HEALTH OUTCOMES IN OLDER ADULTS WITH CARDIOVASCULAR DISEASE

by

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ABSTRACT

In the United States, longevity is increasing, and more adults are living into old age, a stage of life when age-related biologic and physiologic mechanisms predispose individuals to cardiovascular disease (CVD) in a context of complexity related to their age.[1] Two thirds of all patients with CVD are older than 60 years of age, and more than 85% of patients over age 85 years live with some form of CVD.[2] Although acute CVD is a leading cause of morbidity and mortality for adults of any age, older patients are at higher risk for adverse outcomes[2, 3] including mortality, re-hospitalizations, diminished quality-of-life, and functional decline. Many older adults with acute CVD are managed based on evidence derived from cohorts of younger patients with the goal of achieving optimal cardiovascular care. Yet broader contextual health challenges exit in older populations.[4] For example, multimorbidity, polypharmacy, cognitive decline, sarcopenia, and frailty are among the geriatric syndromes common in this population that can be exacerbated during their acute cardiovascular illness. Because these geriatric conditions frequently coexist with acute cardiovascular disease, the care for older patients is complex and can have a major impact on the healthcare system as a whole.

In this thesis, I attempted to study older population in two domains. First, I evaluated the influence of two geriatric syndromes, frailty and sarcopenia, on health outcomes among older adults with acute cardiovascular illness from patient perspective. Second, I evaluated the impact of acute cardiovascular illness on healthcare utilization and cost among older patients from epidemiologic perspective. Seven manuscripts are included in this dissertation.

Domain 1: Assessment of geriatric syndromes in older adults with cardiovascular disease.

Domain 2: Healthcare utilization and cost among older adults with cardiovascular disease.

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DEDICATION

To my son, Carl-Philippe Damluji. Success is the sum of many small achievements and failure is an invaluable opportunity to improve. I hope that your life is driven by learning!

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INTRODUCTION

Despite major advances in management, cardiovascular disease (CVD) remains the leading cause of morbidity and mortality in the United States and throughout the world. Older patients are particularly susceptible to CVD; prevalence extends to more than two thirds of adults >60 years of age and to more than 85% of those aged ≥85 years.[2] Of the 23.6 million adults that the American Heart Association predicts will die from CVD by 2030[2], advanced age is leading mortality risk.[3] Moreover, risks of CVD-related hospitalizations, poor quality of life, functional decline, and other detrimental sequelae are also disproportionate in older adults. While numerous trials have focused on treatment and prevention of CVD in younger adults, care for elderly that best achieves survival as well as improved quality of life and function remains relatively uncertain.[5] Despite a tradition of evidence-based CVD management, therapeutic choices for older candidates are commonly confounded by the presence of multimorbidity (i.e., concomitant cardiac and non-cardiac comorbidities), as well as interrelated issues of polypharmacy, cognitive impairment, frailty, falls, functional decline, and other age-related complexities of care.[6]

Whereas CVD pathophysiology is generally considered the primary determinant of cardiovascular instability in younger CVD patients, geriatric syndromes become progressively more likely to play a co-dominant role among older adults. Geriatric syndromes essentially entwine with CVD physiology and presentation, such that diagnosis, prognosis, and management are typically transformed.[6] Frailty is also common among older adults, particularly among elderly with CVD.[7] Despite methodological and conceptual debates regarding the optimal method to assess frailty, there is general agreement in defining frailty as a state of increased vulnerability to stressors, with limited reserves to stabilize declines across multiple physiologic systems.[8] Frail adults with CVD typically suffer with worse disease outcomes, as well as

increased susceptibility to harmful effects from standard therapies. Disability refers to a physical or mental condition that limits a person's movements, senses, or activities. Whereas younger adults with CVD are usually able to fully recover after a successful CVD hospitalization or therapy, full recuperation is less certain among older adults with similar disease. Multimorbidity, frailty, polypharmacy, and other geriatric syndromes compound risks of disability in hospitalized elderly, especially in the context of acute illness, deconditioning, cognitive impairment, poor sleep quality, poor nutrition, dehydration, over-sedation, and other common geriatrics patterns.[6]

Older patients with CVD have high susceptibility to cognitive impairment including delirium or dementia.[9, 10] Both forms of cognitive impairment predispose for rehospitalizations and post-acute care after cardiovascular illness.[11] Low skeletal muscle mass and reduced muscle strength are parameters of sarcopenia, which is defined as "a progressive and generalized skeletal muscle disorder that is associated with increased likelihood of adverse outcomes including falls, fractures, physical disability, and mortality".[12] Sarcopenia plays an important role in development and progression of patient's frailty, which has been linked to poor outcome and reduced functional capacity in patients with cancer, chronic obstructive pulmonary disease, diabetes mellitus, cirrhosis, rheumatoid arthritis, and congestive heart failure.[13-19]

While CVD has been extensively studied in terms of disease mechanisms, the impact of non-disease aspects of care becomes increasingly relevant in old age. Geriatric syndromes arise from the same underlying molecular and biological substrate as CVD, and inherently confound many precepts of disease-based care.[6] Treating CVD amidst frailty, sarcopenia, multimorbidity, polypharmacy and other geriatric dimensions is now typically left to physician judgement, but research holds the potential to better clarify and respond to these challenges with more information regarding complex interdynamics and implications regarding qualitative (e.g.,

quality of life, patient reported outcomes) and quantitative (e.g., mortality, function, cognition, lengths of stay, rehospitalization) endpoints.[6]

Challenges in the management of older adults with CVD are numerous. Prior studies revealed that older adults who exhibit frailty were less likely to receive the same extent of therapy as compared to adults without frailty.[20] For example, the use of guideline-directed medical therapy with ACEi and beta-blockers was lower when frailty was encountered, and these patients were less likely to be admitted to coronary care units and to undergo cardiac catheterization or coronary artery bypass surgery.[21, 22] Furthermore, adults ≥80 years usually have higher prevalence of diabetes mellitus, HF, atrial fibrillation, renal failure, anemia, chronic kidney disease, and dementia.[23, 24] As such, treatment with invasive procedures that requires prolonged dual anti-platelet therapy with or without the need for anti-thrombotic therapy for cerebrovascular vascular accident prevention, may not produce the same results in comparison to younger counterparts with a single disease process. The risk of contrast induced nephropathy after coronary angiography is higher in older adults, which often reinforces rationale for conservative approaches. Generally, pharmacotherapy is challenging in older adults as reduced renal function results in different bioavailability and drug elimination profiles. Drug-drug and drug-disease interactions are common specially in setting of polypharmacy.[25] Intolerance to beta-blockers because of underlying fatigue may exert a significant challenge to achieve a reduced work load of the heart. Many older adults are intolerant to statin therapy because of muscle aches. Impaired mobility may mask underlying exertional symptoms. Similarly, impaired cognition may diminish adherence to medications and diet.[26] In this thesis, I attempted to study older patient populations with cardiovascular disease in two major domains:

DOMAIN 1: GERIATRIC SYNDROMES AMONG OLDER ADULTS WITH CARDIOVASCULAR DISEASE

First, we estimated the prevalence of frailty among older patients with acute myocardial infarction (AMI) and evaluated whether frailty acts as an effect measure modifier in the association between percutaneous coronary intervention (PCI) and hospital mortality using the Premier Healthcare Database. Second, we evaluated the influence of frailty measured using the Fried frailty phenotype on geriatric outcomes among older adults with history of coronary heart disease using the National Health and Aging Trends Study. Then, we examined the influence of the physical frailty phenotype on cardiovascular outcomes among older adults with no history of coronary heart disease. Third, we examined the influence of sarcopenia, a progressive and generalized skeletal muscle disorder, on health-related quality of life among older adults with aortic valve disease in a retrospective cohort study with *de novo* data collection.

DOMAIN 2: HEALTHCARE UTILIZATION AND COST AMONG OLDER ADULTS WITH CARDIOVASCULAR DISEASE

Fourth, we examined the healthcare utilization and cost among older adults admitted with sudden cardiac arrest using data from the Healthcare Cost and Utilization Project. Fifth, we evaluated the use of PCI among very older adults with acute myocardial infarction using the Premier Healthcare Database. Sixth, we expanded this work to evaluate the effectiveness of PCI among older adults with ST-elevation myocardial infarction (STEMI) and cardiogenic shock in the United States using data from the Healthcare Cost and Utilization Project. Seventh, we examined the healthcare access of older adults with aortic valve disease to transcatheter aortic valve replacement (TAVR) procedures using the Florida Agency for Health Care Administration inpatient database.

