >15 were more likely to be older (median age 75 vs 73 years for HFRS 5-to- 15 group and 68 years for HFRS <5 group) and female (54.1% vs 48.7% for HFRS 5-to-15 group and 43.0% for HFRS <5 group) and to have a higher prevalence of hypertension, coagulopathy, and thrombocytopaenia, in addition to a lower prevalence of previous AMI, previous percutaneous coronary intervention, previous coronary artery bypass graft, HF, and diabetes, than were patients with an HFRS <5 and HFRS 5 to 15 ($p < 0.001$ for all) (Table 1).

The most common cause of admission was AMI (28.7%), followed by ischemic stroke (23.8%), AF (21.0%), HF (16.2%), hemorrhagic stroke (5.9%), PE (4.0%), and cardiac arrest (0.4%). The cohort admitted with ischemic stroke had the highest proportion of patients with an HFRS >15 (10.8%), followed by hemorrhagic stroke and cardiac arrest (9.1% and 2.5%). Similarly, cohorts admitted with cardiac arrest had the highest proportion of patients with an HFRS 5 to 15 (70.4%), followed by ischemic stroke and hemorrhagic stroke (66.9% and 54.9%, respectively). The cohort admitted with AF had the highest proportion of patients with an HFRS <5, followed by AMI and PE (80.3% vs 76.7% and 74.1%) (Figure 1, Supplementary Table 2-8).

The most common cause of CVD admission in the HFRS <5 cohort was AMI (36.9%), followed by AF (28.2%) and HF (17.4%). Ischemic stroke was the most common CVD admission for the HFRS 5-to-15 group (43.3%), followed by AMI (17.8%) and HF (15.6%). Similarly, ischemic stroke was the most common CVD admission for the HFRS of >15 groups (75.4%), followed by hemorrhagic stroke (15.5%) and AMI (4.3%) (Figure 2).

Patients with HFRS >15 had higher unadjusted rates of all-cause mortality than did their counterparts with lower frailty (10.3% vs 7.6 for HFRS 5-to-15 group and 2.2% for HFRS <5 group, $p < 0.001$). Increased unadjusted rates of all-cause mortality for patients with high-risk frailty were also observed in patients admitted with AMI, ischemic stroke, AF, HF, and PE but not for patients admitted with cardiac arrest or hemorrhagic stroke (all $p < 0.001$) (Supplementary Figure 2, Table 2).

On adjustment for baseline covariates, increasing frailty risk was associated with increased odds of all-cause mortality. Patients with an HFRS of 5 to 15 or HFRS >15 admitted for AF had the highest odds of all-cause mortality (aOR 17.69, 95% CI 16.08 to 19.45 for HFRS >15 group, aOR 6.75, 95% CI 6.51 to 7.00 for HFRS 5-to-15 group). Increased odds of mortality were observed with worsening

Table 1
Patient characteristics for all cardiovascular admissions according to HFRS

Characteristics	Hospital Frailty Risk Score			Overall p Value
	Low <5 (59.8%)	Intermediate 5−15 (36.7%)	High >15 (3.5%)	
Number of weighted discharges	5,573,033	3,422,700	321,665	<0.001
Age (years), median (IQR)	68 (58, 78)	73 (62, 82)	75 (63,84)	<0.001
Female sex	43.0%	49.7%	54.1%	<0.001
Ethnicity				<0.001
White	74.8%	70.4%	65.0%	
Black	12.3%	15.6%	19.2%	
Hispanic	7.6%	8.0%	8.8%	
Other	5.3%	6.0%	7.0%	
Weekend admission	23.4%	25.3%	26.3%	<0.001
Primary expected payer				<0.001
Medicare	58.9%	70.5%	72.4%	
Medicaid	9.5%	8.7%	9.6%	
Private insurance	24.6%	15.4%	13.1%	
Self-pay	4.2%	3.1%	3.0%	
No charge	0.4%	0.2%	0.2%	
Other	2.6%	2.1%	1.8%	
Median household income (percentile)				<0.001
0-25th	29.8%	31.0%	31.2%	
26th−50th	27.1%	26.4%	25.5%	
51st-75th	24.0%	23.7%	23.7%	
76th−100th	19.1%	18.8%	19.6%	
Homelessness	0.5%	0.4%	0.4%	<0.001
Comorbidities				
Atrial fibrillation	38.1%	32.3%	30.9%	<0.001
Dyslipidemia	52.5%	53.7%	54.2%	<0.001
Thrombocytopenia	3.4%	5.6%	6.0%	<0.001
Smoking	9.6%	8.1%	8.6%	<0.001
Previous AMI	10.8%	10.3%	7.4%	<0.001
Previous PCI	11.8%	9.7%	6.2%	<0.001
Previous CABG	8.5%	8.5%	5.9%	<0.001
Anemias	12.7%	22.6%	23.5%	<0.001
Congestive heart failure	43.7	43.6%	29.4%	<0.001
Valvular disease	7.2%	6.8%	3.9%	<0.001
Hypertension	61.7%	61.6%	71.5%	<0.001
Peripheral vascular disorders	6.6%	9.1%	8.6%	<0.001
Coagulopathy	4.8%	8.2%	9.2%	<0.001
Diabetes Mellitus	26.9%	28.4%	21.5%	<0.001
Liver disease	2.7%	4.0%	2.9%	<0.001
Chronic renal failure	14.8%	32.4%	32.6%	<0.001
Bed size of hospital				<0.001
Small	19.5%	17.2%	13.0%	
Medium	30.0%	28.9%	25.6%	
Large	50.5%	53.9%	61.4%	
Hospital region				<0.001
Northeast	19.2%	17.4%	15.0%	
Midwest	22.3%	22.6%	25.4%	
South	41.1%	41.3%	40.6%	
West	17.4%	18.8%	19.0%	
Location/teaching status of hospital				<0.001
Rural	10.1%	8.1%	4.5%	
Urban non-teaching	24.0%	21.4%	15.5%	
Urban teaching	65.9%	70.5%	80.0%	
Length of stay (days), median (IQR)	3 (2, 4)	4 (2, 7)	7 (4, 13)	<0.001
Total charges (USD), median (IQR)	35,715 (18,233, 71,510)	45,681 (25,231, 91,144)	77,672 (40,321, 162,236)	<0.001
All-cause in-hospital mortality	2.2%	7.6%	10.3%	<0.001

AMI = acute myocardial infarction; CABG = coronary artery bypass graft; IQR = interquartile range; PCI = percutaneous coronary intervention; USD = US dollar.

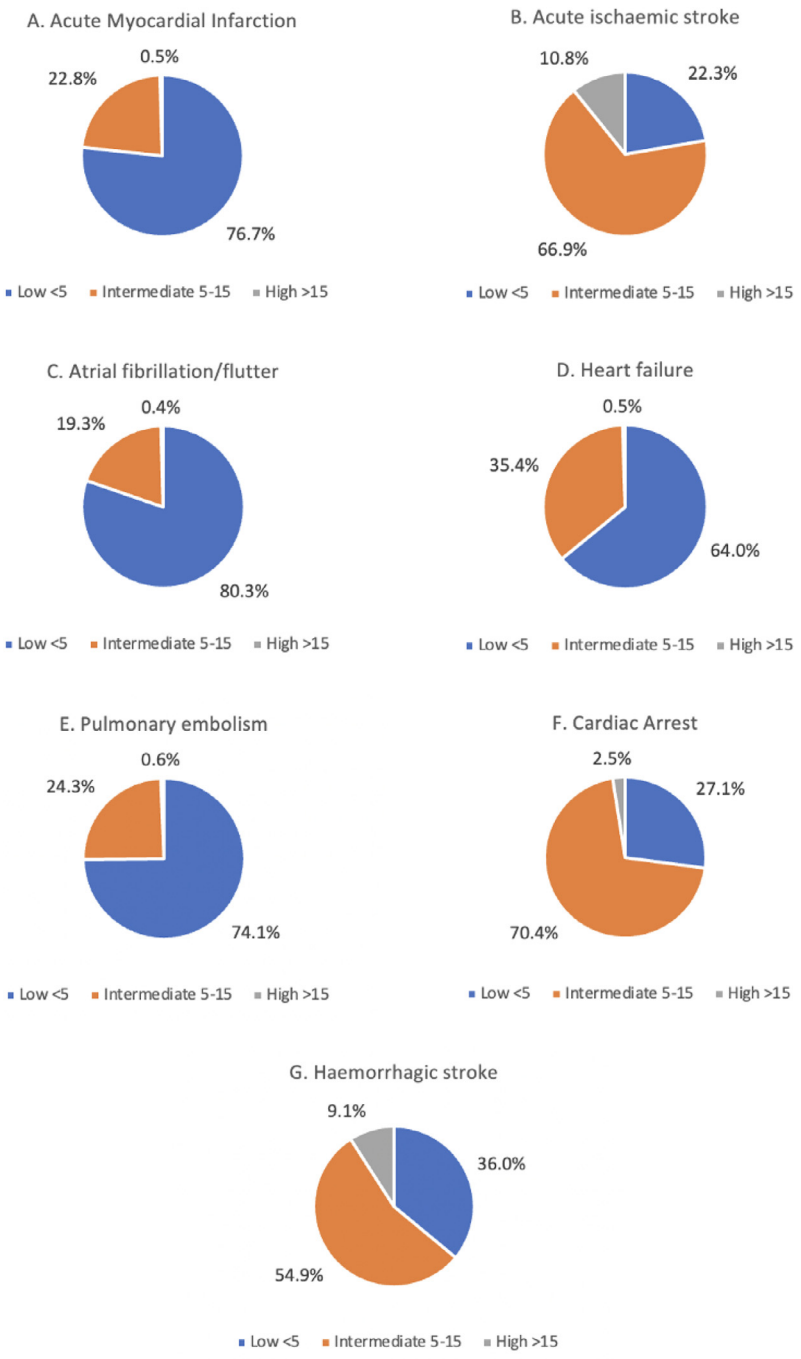

Figure 1. Distribution of each HFRS category within each of the selected cardiovascular admission causes.

frailty status across a broad range of different CV causes for admission. The HFRS >15 group was associated with in an increased odds of mortality for patients admitted with AMI, ischemic stroke, HF, and PE admission diagnoses ($p < 0.001$). Interestingly, a decreased odds of mortality in the HFRS >15 group was observed in patients admitted for cardiac arrest and hemorrhagic stroke only (aOR 0.46, 95% CI 0.39 to 0.55 for patients with cardiac arrest with an HFRS >15, aOR 0.86, 95% CI 0.83 to 0.88 for patients with hemorrhagic stroke with an HFRS >15) (Figure 3, Table 3).

Discussion

To the best of our knowledge, this is the first study to examine the prevalence, clinical characteristics, and in-hospital mortality of patients admitted with a broad range of acute CV presentations on a nationwide scale based on their frailty status. We report several important findings. Firstly, we report the most common CVD admissions across frailty categories, with AMI being the most common in patients with a low frailty score, and ischemic stroke being the most