CHAPTER 1

FRAILTY AMONG OLDER ADULTS WITH ACUTE MYOCARDIAL INFARCTION AND OUTCOMES FROM PERCUTANEOUS CORONARY INTERVENTIONS

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INTRODUCTION

In the United States, the older patient population is expanding rapidly, particularly among those above 75 years of age.[27] There were 19 million aged 75 years or older in 2012, representing 6% of the total population, and these estimates are projected to increase to 46 million in 2050, representing 11.5% of the population.[28] This population is particularly susceptible to cardiovascular disease and its complications.[6] While outcomes have improved markedly over the past decades, the care for older adults with cardiovascular disease is often complicated by the presence of geriatric syndromes including multimorbidity, polypharmacy, functional decline, falls, and frailty.[6]

Frailty is highly prevalent among older adults with cardiovascular disease.[21] It is a state of increased vulnerability to stressors, with limited reserves to stabilize declines across multiple physiologic systems,[8] and is therefore of particular importance when an older adult experiences a severe stress, such as an acute myocardial infarction (AMI). A few small studies have estimated the prevalence of frailty in older patients with severe coronary artery disease,[29-33] but national estimates of frailty in older patients specifically with acute myocardial infarction (AMI) are rare. To facilitate the study of frailty from epidemiologic and population health perspectives, Segal and colleagues developed and validated a Claims-based Frailty Index (CFI) [34, 35] that approximates the widely-used Fried physical frailty phenotype,[36-38] which relies on measures that are often not available from clinical encounters.

Most importantly, the best treatment for older adults, and in particular for frail older adults, with AMI remains unclear. The extents to which suboptimal outcomes in frail older adults are primarily attributable to the acute stressor (i.e. AMI) or due to the underuse or overuse of procedures aimed to reestablish coronary perfusion are not known. In this study, we aimed to quantify the prevalence of frailty among older patients with AMI in the United States and to examine the influence of frailty on hospital mortality in a large population-based study. Finally, we aimed to understand whether frailty is responsible for heterogeneity in outcomes from percutaneous coronary intervention (PCI) during the AMI admission.

METHODS

Data

This study utilized the Premier Healthcare Database (Premier, Inc., Charlotte, NC) that is populated with detailed patient-level information from over 750 hospitals in the U.S. It contains information from more than 717 million hospital encounters, which is approximately one in five discharges in the United States. Data available for this study include demographic characteristics, disease status, as well as billed services in a de-identified patient daily service record. Each patient enrolled in this database has a unique identifier, which allows tracking of individual patients across inpatient and hospital-based outpatient settings within the same hospital system. The data that support the findings of this study will not be made available to other researchers because of restrictions in the data use agreement between Premier Inc. and Johns Hopkins Medicine.

Population

The study population included patients aged 75 years or older who were admitted to the hospital with AMI between July 2000 and January 2016 in the United States. Patients were

excluded if they died in the Emergency Department prior to hospital admission. AMI was defined *apriori* as the primary admission diagnosis using ICD-9 and ICD-10 Clinical Modification codes (ICD-9: 410; ICD-I21). [39-43]

Claims-based Frailty Index

Segal and colleagues previously developed and validated the CFI.[34, 35] Briefly, diagnoses considered reflective of the underlying domains of the physical frailty phenotype were identified and a model optimized against the measured Fried frailty phenotype. We used the CFI to identify frailty among individuals in this cohort using data from inpatient and outpatient encounters in the 6 months prior to each patient's index AMI admission. Each variable from these encounters was coded as present or absent and then multiplied by the beta-coefficient, obtained from the original regression, to get a continuous score (Table 1).[34]

Similar to the methods used in the development and the validation of the CFI, we used a probability cutoff of 0.20 to classify individuals admitted with AMI as frail versus non-frail. It should be noted that the CFI was developed and validated against a performance-based test, the Fried frailty phenotype, as such we use the term physical frailty interchangeably with frailty identified by the CFI throughout the manuscript.

Study Outcome

Our primary outcome was in-hospital mortality, defined as death occurring after admission and before hospital discharge.

Comorbidities and Procedures

All comorbid conditions were defined in accordance with the Elixhauser Comorbidity Software, which was developed as part of the Healthcare Cost and Utilization Project by the Agency for Healthcare Research and Quality.[44, 45] For each patient, we selected the first

admission for AMI observed in the data. For this analysis, readmissions for AMI after this index admission were excluded. In a similar fashion, patients who received PCI or CABG during their index admission for AMI were identified.

Statistical Analysis

We first aggregated data across all years and used descriptive statistics to describe the cohort participants' baseline demographics, cardiovascular and non-cardiovascular comorbidities, and use of cardiovascular procedures stratified by frailty status. We then characterized the cohort stratified by cardiovascular procedure (PCI, CABG, and medical therapy alone). Given the infrequent use of CABG in the frail population, individuals treated with CABG were excluded from further analyses. Differences between groups were tested using t-tests and Chi-squared tests, as appropriate. To describe secular trends, we plotted the prevalence of frailty, the prevalence of use of PCI, and the in-hospital mortality rate within the cohort by calendar year. We then calculated the odds of in-hospital mortality by frailty status to examine the influence of frailty on hospital outcome during AMI admission, inclusive of patients receiving any therapies. To understand whether frailty simply recapitulates age, we also examined the influence of frailty on hospital mortality adjusting for age, as age strongly determines the CFI score.

For a crude odds ratio, we calculated the odds of in-hospital mortality for those receiving PCI and those not receiving PCI, separately for frail and non-frail cohort members. We then used multivariable logistic regression to evaluate the influence of PCI on hospital mortality during index AMI admission, controlling for possible confounders, in separate models for the frail and non-frail cohort members. In the frail model, the covariates the contributed to the CFI were excluded from the model. The multivariable model included pulmonary circulatory disorder,

valvular heart disease, peripheral vascular disease, paralysis, stroke or transient ischemic attack, chronic lung disease, diabetes with and without complications, hypothyroidism, renal failure, liver disorder, ulcer, lymphoma, tumors, or metastasis, weight loss, electrolyte and fluid disorder, iron deficiency anemia, alcoholism, drug over dose, psychiatric disorder, and year of admission. These stratified analyses were repeated using forward and backward logistic regression to help identify a parsimonious model.

To examine effect measure modification, we fit a multivariable logistic regression model that included frailty interacting with PCI. To understand the influence of PCI on hospital mortality among frail older patients alone, the mortality rate was calculated by treatment status (PCI vs no-PCI) adjusting for confounders (see model above). Finally, to understand the influence of PCI by age, we plotted the mortality rate of those who were treated with vs. without PCI by age during their index AMI admission. All statistical analyses were performed using STATA version 15 MP (Stata-Corp, College Station, TX). We considered p value of <0.05 as significant and all tests were two sided. This study was approved by the Institutional Review Board at Johns Hopkins University.

RESULTS

From 2000 to 2016, we identified 469,390 encounters for patients ≥ 75 years admitted with AMI. (Table 2) The average age of this cohort was 82 years; 53% were women and were 75% were white. Among the total cohort, the prevalence of frailty was 19%. Frail patients were older, more likely to be women and ethnic minority members, and had more cardiovascular and non-cardiovascular comorbidities. While the prevalence of frailty increased in the early years, it remained relatively stable in the later years (Figure 1).

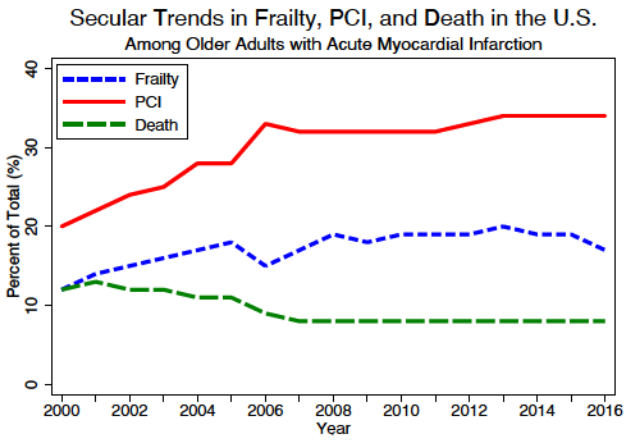


Figure 1. Secular trends in frailty, percutaneous coronary intervention, and hospital mortality in the Premier Healthcare Database from 2000 to 2016. The denominator is total patients 75 ≥ years with first acute myocardial infarction.

Relative to non-frail older adults, frail older patients with AMI were more likely to die during the index AMI admission. In the entire cohort, frailty increased hospital mortality by 43% (Frailty OR 1.43, 95% C.I 1.39-1.46). When this estimate was adjusted for age, frailty remained a significant predictor of hospital mortality (OR 1.16, 95% C.I 1.13-1.19). When adjusting for cardiovascular and non-cardiovascular comorbidities, frailty remained associated with mortality (OR 1.25, 95% C.I 1.22-1.28).

In this cohort of older adults admitted with AMI, the overall mortality rate was 10.3%, and it was higher in the frail than non-frail patients (Frail: 13.2% vs. Non-frail: 9.6%, p-value <0.001). When evaluating the secular trends over the 17-year study period, the rate of utilization of PCI increased in the early years of the study and this was paralleled by a consistent decline in

the overall in-hospital mortality rates. Patients treated with PCI were younger and their comorbidity burden was less than that of non-PCI treated patients (Table 3). Across all years, PCI-treated patients had lower in-hospital mortality (PCI vs non-PCI: 6% vs 12%, $p<0.001$).

Frail patients were less likely to receive percutaneous revascularization with PCI than non-frail patients (15% vs 33%, $p<0.001$) and much less likely to receive surgical revascularization with CABG (frail 1% vs non-frail 9%, $p<0.001$) during the AMI admission. The prevalence of frailty in PCI-treated patients was 9.9% and 23.1% in patients without intervention. The rate of utilization of PCI during index AMI admission was significantly higher in non-frail older adults at all ages, but the utilization of PCI in even non-frail older adults decreased dramatically in patients over 85 years of age (Figure 2).