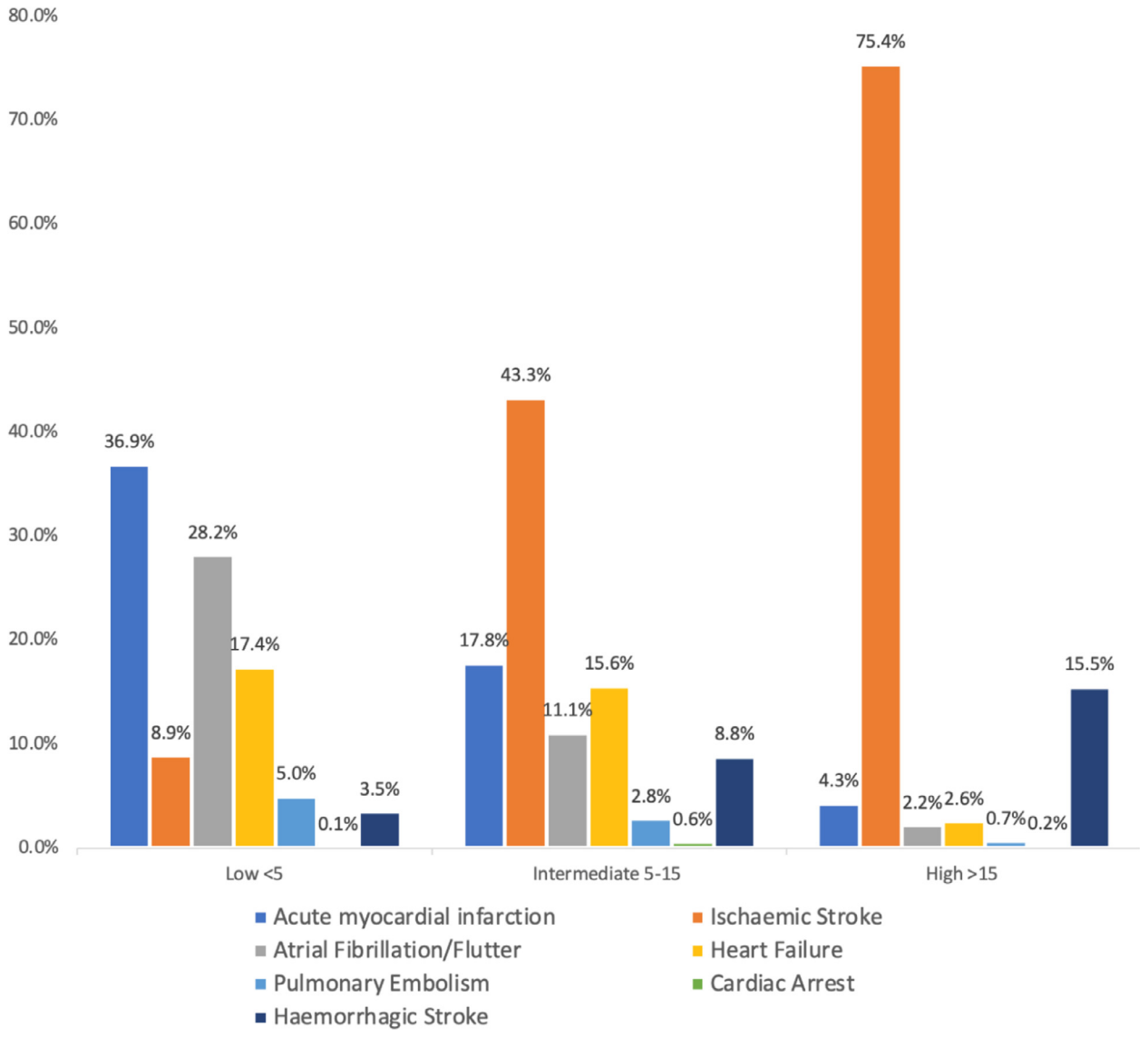

Figure 2. Distribution of selected cardiovascular admission causes within each HFRS category.

Table 2
Prevalence of the cardiovascular admission diagnoses and associated in-hospital deaths based on HFRS

Admission diagnosis		Hospital Frailty Risk Score			Overall *P*-value
		Low <5 (59.8%)	Intermediate 5-15 (36.7%)	High >15 (3.5%)	
Acute myocardial infarction (n = 2,677,890)	**Prevalence**	36.9%	17.8%	4.3%	<0.001
	In-hospital mortality	2.2%	12.7%	15.4%	<0.001
Ischemic stroke (n = 2,217,925)	**Prevalence**	8.9%	43.3%	75.4%	<0.001
	In-hospital mortality	2.0%	3.8%	8.9%	<0.001
Atrial fibrillation/flutter (n = 1,959,699)	**Prevalence**	28.2%	11.1%	2.2%	<0.001
	In-hospital mortality	0.3%	2.9%	8.0%	<0.001
Heart failure (n = 1,511,459)	**Prevalence**	17.4%	15.6%	2.6%	<0.001
	In-hospital mortality	1.7%	5.4%	12.3%	<0.001
Pulmonary embolism (n = 375,940)	**Prevalence**	5.0%	2.8%	0.7%	<0.001
	In-hospital mortality	1.4%	8.5%	10.6%	<0.001
Cardiac arrest (n = 28,790)	**Prevalence**	0.1%	0.6%	0.2%	<0.001
	In-hospital mortality	71.7%	74.0%	55.2%	<0.001
Hemorrhagic stroke (n = 545,695)	**Prevalence**	3.5%	8.8%	15.5%	<0.001
	In-hospital mortality	17.8%	20.7%	15.0%	<0.001

HFRS = Hospital Frailty Risk Score.

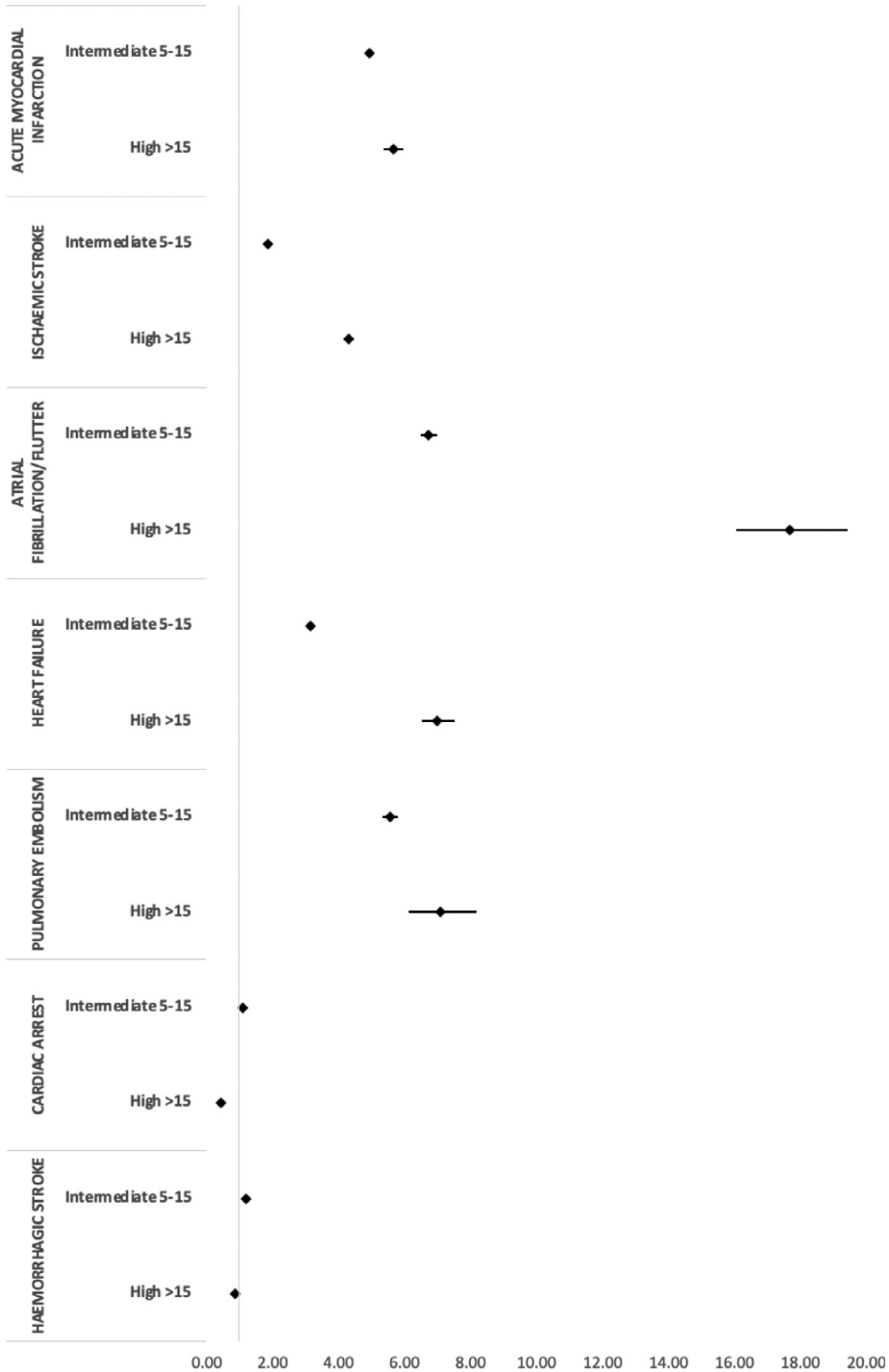

Figure 3. Adjusted mortality rates for different frailty risk category and selected cardiovascular admission causes. Reference group is low HFRS score <5 for each CVD admission diagnosis.

Multivariable logistic regression model adjusted for age, gender, race, weekend admission, elective admission, primary expected payer, median household income, hospital bed size, region and teaching status, thrombocytopenia, previous PCI, previous AMI, previous CABG, anemia, coagulopathies, liver disease, metastatic disease, and peripheral vascular disease. CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention.

common in patients with an intermediate and high frailty score. Secondly, we report important frailty-based differences in baseline characteristics across patients with different CVD admission diagnoses. Finally, patients with an intermediate and high frailty score had increased all-cause mortality compared with their counterparts with lower risk across most CVD admission diagnoses, except in cardiac arrest and hemorrhagic stroke categories.

The association between frailty and CVD has been widely explored in the literature.[2,4–7] Frailty has been shown to be a predictor of incident CVD.[6,11] CVD is associated with a threefold increase in prevalent frailty, and frailty