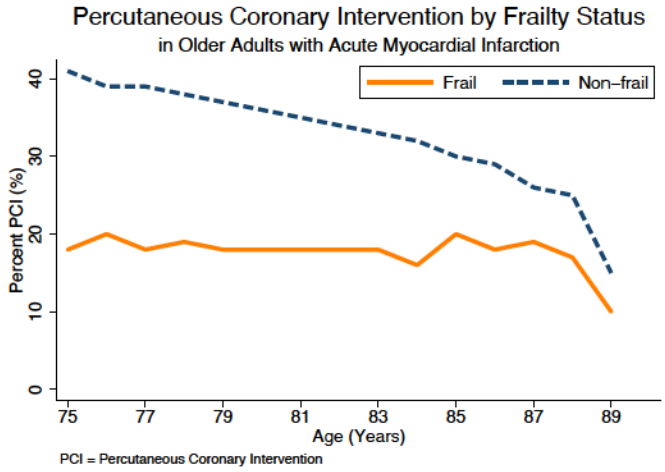
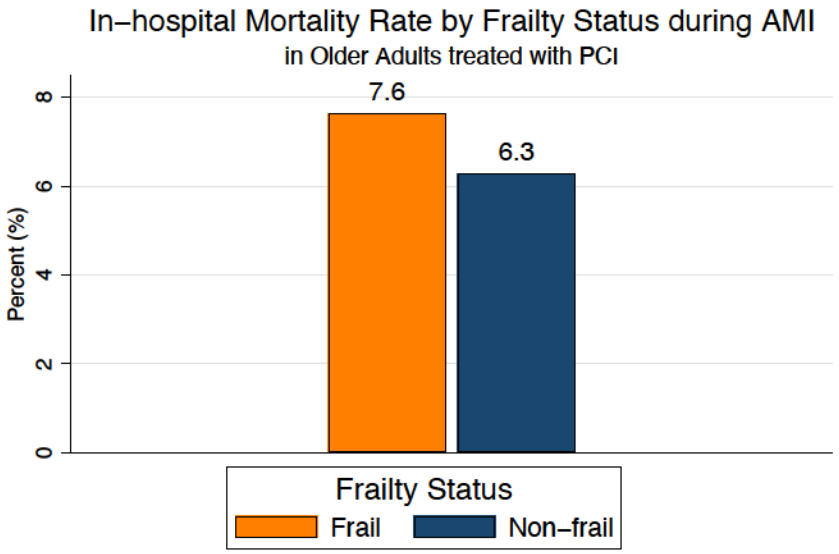


Figure 2. Percutaneous coronary intervention use in older patients by frailty status during acute myocardial infarction. Percutaneous coronary intervention use in older patients by frailty status during first observed acute myocardial infarction in the Premier Healthcare Database. The denominator is total patients 75 ≥ years with first observed acute myocardial infarction.

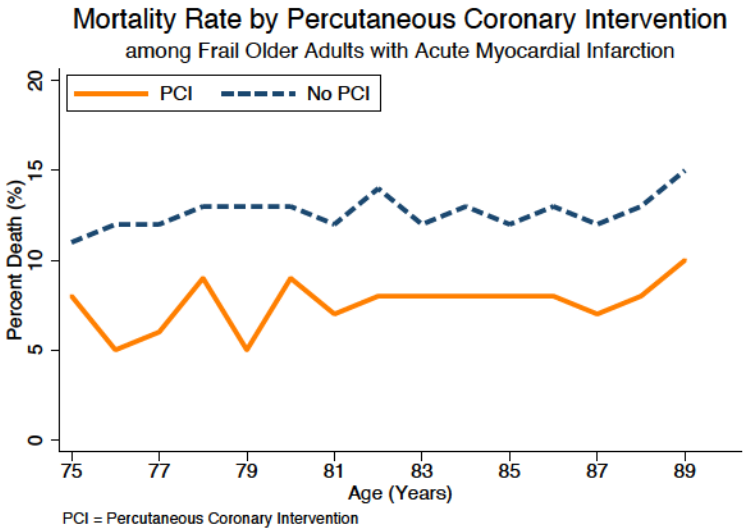
In an unadjusted model including the whole cohort, the use of PCI was associated with more than 51% reduction in hospital mortality (OR 0.49, 95% C.I. 0.47 to 0.50). Frail older

adults benefited from PCI with a mortality reduction of 41% (OR 0.59, 95% C.I 0.55 to 0.0.63), although non-frail patients experienced improvement in survival after PCI, 51% (OR 0.49 95% C.I 0.47 to 0.50) compared patients managed medically. Similarly, frail older adults benefited from CABG with a mortality reduction of 23% (95% C.I 7% to 35%), although non-frail patients experienced a greater improvement in survival after PCI, 26% (95% C.I 23% to 29%), compared to the medical management group. In the multivariable analysis, adjusting for cardiovascular and non-cardiovascular comorbidities, non-frail older adults treated with PCI had lower hospital mortality (OR 0.58, 95% C.I 0.56 to 0.60) than frail adults, although they too are associated with substantial survival benefit (OR 0.67, 95% C.I 0.63 to 0.71). The interaction between PCI and frailty was significant (p-value for interaction < 0.001) supporting a differential benefit in the frail and non-frail patient populations; the absolute mortality difference was 1.3%. Among frail older patients, the adjusted mortality was lower among those who received PCI than those who received medical management alone (Figure 3). This association with survival was consistent across all older age groups (Figure 4).



AMI = Acute Myocardial Infarction; PCI = Percutaneous coronary intervention

Figure 3. Hospital mortality by frailty status in patients treated with percutaneous coronary intervention. Hospital mortality by frailty status in older patients treated with percutaneous coronary intervention during first observed acute myocardial infarction in the Premier Healthcare Database.



PCI = Percutaneous Coronary Intervention

Figure 4. Mortality rate by percutaneous coronary intervention. Mortality rate by percutaneous coronary intervention among frail older adults with acute myocardial infarction.

DISCUSSION

This is the largest study to examine the prevalence and impact of frailty in older adults aged ≥ 75 years admitted with AMI in the United States. We found that the prevalence of frailty in older adults during an AMI hospitalization is 19%. During these admissions, frail older patients were less likely to receive PCI or CABG as a treatment for AMI, as compared to non-frail adults. When we examined secular trends over the 17-year period of the study, the rate of PCI utilization increased and morality decreased, even though the prevalence of the physical frailty syndrome increased. Frail older adults experienced higher hospital mortality during their AMI admission and were more likely to be discharged to rehabilitation or hospice care. Throughout the study period, PCI was associated with survival in frail older patients, although this association was stronger in non-frail patients.

The prevalence of frailty during AMI or severe multivessel disease was studied previously, but the estimates were variable.[21] This may be due to the lack of uniformity in the tools used to identify physical frailty phenotype in the setting of AMI and small study sizes. Afilalo and colleagues summarized this body of evidence in a seminal review.[21] Purser et al reported that the prevalence of frailty in patients with multivessel coronary disease is 27%; this study measured frailty as the Fried phenotype and included only 309 patients.[31] In a study from the Mayo Clinic of 629 patients undergoing PCI, the prevalence of the Fried phenotype frailty was 19%,[33] identical to the point prevalence we observed in this study.

When physicians encounter patients with physical frailty or multisystem degeneration in clinical practice, a less aggressive approach to therapy is usually selected. In a study of 307 patients aged 75 years or older with non-ST elevation myocardial infarction, coronary angiography was attempted in only 15.4% and revascularization was performed in only 6.7% of

the frail older patients.[30] In the study described above, of the 309 patients aged 70 years or older with multivessel coronary disease or left main involvement who underwent cardiac catheterization, only 45.6% and 8.8% of the patients deemed frail in accordance with the Fried phenotype received PCI and CABG, respectively.[31] Our study complements these findings as it adds national estimates from a large sample of older patients with AMI. In almost ninety thousand frail patients, we found that PCI was attempted in only 16% and CABG was utilized in only 1.4% of the sample. These results may suggest that clinicians try to avoid exposing older patients to invasive procedures because of their increased risk for complications. Recommendations regarding use of PCI in frail older adults in the context of AMI are not based on clinical trial evidence, thus good clinical judgement was advised in the position statement from the American Heart Association Council on Clinical Cardiology. [23, 46]

Several prior studies reported that frailty increased the risk for hospital mortality in the setting of multivessel coronary disease and PCI. [30, 31] We addressed whether baseline frailty modified the relationship between PCI and in-hospital mortality. In our study, frail older patients experienced substantial improvement in survival, even though that benefit was less than that experienced by non-frail older patients. It is also plausible that there is underlying "selection bias" in which PCI is given to those patients with lesser degrees of frailty, which results in no-PCI group having higher proportions of patients with frailty burden. These results emphasize that PCI in frail patients was associated with survival after development of AMI. While clinical trial data is needed in this growing population of older patients, revascularization should not reflexively be withheld solely because of the presence of frailty.[47] Frailty status assessment should be integrated in the assessment of older patients being considered for invasive

cardiovascular procedures to allow for informed, shared decision-making about revascularization.