Table 3
Adjusted odds of mortality in different HFRS categories and selected cardiovascular admission diagnoses

Admission diagnosis	Hospital Frailty Risk Score			
	Intermediate 5−15 (36.7%)		High >15 (3.5%)	
	aOR	p Value	aOR	p Value
Acute myocardial infarction (n = 2,677,890)	4.95 [4.86−5.02]	<0.001	5.67 [5.39−5.96]	<0.001
Ischemic stroke (n = 2,217,925)	1.88 [1.84−1.92]	<0.001	4.31 [4.20−4.43]	<0.001
Atrial fibrillation/flutter (n = 1,959,699)	6.75 [6.51−7.00]	<0.001	17.69 [16.08−19.45]	<0.001
Heart failure (n =1,511,459)	3.15 [3.08−3.22]	<0.001	7.01 [6.52−7.53]	<0.001
Pulmonary embolism (n = 375,940)	5.58 [5.34−5.82]	<0.001	7.09 [6.14−8.18]	<0.001
Cardiac arrest (n = 28,790)	1.12 [1.05−1.20]	<0.001	0.46 [0.39−0.55]	<0.001
Hemorrhagic stroke (n = 545,695)	1.21 [1.20−1.23]	<0.001	0.86 [0.83−0.88]	<0.001

Reference group is low HFRS score <5 for each CVD admission diagnosis. Multivariable logistic regression model adjusted for age, sex, race, weekend admission, elective admission, primary expected payer, median household income, hospital bed size, region and teaching status, thrombocytopenia, previous PCI, previous AMI, previous CABG, anemia, coagulopathies, liver disease, metastatic disease, peripheral vascular disease.

aOR = adjusted odds ratio; CI = confidence interval; HFRS = Hospital Frailty Risk Score.

increases odds of CVD by 35%.[6] This relation is believed to be due to similar underlying biological pathways.[6] CVD and frailty share similar biomarkers such as interleukin 6 and high levels of factor VIII, *d*-dimer, fibrinogen, and C-reactive protein.[12−14] The pathways in conjunction with low physical activity and poor nutrition could lead to decreased physiological reserves and increased susceptibility to stress, leading to frailty.[15] In addition, these factors can lead to a prothrombotic state and increased levels of inflammation, leading to increased risk of CV events and adverse outcomes.[12−14]

The HFRS was nationally validated using a cohort of >1 million patients in the United Kingdom, of whom 37.6% had an intermediate risk of frailty and 20% had a high risk of frailty.[9] In our cohort of 9 million US patients hospitalized with CVD, there was a lower proportion of patients at intermediate or high risk of frailty. The prevalence of frailty among overall patients with CVD was previously estimated between 15% and 19%,[7,15,16] and up to 40.9% in studies using the HFRS.[17,18] Variable prevalence of frailty in the literature could be partially explained by differences in the cohorts studied but also and importantly by differences in definitions used and what is considered to represent frailty, with studies using definitions derived from Rockwood et al,[19] Fried et al,[16] and Gill et al.[7,9,16,19,20] There is a challenge to defining frailty because there is no standardized measurement, but the HFRS represents a potentially advantageous option owing to its dependence on the widely available ICD coding system.[21] The HFRS follows the deficit model (combining impairments) and has been validated against the Rockwood and Fried scores; however, it can be quite challenging for clinicians to calculate because of a lack of automated computation.[22] Similarly to other studies, we observed that patients with increasing frailty are likely to be older and female, and to have longer hospital stays and total costs.[2,5,7,9,18,22]

This study found important variations in frailty status across different CVD admissions. Among patients with intermediate or high frailty risk, the most prevalent CVD admission was acute ischemic stroke. This may be explained by the inclusion of the sequelae of stroke in the HFRS, but other contributors, such as older age, which increases the risk of both stroke and frailty, with 70% of strokes occurring after the age of 65, are also important.[23] AF has been reported to be prevalent in 15% of the population with frailty, although we report an interesting pattern of a decreasing proportion of AF admission with increasing frailty.[24] Again, this could be mediated by varying definitions of frailty because the previous study used scores devised by Fried et al[16] and Rockwood et al.[19] Studies using the HFRS indicated a similar distribution of frailty status to this study among patients with AF, with most patients at low risk of frailty and only a small percentage at high risk of frailty.[25] This study shows admission for HF decreases with increasing frailty yet is still common, with >3 in 10 patients admitted with HF at intermediate or high risk of frailty. Our findings are supported by other studies that show intermediate or high risk of frailty is present in up to 1 in 5 patients hospitalized with HF and is associated with a longer length of stay and increased total charges.[22,26] This could be explained by an increased number of co-morbidities in the population with HF, with a high prevalence of dyslipidemia, anemia, and hypertension.[22] This agrees with multiple studies that showed patients with increased HFRS have a higher Charlson co-morbidity score, in line with the HFRS being based on the total co-morbidity burden of patients.[9,18,22] There are no studies describing the prevalence of PE, cardiac arrest, and hemorrhagic stroke among patients with frailty who are hospitalized.

Interestingly, AF was a rare cause of admission in the high-risk group but was associated with the worst prognosis in these patients. The association between AF and mortality has been reported in multiple studies because the prevalence of AF increases with age and co-morbidity burden, and increases the risk of stroke and its associated complications.[27,28] Studies have suggested that patients with frailty also have a larger left atrial volume, which is one of the main cardiac abnormalities linked to the development of AF and systolic dysfunction.[29] Furthermore, patients with incident AF are commonly on anticoagulant medications, which increases risk of bleeding and further complications such as hemorrhage.[27] However, studies report that patients with AF and increasing frailty are less likely to be treated with oral anticoagulants, which can lead to increased likelihood of downstream thrombotic events and poorer outcomes.[25,29] We report that HF was independently associated with higher odds of mortality with

increasing frailty, as seen in other studies.[22,26] Our findings of cardiac arrest and hemorrhagic stroke, although different to the other CVD admissions of interest, could have several explanations. These conditions have substantial mortality per se, with little modification by HFRS. This analysis encompassed only patients who were admitted owing to cardiac arrest, leading to potential selection bias, so it is possible that many of the patients with frailty did not survive to admission, and only those with the most favorable prognosis survived to admission. It is possible that the poor outcomes in these patient groups occur independently of frailty status.[30,31]

There are important clinical implications of this study. This study indicates that patients with intermediate-to-high frailty risk represent a substantial portion of the population admitted for CVD and raises the importance of frailty assessment by cardiologists. A co-existence of frailty and CVD is becoming even more important owing to an aging population with higher morbidity burden. Patients with frailty admitted with CVD have higher mortality rates and burden the healthcare system, and knowledge of the trends in CVD admission is fundamental to improve the outcomes of this clinically at-risk population. This study may support the early identification and management of CVD in patients with frailty, particular in primary care, although whether this would affect acute admissions is not known.