We acknowledge several limitations in this work. First, we identified diagnoses based on ICD-9 and ICD-10 administrative codes. Diagnoses that are not directly tied to reimbursement may be "undercoded", as may be the case with the elements of the CFI. Despite this limitation, many healthcare settings are increasingly adept at using their claims and EHR data in real-time to inform patient care; and in this regard the CFI may be a valuable resource for identification of frail older adults at risk of adverse health events and higher utilization of healthcare resources during their AMI admission. Second, risk scores to predict hospital mortality after AMI were not used in this analysis because existing risk scores (e.g. NCDR CathPCI Risk Score System) include some variables that were used to define the CFI (e.g. age, heart failure, stroke…etc.).[48] Second, CFI is an imperfect surrogate for gold standard criteria, but CFI is an important tool to study frailty from a population level when the measurement of underling domains are not available. While the adjustments utilized in our study were comprehensive, residual confounding may still exist. Finally, Premier Healthcare Database contains inpatient and outpatient data for patients followed within the same hospital system (i.e. this analysis included only patients who sought care in the same hospital system of their AMI admission). Patients without data from outpatient visits preceding their index AMI admission, due to receipt of care at other institutions, were necessarily omitted from the cohort. However, we have no reasons to believe they would have been more or less frail than the included patients. Additionally, a recent study that used a Hospital Frailty Risk Score derived from ICD-10 diagnostic codes for patients 75 years or older admitted to the National Health Service in England reported prevalence estimates similar to

those of our study. [49] Finally, frailty by itself can be a spectrum that ranges from mild to severe form. In this study, the effect of PCI on this severity spectrum cannot be ascertained.

This study has several important strengths. First, this is the largest population-based study to examine the prevalence of frailty in adults admitted with AMI by the treatment they received in "real world" clinical practice. Second, the CFI for identification of frailty used claims data which are fairly ubiquitous; this may allow for other population-based studies of frailty in different contexts within cardiovascular medicine. Third, our study used data on frailty status collected from inpatient and outpatient visits 6-months *prior* to the AMI admission. This is especially important because we were able to measure frailty status *prior* to the acute stressor and this probably represents the individual at their baseline. Fourth, in-hospital mortality should/could be a therapeutic "target" in very-old patients more than 85 years of age, which in contrast could be an understandable target in patients aged 75-85 years. This is especially important because the World Health Organization reported that coronary heart disease deaths will increase by 120-137% during the next two decades, and a person aged 80 years can expect about 9 remaining years of life.[50] Finally, this analysis is the first to examine frailty as an effect measure modifier in the association between PCI and hospital mortality. This analysis will expand the field by focusing on the integration of frailty assessment during AMI and appropriate choice of therapies for the frail older adult group.

Future research efforts should focus on studying how frailty may be mitigated in the setting of AMI (i.e. physical strengthening and rehabilitation programs, nutritional support) and directing even more appropriate treatments for AMI to target this vulnerable patient group (i.e. shorter dual antiplatelet therapy to reduce the risk of bleeding, type of stents (drug-eluting vs. bare metal), blood pressure and cholesterol targets as secondary prevention goals). While

improvement in hospital mortality is an important hard clinical outcome after PCI, quality of life measures and survival after discharge should be integrated into future research on PCI in frail older adults. Finally, validation of simple bed-size measures of frailty (e.g. essential frailty toolset, gait speed) during AMI and identification of novel biomarkers to reflect frailty status are essential to advance the field of frailty and multisystem degeneration in the setting of acute cardiovascular illness.[38, 51]

CONCLUSION

In this large study, we report that the prevalence of physical frailty syndrome in adults 75 ≥ years or older during first observed AMI admission was 19%; frailty was much more prevalent among patients who were not treated with PCI or CABG. While overall survival after AMI has improved over the past two decades, partly due to increased utilization of early revascularization, the prevalence of frailty has increased as the age of patients admitted with AMI is also rising. As shown in smaller studies, frail older patients are less likely to receive revascularization therapies with PCI or CABG and have higher in-hospital mortality rates. Frailty acts as an effect measure modifier in the relationship between PCI and in-hospital mortality, but PCI in frail older adults was still associated with survival as compared to medically treated patients. Frailty assessment should be considered in the treatment paradigm for older adults admitted with AMI and clinicians should recognize that frail patients may benefit from intervention.

CLINICAL PERSPECTIVE

Competency in Medical Knowledge: The prevalence of physical frailty syndrome in adults 75 years or older during acute myocardial infarction admission is 19%. In the past decade, the use of PCI and CABG is lower in frail older adults.

Competency in Patient Care: Frailty assessment may importantly inform the treatment paradigm for older adults admitted with AMI. While frails patients are at an increased risk for hospital mortality during AMI hospitalization, judicial use of revascularization with PCI in frail older patients is still associated with survival benefit.

FIGURE LEGENDS

Figure 1. Secular trends in frailty, percutaneous coronary intervention, and hospital mortality in the Premier Healthcare Database from 2000 to 2016. The denominator is total patients 75 ≥ years with first acute myocardial infarction.

Figure 2. Percutaneous coronary intervention use in older patients by frailty status during acute myocardial infarction. Percutaneous coronary intervention use in older patients by frailty status during first observed acute myocardial infarction in the Premier Healthcare Database. The denominator is total patients 75 ≥ years with first observed acute myocardial infarction.

Figure 3. Hospital mortality by frailty status in patients treated with percutaneous coronary intervention. Hospital mortality by frailty status in older patients treated with percutaneous coronary intervention during first observed acute myocardial infarction in the Premier Healthcare Database.

Figure 4. Mortality rate by percutaneous coronary intervention. Mortality rate by percutaneous coronary intervention among frail older adults with acute myocardial infarction.

Table 1. Claims-based frailty index variables.

Variables
• Admission in past 6 months • Age • Arthritis (any type) • Charlson comorbidity index (>0, 0) • Cognitive Impairment • Congestive heart failure • Chronic skin ulcer • Depression • Falls • Gout • Impaired mobility • Male sex • Musculoskeletal problems • Mycoses • Paranoia • Parkinson disease • Pneumonia • Skin and soft tissue infection • Stroke • Urinary tract infection • White race

TABLE 2. Demographic characteristics in older adults with acute myocardial infarction by baseline frailty status in Premier Healthcare Database from 2000 to 2016.

Variable	Total n = 469,390	Frail[a] n = 89,820	Non-Frail n = 379,570	*p*-value
Demographic characteristics				
Age, years, mean (SD)	82.3(4.69)	85.9(3.68)	81.5(4.49)	<0.001
Male, %	46.8	33.4	50.0	<0.001
White ethnicity, %	75.1	48.9	81.3	<0.001
Cardiovascular comorbidities				
Congestive heart failure, %	9.16	28.4	4.62	<0.001
Valvular heart disease, %	4.00	10.9	2.36	<0.001
Pulmonary Circulation Disorder, %	1.29	3.76	0.70	<0.001
Peripheral Vascular Disease, %	17.5	22.1	16.5	<0.001
Non-cardiovascular comorbidities				
Paraplegia, %	2.89	4.79	2.43	<0.001
Neurologic disorder, %	11.1	18.6	9.25	<0.001
Chronic lung disease, %	25.4	31.3	24.0	<0.001
Diabetes mellitus, %	30.7	35.9	29.5	<0.001
Diabetes with complications, %	6.95	10.12	6.19	<0.001
Hypothyroidism, %	17.4	22.8	16.1	<0.001
Renal failure, %	23.9	34.9	21.3	<0.001
Liver disease, %	0.85	1.12	0.79	<0.001
Peptic ulcer disease, %	0.11	0.14	0.10	<0.001
AIDS, %	0.01	0.01	0.01	0.59
Lymphoma, %	0.77	1.10	0.69	<0.001
Metastasis, %	1.33	1.81	1.22	<0.001
Tumor, %	3.12	4.59	2.77	<0.001

Arthritis, %	3.14	4.58	2.79	<0.001
Coagulopathy, %	6.64	7.93	6.33	<0.001
Obesity, %	6.84	6.53	6.91	<0.001
Weight loss, %	4.64	8.44	3.74	<0.001
Electrolyte disorder, %	31.1	47.1	27.3	<0.001
Blood loss, %	2.33	3.84	1.97	<0.001
Iron deficiency anemia, %	27.2	42.8	23.5	<0.001
Alcohol intoxication, %	1.05	0.77	1.12	<0.001
Drug abuse, %	0.21	0.33	0.19	<0.001
Psychiatric disorder, %	2.37	4.38	1.89	<0.001
Depression, %	8.65	15.95	6.92	<0.001
Cardiovascular procedures				
Diagnostic coronary angiography, %	50.8	26.7	56.5	<0.001
PCI, %	29.8	15.4	33.2	<0.001
CABG, %	7.33	1.40	8.73	<0.001
Hospital outcomes				
In-hospital mortality, %	10.3	13.2	9.63	<0.001
Discharged home, %	41.9	28.2	45.2	<0.001
Discharged to hospice, %	3.00	5.77	2.34	<0.001
Discharged to rehabilitation, %	20.9	29.7	18.8	<0.001

Abbreviations: AIDS = acquired immune deficiency virus; PCI = Percutaneous coronary intervention; CABG = coronary artery bypass surgery. [a]Frailty was defined according to the claims-based frailty index derived from inpatient and outpatient data from 6 months prior to the acute myocardial infarction admission.

Table 3. Demographic characteristics in older adults with acute myocardial infarction by their treatment status in Premier Healthcare Database from 2000 to 2016.

Variable[α]	Total (n = 469,827)	PCI (n = 140,089)	Non-PCI (n = 329,738)
Demographic characteristics			
Age, years, mean	82.3 (75.0-89.0)	80.9 (75.0-89.0)	82.9 (75.0-89.0)
Male, %	46.8 (46.6-46.6)	51.0 (50.7-51.3)	45.0 (44.8-45.1)
White ethnicity, %	75.1 (75.0-75.3)	76.1 (75.9-76.3)	74.7 (74.5-74.8)
Frailty[β], %	19.1 (19.0-19.2)	9.89 (9.73-10.0)	23.1 (22.9-23.2)
Cardiovascular comorbidities			
Congestive heart failure, %	9.16 (9.08-9.24)	4.58 (4.47-4.69)	11.1 (11.0-11.2)
Valvular heart disease, %	4.00 (3.94-4.05)	2.21 (2.13-2.28)	4.76 (4.69-4.83)
Pulmonary Circulation Disorder, %	1.29 (1.25-1.31)	0.68 (6.37-7.24)	1.54 (1.50-1.58)
Peripheral Vascular Disease, %	17.5 (17.4-17.6)	15.9 (15.7-16.1)	18.2 (18.0-18.3)
Non-cardiovascular comorbidities			
Paraplegia, %	2.89 (2.83-2.93)	1.61 (1.54-1.67)	3.43 (3.36-3.49)
Neurologic disorder, %	11.1 (10.9-11.1)	6.72 (6.58-6.85)	12.9 (12.7-13.0)
Chronic lung disease, %	25.4 (25.3-25.5)	20.8 (20.5-20.9)	27.4 (27.2-27.5)
Diabetes mellitus, %	30.7 (30.5-30.9)	29.0 (28.7-29.2)	31.5 (31.2-31.6)
Diabetes with complications, %	6.95 (6.89-7.02)	5.38 (5.26-5.49)	7.62 (7.52-7.70)
Hypothyroidism, %	17.4 (17.3-17.5)	15.8 (15.5-15.9)	18.1 (17.9-18.2)
Renal failure, %	23.9 (23.7-24.0)	18.5 (18.2-18.6)	26.2 (26.0-26.3)
Liver disease, %	0.85 (0.82-0.88)	0.66 (0.62-0.71)	0.93 (0.90-0.96)
Peptic ulcer disease, %	0.11 (0.10-0.12)	0.10 (0.10-0.12)	0.11 (0.08-0.11)
AIDS, %	0.01 (0.00-0.01)	0.01 (0.00-0.01)	0.01 (0.00-0.01)
Lymphoma, %	0.77 (0.74-0.79)	0.59 (5.52-6.63)	0.85 (8.16-8.79)
Metastasis, %	1.33 (1.30-1.36)	0.78 (0.73-0.82)	1.57 (1.52-1.61)
Tumor, %	3.12 (3.07-3.17)	2.46 (2.37-2.54)	3.40 (3.33-3.46)
Arthritis, %	3.14 (3.08-3.18)	3.03 (2.94-3.12)	3.18 (3.12-3.24)
Coagulopathy, %	6.64 (6.56-6.67)	5.09 (4.97-5.20)	7.30 (7.20-7.38)

Obesity, %	6.84 (6.76-6.91)	7.84 (7.69-7.98)	6.41 (6.32-6.49)
Weight loss, %	4.64 (4.58-4.70)	2.66 (2.57-2.74)	5.49 (5.41-5.56)
Electrolyte disorder, %	31.1 (30.9-31.1)	21.3 (21.0-21.4)	35.2 (35.0-35.3)
Blood loss, %	2.33 (2.28-2.36)	1.66 (1.59-1.73)	2.61 (2.55-2.66)
Iron deficiency anemia, %	27.2 (27.0-27.3)	21.0 (20.8-21.2)	29.8 (29.6-29.9)
Alcohol intoxication, %	1.05 (1.02-1.08)	0.93 (0.88-0.98)	1.11 (1.06-1.14)
Drug abuse, %	0.21 (0.20-0.22)	0.18 (0.15-0.20)	0.23 (0.21-0.24)
Psychiatric disorder, %	2.37 (2.32-2.41)	1.62 (1.55-1.68)	2.69 (2.63-2.74)
Depression, %	8.65 (8.56-8.73)	6.40 (6.27-6.53)	9.61 (9.50-9.70)
Diagnostic coronary angiography, %	50.8 (50.6-50.9)	100	31.9 (31.7-32.0)
Hospital outcomes			
In-hospital mortality, %	10.3 (10.2-10.4)	6.22 (6.09-6.34)	12.1 (11.9-12.1)
Discharged home, %	41.9 (41.8-42.1)	64.7 (64.4-64.9)	32.3 (32.1-32.4)
Discharged to hospice, %	3.00 (2.94-3.04)	0.77 (0.72-0.82)	3.94 (3.87-4.01)
Discharged to rehabilitation, %	20.9 (20.7-21.0)	12.4 (12.2-12.5)	24.5 (24.3-24.6)

Abbreviations: AIDS = acquired immune deficiency virus; PCI = Percutaneous coronary intervention; CABG = coronary artery bypass surgery. [α] All estimates were presented with 95% confidence interval. [β] Frailty was defined according to the claims-based frailty index derived from inpatient and outpatient data from 6 months prior to the acute myocardial infarction admission.

CHAPTER 2

PHYSICAL FRAILTY AND FIVE-YEAR GERIATRIC AND CARDIOVASCULAR OUTCOMES AMONG OLDER WITH AND WITHOUT CORONARY HEART DISEASE IN THE NATIONAL HEALTH AND AGING TRENDS STUDY

INTRODUCTION

In the United States, the rapid expansion of the older population introduced complexities in the management of acute cardiovascular disease owing to the concomitant presence of geriatric syndromes.[52] Of these syndromes, *frailty* is a clinical state in which there is increased vulnerability to stressors due to diminished reserves across multiple physiologic systems resulting in functional decline, complications, and high mortality from disease and therapeutic interventions.[53, 54] The prevalence of frailty in older patients with coronary heart disease (CHD) vary widely depending on the instrument used. However, utilizing the most frequently cited instrument, the Fried frailty phenotype[36], it is estimated that older patients living with coronary heart disease exhibit frailty in approximately 19-27% of the time.[29, 31, 33, 55] Frailty modifies the effect of treatment in patients with CHD and may lead to worsening in other geriatrics risks including physical or cognitive function as older adults live into their older years.[55]

There are five core domains that define physical frailty phenotype: slowness, weakness, low physical activity, exhaustion, and shrinking.[36] Symptoms in any one of these domains attributed to frailty can also be related to the underlying disease process. For example, a patient with CHD can also exhibit the cardinal domains of frailty like slowness, weakness, low physical activity, or exhaustion due to the degree of impairment in their coronary blood flow and subsequent physiologic changes in the cardiovascular systems. In prior studies on frailty among

patients with concomitant CHD, the clinical assessment of both frailty and presence or absence of CHD occurred simultaneously. The temporal relationship between CHD, frailty, and clinical outcomes including health-related quality of life in older adults remains largely unknown. In this study, we aimed to (1) evaluate the influence of frailty, measured by the Fried frailty phenotype, on geriatric outcomes among older adults with history of CHD using the National Health and Aging Trends Study (NHATS). Then, we examined the influence of physical frailty phenotype on cardiovascular outcomes among older adults with no history of CHD during five-year follow-up.

METHODS

The Source and Study Population

We examined the 2011 NHATS baseline cohort.[56] NHATS is a prospective cohort study funded by the National Institute on Aging (U01AG032947) that aimed to study functioning in later life. The source population for this study is derived from a sample of Medicare beneficiaries ages 65 and older, a nationally representative cohort of older patients in the community. These older adults were interviewed in 2011 during their baseline visit and annual re-interview was performed for each participant to document changes, trends, and dynamics in later life functioning.[56] Detailed information on geriatric risks including frailty, physical and cognitive capacity, activities of daily living, the social, physical, and technological environment were collected. African Americans and patients from older ages were oversampled from the Medicare enrollment file. For each participant, the NHATS repository is linked to Medicare data that were available prior to 2011 baseline visit.

The study population included adults ≥65 years of age enrolled during the 2011 NHATS baseline visit in the United States, who also had linked Medicare data available for analysis prior

to their baseline visit. For each participant, CHD was identified 12 months *prior* to the 2011 NHATS baseline visit using International Classification of Diseases-9th Revision (ICD-9) 410-414, 410.0-410.9, 410.00-410.02, 410.10-410.12, 410,20-410,22, 410.30-410.32, 410.40-410.42, 410.50-410.52, 410.60-410.62, 410.70-410.72, 410-80- 410.82, 410.90-41.92, and 4292.