This study has several limitations inherent to the use of the NIS database. Firstly, coded data for the NIS could be subject to selection bias because of inaccurate coding or missing data. Secondly, detailed clinical information such as pharmacological treatment that can mediate outcomes could not be investigated because it was not available from the NIS. The impact of differential pharmacological management in the population with frailty on outcomes may be an area for further research. Thirdly, because this is an observational study, confounding bias could not be fully eliminated despite the broad scope of conditions covered by the NIS, and therefore, causality between frailty, CVD admission, and mortality cannot be proved. Finally, the NIS only captures information on in-hospital events, and therefore, a more detailed analysis of longitudinal outcomes could not be assessed.[32]

In conclusion, the causes of CVD admission vary with frailty status, with AMI being the most common in patients with a low risk of frailty, whereas ischemic stroke is the most common in patients with intermediate or high risk of frailty. Increasing frailty in patients admitted for AMI, ischemic stroke, AF, HF, and PE is associated with an increased all-cause mortality. Future, more granular studies are necessary to guide care and improve the CVD outcomes in patients with frailty in an ever-aging population.

Disclosures

The authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2022.12.029.

1. Xue QL. The frailty syndrome: definition and natural history. *Clin Geriatr Med* 2011;27:1–15.
2. Ramsay SE, Arianayagam DS, Whincup PH, Lennon LT, Cryer J, Papacosta AO, Iliffe S, Wannamethee SG. Cardiovascular risk profile and frailty in a population-based study of older British men. *Heart* 2015;101:616–622.
3. Vasan RS, Enserro DM, Xanthakis V, Beiser AS, Seshadri S. Temporal trends in the remaining lifetime risk of cardiovascular disease among middle-aged adults across 6 decades: the Framingham study. *Circulation* 2022;145:1324–1338.
4. Chung KJNC, Wilkinson C, Veerasamy M, Kunadian V. Frailty scores and their utility in older patients with cardiovascular disease. *Interv Cardiol* 2021;16:e05.
5. Newman AB, Gottdiener JS, McBurnie MA, Hirsch CH, Kop WJ, Tracy R, Walston JD. Fried LP, Cardiovascular Health Study Research Group. Associations of subclinical cardiovascular disease with frailty. *J Gerontol A Biol Sci Med Sci* 2001;56:M158–M166.
6. Afilalo J, Karunananthan S, Eisenberg MJ, Alexander KP, Bergman H. Role of frailty in patients with cardiovascular disease. *Am J Cardiol* 2009;103:1616–1621.
7. Veronese N, Cereda E, Stubbs B, Solmi M, Luchini C, Manzato E, Sergi G, Manu P, Harris T, Fontana L, Strandberg T, Amieva H, Dumurgier J, Elbaz A, Tzourio C, Eicholzer M, Rohrmann S, Moretti C, D'Ascenzo F, Quadri G, Polidoro A, Lourenço RA, Moreira VG, Sanchis J, Scotti V, Maggi S, Correll CU. Risk of cardiovascular disease morbidity and mortality in frail and pre-frail older adults: results from a meta-analysis and exploratory meta-regression analysis. *Ageing Res Rev* 2017;35:63–73.
8. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUP). Available at: https://www.ahrq.gov/data/hcup/index.html. Accessed on 01/09/2023.
9. Gilbert T, Neuburger J, Kraindler J, Keeble E, Smith P, Ariti C, Arora S, Street A, Parker S, Roberts HC, Bardsley M, Conroy S. Development and validation of a Hospital Frailty Risk Score focusing on older people in acute care settings using electronic hospital records: an observational study. *Lancet* 2018;391:1775–1782.
10. IBM. SPSS Statistics for Macintosh. version 27.0 Armonk, NY: IBM Corp. https://www.ibm.com/support/pages/how-cite-ibm-spss-statistics-or-earlier-versions-spss.
11. Newman AB, Simonsick EM, Naydeck BL, Boudreau RM, Kritchevsky SB, Nevitt MC, Pahor M, Satterfield S, Brach JS, Studenski SA, Harris TB. Association of long-distance corridor walk performance with mortality, cardiovascular disease, mobility limitation, and disability. *JAMA* 2006;295:2018–2026.
12. Walston J, McBurnie MA, Newman A, Tracy RP, Kop WJ, Hirsch CH, Gottdiener J. Fried LP, Cardiovascular Health Study. Frailty and activation of the inflammation and coagulation systems with and without clinical comorbidities: results from the cardiovascular Health Study. *Arch Intern Med* 2002;162:2333–2341.
13. Di Napoli M, Papa F. Villa Pini Stroke Data Bank Investigators. Inflammation, hemostatic markers, and antithrombotic agents in relation to long-term risk of new cardiovascular events in first-ever ischemic stroke patients. *Stroke* 2002;33:1763–1771.
14. Patterson CC, Blankenberg S, Ben-Shlomo Y, Heslop L, Bayer A, Lowe G, Zeller T, Gallacher J, Young I, Yarnell J. Which biomarkers are predictive specifically for cardiovascular or for non-cardiovascular mortality in men? Evidence from the Caerphilly prospective study (CaPS). *Int J Cardiol* 2015;201:113–118.
15. Damluji AA, Huang J, Bandeen-Roche K, Forman DE, Gerstenblith G, Moscucci M, Resar JR, Varadhan R, Walston JD, Segal JB. Frailty among older adults with acute myocardial infarction and outcomes from percutaneous coronary interventions. *J Am Heart Assoc* 2019;8:e013686.
16. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA. Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;56:M146–M156.
17. Nghiem S, Afoakwah C, Scuffham P, Byrnes J. Hospital Frailty Risk Score and adverse health outcomes: evidence from longitudinal record linkage cardiac data. *Age Ageing* 2021;50:1778–1784.
18. Kundi H, Wadhera RK, Strom JB, Valsdottir LR, Shen C, Kazi DS, Yeh RW. Association of frailty with 30-day outcomes for acute