Frailty Assessment

During NAHTS baseline visit, frailty was assessed utilizing a paradigm developed by Fried et al [36], the Physical Frailty Phenotype, which was grounded on five domains: exhaustion, low physical activity, weakness, slowness, and shrinking (i.e. unintentional weight loss), with ≥3/5 criteria required for a diagnosis of *frailty*. Detailed definition of meeting each criterion was previously published.[57] Multiple imputation method was adapted from a previously published work that used one randomly-assigned imputed frailty data out of 10 replicas.[57]

Cardiovascular Outcomes

Major adverse cardiovascular event was defined as death from any cause, acute myocardial infarction, any subsequent CHD, stroke, or peripheral vascular disease, whichever comes first. Secondary cardiovascular endpoints included each of these individual components identified in the Center of Medicare and Medicaid Services database during the five year follow-up. Further, any primary hospital admission for subsequent CHD was identified and reported separately.

Geriatric Outcomes

For each patient, specific geriatric outcomes were assessed during the NHATS follow-up visits. These geriatric outcomes included measures of functioning (activities of daily living (ADL) and instrumental activities of daily living (IADL), and functional limitations), cognitive function (any form of cognitive impairment, dementia/Alzheimer's disease), disability, and

mobility disability. For each older participant, the Katz scale was performed to assess the independence in (1) *self-care* (ADL: bathing, dressing, eating, toileting); (2) *household activities* (IADL: doing laundry, preparing meals, shopping for groceries, for personal items, medication management, handling bills and banking); (3) *mobility* (getting around inside, going outside, getting out of bed).[57] Screening for cognitive dysfunction was performed to assess functions related to memory, orientation, and executive function. For patients with severe cognitive impairment, a proxy interview was conducted where the proxy was asked about the function of the participant. Dementia status was ascertained using the following instruments: (1) a physician report indicating that the participant has dementia or Alzheimer's disease; (2) a scoring indicating a probable dementia administered to proxies; (3) results from cognitive tests that evaluate memory, orientation, and executive function.[58] Disability was measured using the American Community Survey Disability Questions. Outcomes related to *mobility*, *self-care*, and *household* activities were performed independently for each participant during follow-up visits. Loss of independence was defined as patients reporting never or rarely go outside or they use devices to go outside.

Demographic Characteristics, Medical Conditions, and Healthcare Utilization

Each older adult enrolled in the study was asked whether their physician had ever told them they had any of the following medical conditions: high blood pressure, diabetes mellitus, stroke, any cardiac disorder, arthritis, lung or bone disease, and cognitive impairment or dementia. Hospitalization within the past 12 months, baseline assessment on *selfcare, mobility, and household activities* were self-reported.[57]

Statistical Analysis

Participants were categorized into *two* distinct groups during 2011 NHATS baseline: (1) history of CHD and (2) no-History of CHD. Demographics, smoking status, self-reported disease, hospitalizations, emergency department visits, falls, selfcare, mobility, household activities, depression, anxiety, and cognitive impairment at baseline were reported for frail and the non-frail among those with prior history of CHD. Frequencies and percentages were calculated for categorical variables and mean ± SD for continuous variables. Data on *selfcare, mobility, and household activities* were presented as cumulative proportions at five years for CHD patients by the frail versus non-frail group. Proportional hazard models were used to assess the association between frailty on geriatric outcome among CHD patients during five-year follow-up. Patients were censored if they developed the geriatric outcome of interest or if they were lost to follow-up. We performed an unadjusted Cox proportional hazards model to estimate the impact of frailty on geriatric outcomes among CHD patients (Model 1). To address confounding by age, demographics and other risk factors, we performed 3 additional multivariable Cox models. Model 2 adjusted for age and gender; Model 3 adjusted for age, gender, race/ethnicity, BMI and smoking status. Model 4 adjusted for age, gender, race/ethnicity, BMI, smoking status, diabetes, hypertension and number of comorbid diseases. The assumption for Cox proportional hazard models was checked by plotting the Shoenfeld residuals against survival time for each primary and secondary cardiovascular outcome by frailty group.

For patients without history of CHD, demographics, smoking status, self-reported disease, hospitalizations, emergency department visits, falls, selfcare, mobility, household activities, depression, anxiety, and cognitive impairment at baseline were reported for frail and the non-frail group. Proportional hazard models were used to assess the association between frailty on cardiovascular outcomes among patients without history of CHD during five-year

follow-up. Patients were censored if they developed cardiovascular outcomes of interest or if they were lost to follow-up. First, we performed an unadjusted Cox proportional hazards models to estimate the impact of frailty on MACE and each cardiovascular outcome among non-CHD patients (Model 1). To address confounding by age, demographics and other risk factors, we performed 3 additional multivariable Cox models. Model 2 adjusted for age and gender; Model 3 adjusted for age, gender, race/ethnicity, BMI and smoking status; Model 4 adjusted for age, gender, race/ethnicity, BMI, smoking status, diabetes, hypertension and number of comorbid diseases. NHATS sample weights, strata and clustering elements related to survey design were applied to all regression analyses. All tests are two-sided, and the statistically significant level is set at $p< 0.05$. Data analyses were conducted using SAS (v.9.4; SAS Institute Inc, Cary, North Carolina) and STATA version 15 MP (State Corp., College Station, Texas). The institutional review board at Johns Hopkins University approved this study.

RESULTS

Description of the 2011 NHATS Baseline

Of the 4,656 patients enrolled in 2011 NHATS baseline visit, the mean age was 76 years and 51% of the study population was ≥75 years of age. Female participants constituted 56% of the cohort and the majority enrolled were non-Hispanic Whites. On average, the majority were overweight, and more than half of the cohort smoked at least 1 cigarette per day. The majority of this older population had multiple chronic conditions and 19% of the cohort had 4 or more chronic comorbidities. The most prevalent self-reported medical conditions were hypertension, arthritis, and osteoporosis. Approximately, one quarter of the study population is living with diabetes mellitus, 11% had an ischemic stroke, and only 5% had dementia at baseline.

Older Patients with CHD

Of the 1,397 patients who had history of CHD prior to their baseline NHATS visits, 399 (29%) patients had frailty according to the Fried physical frailty phenotype. Patients who were frail were older, more likely to be women, and belong to ethnic minority, as compared to non-frail patients. Frail patients had a lower mean body mass index and they reported higher prevalence of hypertension, lung disease, and arthritis than non-frail patients. The overall number of chronic comorbid conditions was higher among frail patients, with approximately half of these patients reported having 4 or more chronic medical conditions. Frail patients were more likely to be admitted to the hospital and had more emergency department visits in the 12 months prior to their baseline NHATS visits as compared to non-frail patients. When evaluating measures of disability at baseline, including *selfcare, mobility disability, household activities disability,* patients with frailty were more likely to report significant impairment as compared to non-frail patients. The overall disability level (i.e. difficulties requiring help) among the frail was as high as 79.8%, but only 27.3% for the non-frail group. Frail patients also had high cognitive impairment at baseline and approximately one quarter of them had probable dementia (Table 1).

The cumulative proportion of geriatrics outcomes at five-year follow-up is presented in Table 2. The majority of frail patients had impairment in their ADLs, IADLs, disability, and mobility disability during five-year follow-up as compared non-frail patients. Excluding patients with probable dementia at baseline, patients with frailty had higher likelihood of developing dementia during 5-year follow-up than the non-frail CHD patients (Figure 1).

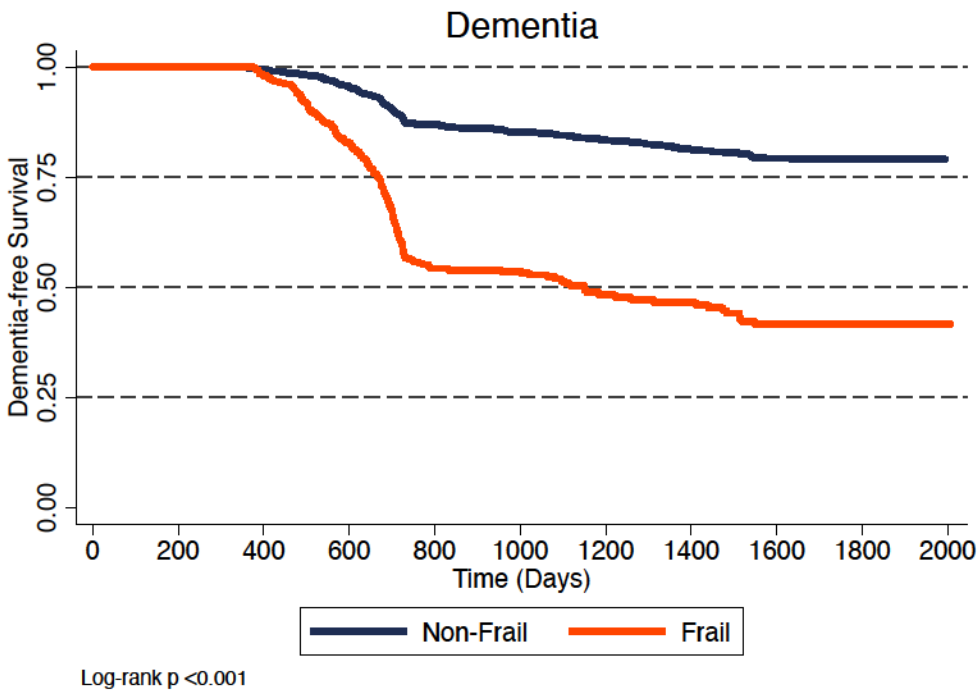


Figure 1. Kaplan-Meier survival curve illustrating the dementia free survival at 5 year in the NHATS-CMS study.