myocardial infarction, heart failure, and pneumonia among elderly adults. *JAMA Cardiol* 2019;4:1084–1091.
19. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, Mitnitski A. A global clinical measure of fitness and frailty in elderly people. *CMAJ* 2005;173:489–495.
20. Gill TM, Baker DI, Gottschalk M, Peduzzi PN, Allore H, Byers A. A program to prevent functional decline in physically frail, elderly persons who live at home. *N Engl J Med* 2002;347:1068–1074.
21. Aguayo GA, Donneau AF, Vaillant MT, Schritz A, Franco OH, Stranges S, Malisoux L, Guillaume M, Witte DR. Agreement between 35 published frailty scores in the general population. *Am J Epidemiol* 2017;186:420–434.
22. Kwok CS, Zieroth S, Van Spall HGC, Helliwell T, Clarson L, Mohamed M, Mallen C, Duckett S, Mamas MA. The Hospital Frailty Risk Score and its association with in-hospital mortality, cost, length of stay and discharge location in patients with heart failure short running title: frailty and outcomes in heart failure. *Int J Cardiol* 2020;300:184–190.
23. Kelly-Hayes M. Influence of age and health behaviors on stroke risk: lessons from longitudinal studies. *J Am Geriatr Soc* 2010;58(suppl 2): S325–S328.
24. Orkaby AR, Kornej J, Lubitz SA, McManus DD, Travison TG, Sherer JA, Trinquart L, Murabito JM, Benjamin EJ, Preis SR. Association between frailty and atrial fibrillation in older adults: the Framingham heart study offspring cohort. *J Am Heart Assoc* 2021;10:e018557.
25. Orlandi M, Dover DC, Sandhu RK, Hawkins NM, Kaul P, McAlister FA. The introduction of direct oral anticoagulants has not resolved treatment gaps for frail patients with nonvalvular atrial fibrillation. *Can J Cardiol* 2022;38:77–84.
26. McAlister FA, Savu A, Ezekowitz JA, Armstrong PW, Kaul P. The Hospital Frailty Risk Score in patients with heart failure is strongly associated with outcomes but less so with pharmacotherapy. *J Intern Med* 2020;287:322–332.
27. Guo Q, Du X, Ma CS. Atrial fibrillation and frailty. *J Geriatr Cardiol* 2020;17:105–109.
28. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation* 1998;98:946–952.
29. Villani ER, Tummolo AM, Palmer K, Gravina EM, Vetrano DL, Bernabei R, Onder G, Acampora N. Frailty and atrial fibrillation: a systematic review. *Eur J Intern Med* 2018;56:33–38.
30. Kochanek KD, Xu J, Arias E. Mortality in the United States, 2019. *NCHS Data Brief* 2020:(395):1–8.
31. Andersen LW, Holmberg MJ, Berg KM, Donnino MW, Granfeldt A. In-hospital cardiac arrest: a review. *JAMA* 2019;321:1200–1210.
32. Khera R, Krumholz HM. With great power comes great responsibility: big data research from the National Inpatient Sample. *Circ Cardiovasc Qual Outcomes* 2017;10:e003846.