In an unadjusted Cox proportional hazards model, frailty was associated with dementia, loss of independence, impairment in ADL and IADL, and mobility disability as compared to non-frail group. Even after adjusting for age, gender, race/ethnicity, body mass index, cardiovascular risk factors, and number of concomitant chronic medical conditions, frailty was still associated with development of these geriatric outcomes during 5-year follow-up in the NHATS study (Table 3).

Older Patients without CHD

Of the 3,262 patients who had no history of CHD prior to their baseline NHATS visits, 521 (16%) patients had frailty according to the Fried frailty phenotype. Patients who were frail were older, more likely to be women and belong to ethnic minority as compared to non-frail patients. Frail patients had higher prevalence of hypertension, diabetes mellitus, history of prior

cardiac disorder (including cardiovascular risk factors), stroke, and dementia, lung disease, and arthritis than non-frail patients. The overall number of chronic comorbid conditions was also higher among frail patients with approximately one third of patients reported having 4 or more chronic medical conditions (Table 4). Frail patients were more likely to be admitted to the hospital and had more emergency department visits in the 12 months prior to their baseline NHATS visits, as compared to non-frail patients. When evaluating measures of disability at baseline, including *selfcare, mobility disability, household activities disability,* patients with frailty were more likely to report significant impairment, as compared to non-frail patients. The overall disability level (i.e. having difficulties requiring help) among the frail group was as high as 72.8 %, but only 16.4% reported having difficulties requiring help in the non-frail group. Frail patients also had high cognitive impairment at baseline and approximately one quarter of them had probable dementia at baseline (Table 4).

The cumulative proportion of cardiovascular outcomes at five-year follow-up is presented in Table 5. Frail patients developed more cardiovascular outcomes than the non-frail at five-year follow-up including major adverse cardiovascular event, death, acute myocardial infarction, stroke, peripheral vascular disease, or any CAD (Table 5; Figures 2-6).

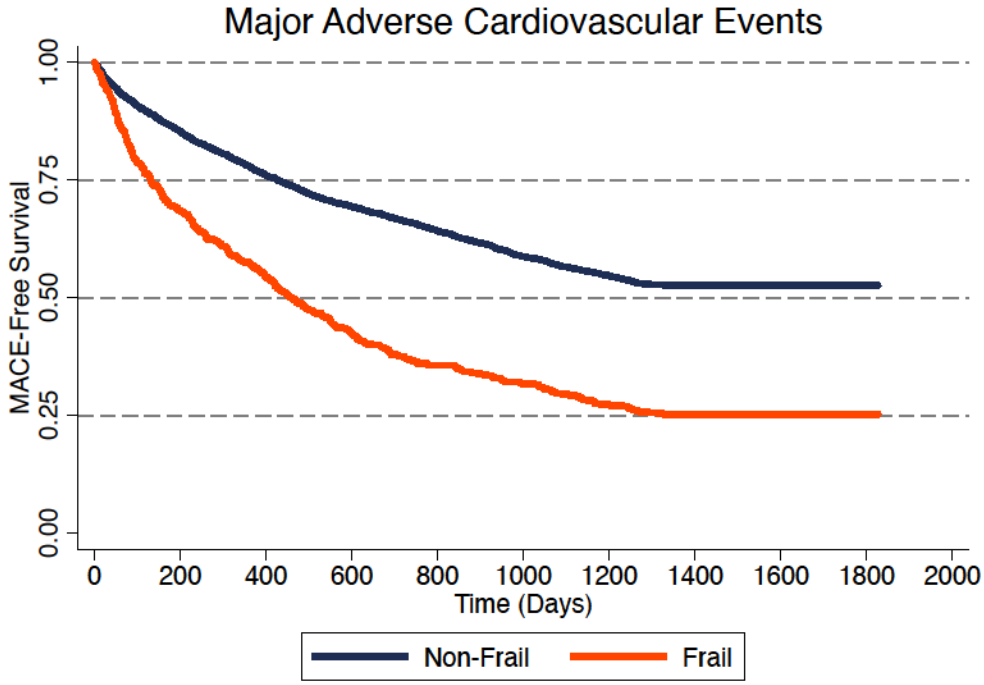


Figure 2. Kaplan-Meier survival curve illustrating the major-adverse cardiovascular event-free survival at 5 year in the NHATS-CMS study among patients without history of coronary heart disease (Log-rank $p<0.001$).

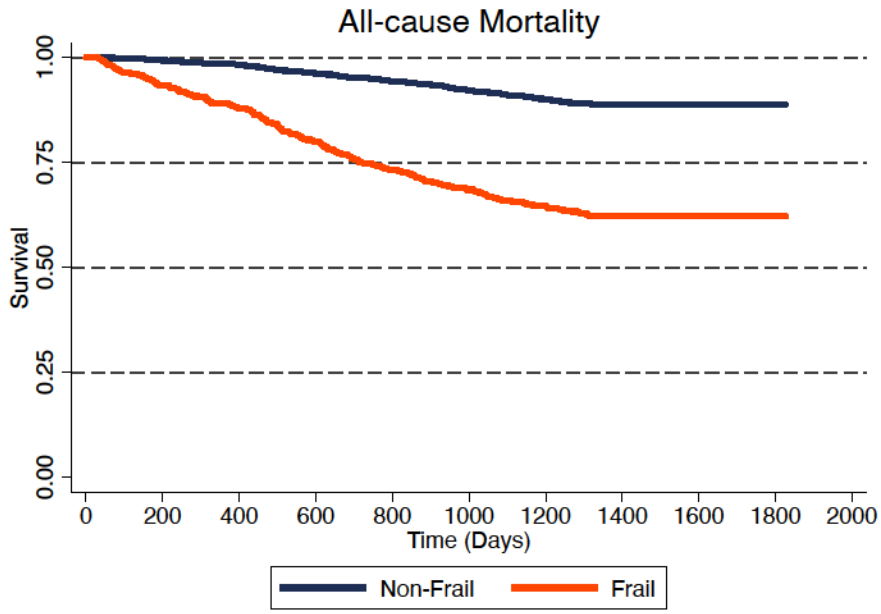


Figure 3. Kaplan-Meier survival curve illustrating the survival at 5 year in the NHATS-CMS study among patients without history of coronary heart disease (log-rank $p<0.001$).

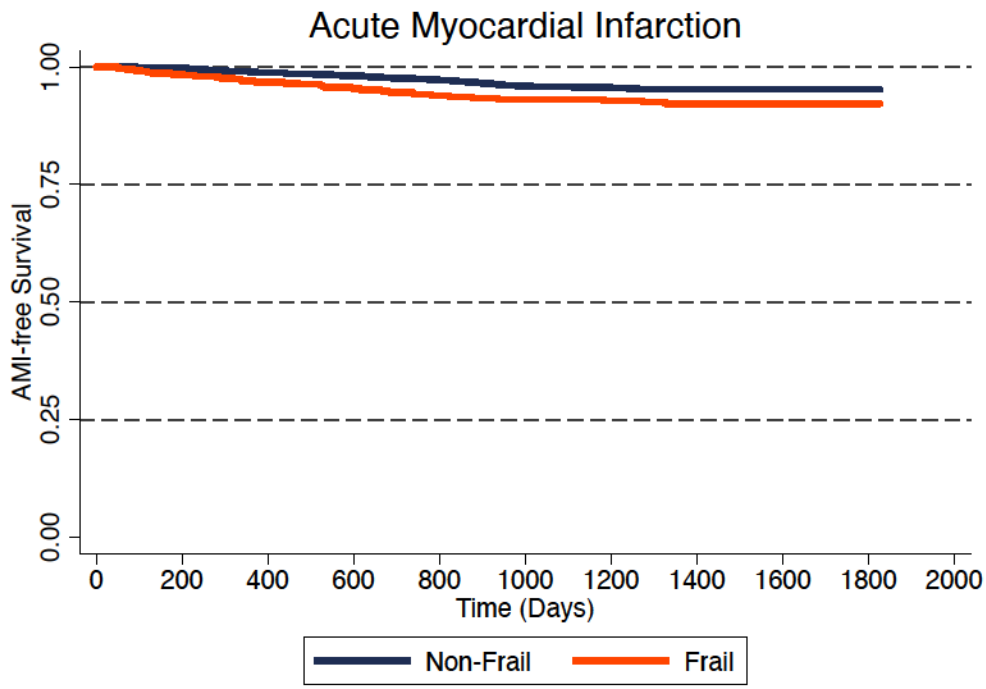


Figure 4. Kaplan-Meier survival curve illustrating acute myocardial infarction-free survival at 5 year in the NHATS-CMS study among patients without history of coronary heart disease (log-rank p=0.003).

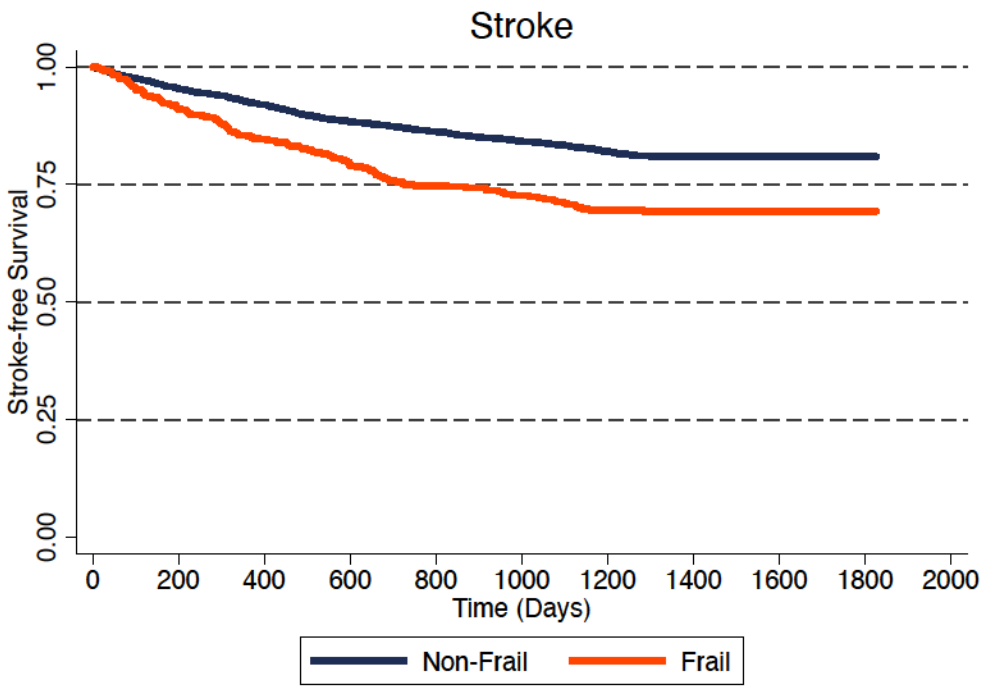


Figure 5. Kaplan-Meier survival curve illustrating stroke-free survival at 5 year in the NHATS-CMS study among patients without history of coronary heart disease (log-rank $p<0.001$).

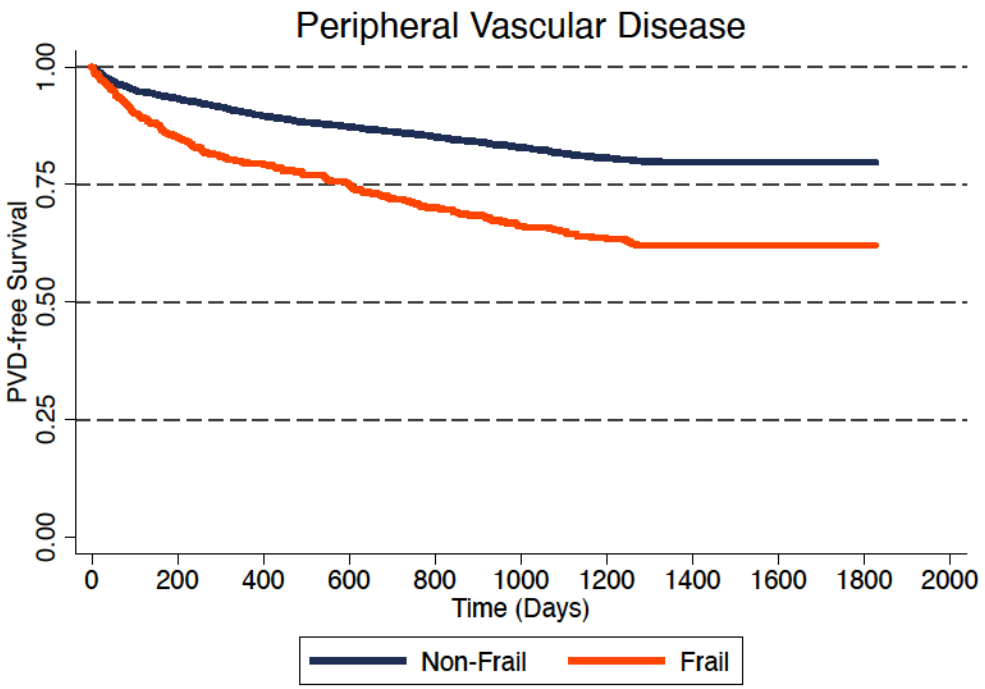


Figure 6. Kaplan-Meier survival curve illustrating peripheral vascular disease-free survival at 5 year in the NHATS-CMS study among patients without history of coronary heart disease (log-rank $p<0.001$).

In an unadjusted Cox proportional hazards model, frailty was associated with major adverse cardiovascular event and each individual endpoint: all-cause death, acute myocardial infarction, stroke, peripheral vascular disease, and any subsequent CAD, as compared to non-frail patients. After adjusting for age, gender, race/ethnicity, body mass index, cardiovascular risk factors, and number of concomitant chronic medical conditions, frailty was associated with major adverse cardiovascular event, death, stroke, and peripheral vascular disease at 5-year follow-up in the NHATS study (Table 6).

DISCUSSION

In this large prospective cohort study, we examined the influence of frailty on geriatric outcomes among older adults with history of CHD. We also evaluated the association between frailty and cardiovascular outcomes among older adults without history CHD during the 2011 baseline NHATS visit. The major findings of this study are as follows: (1) Among CHD patients, those who have baseline physical frailty, as measured by the Fried Frailty Phenotype, had high prevalence of multiple chronic conditions, baseline disability, mobility-disability, and cognitive dysfunction than non-frail patients; (2) CHD patients with baseline frailty had higher rates of healthcare utilization with more emergency department visits, admission to the inpatient service, and longer hospital length of stay; (3) At five-year follow, CHD-patients with baseline frailty had an accelerated development of geriatric syndromes, as compared to non-frail patients including impairment in the activities of daily living and instrumental activities of daily living, disability, mobility disability, loss of independence, and incident dementia; (4) Among patients without history of CHD, we found that the prevalence of frailty was lower than those with CHD patients; (5) Among non-CHD patients, frailty was associated with development of major

adverse cardiovascular events at five years even after adjusting for demographic characteristics and traditional cardiovascular risk factors.

The prevalence of frailty varies depending on the tool utilized to measure frailty and on the clinical characteristics of the study population .[54] In patients with multivessel coronary disease, Purser and colleagues found that the prevalence of frailty was 27% using the Fried frailty phenotype (n=309). In another study, frailty was encountered in 21% among older patients with CHD who underwent percutaneous coronary intervention (n=629).[21, 59] Consistent with these estimates, we found that patients with preexisting CHD have higher prevalence of physical frailty phenotype as compared to non-CHD patients (CHD: 29% vs non-CHD: 16%). Many published reports found that frailty is positively correlated with different forms of cardiovascular disease.[29, 60, 61] This can potentially be explained by differences in underlying medical, mental, and social factors between patients with and without cardiovascular disease in general and those with CHD in particular. Those with CHD are older, have high burden of cardiovascular illness, cognitive impairment, multimorbidity, and higher prevalence of cardiovascular risk factors. Further, those with history of CHD were more likely to be disabled at baseline or have an impairment in their activities of daily living or instrumental activities of daily living than non-CHD patients. A prior study have found that cardiovascular disease is a risk factor for development of frailty when assessed using the Fried criteria.[62] In the Women's Health Initiative Observational Study, CHD was more common among frail women, but it was also an independent risk factor for development of incident frailty during three year follow-up.[63] These studies were consistent with our results emphasizing the association between CHD and frailty. Walston and colleagues found a strong association between the geriatric syndrome of frailty with metabolic alteration including inflammation, altered carbohydrate metabolism, and increase in

coagulopathy.[64] Such metabolic perturbation among older frail individuals without history of CHD may explain the increased risk of incident cardiovascular disease and in our study.

We also attempted to understand the association between frailty and various geriatric syndromes among patients with baseline CHD. Prior studies found that frailty is associated with a range of geriatric syndromes including disability, falls, fractures, mobility disability, worsening in quality of life, loneliness, cognitive decline and dementia.[65] We extended these results to patients with preexisting CHD which emphasize the importance of measuring frailty as part of clinical cardiovascular practice. Frailty has a substantial impact on the aging process, but patients with preexisting CHD exhibit accelerated risk as a result of the interaction between geriatric syndromes and the disease process. Frailty assessment instruments specifically tailored to diagnose physical frailty during acute cardiovascular illness are needed because of the substantial impact of frailty on older patients with CHD.

The assessment of frailty is challenging, particularly during acute cardiovascular illness, but significant value for systematically assessing these domains can be summarized as follows:

- to predict the risk of adverse outcomes and accordingly guide patients through the process of informed decision making for cardiovascular therapies and end-of-life choices;
- to tailor the delivery of cardiovascular therapies to maximize the likelihood of patient-centered beneficial effects while avoiding costly yet futile (or even harmful) interventions;
- to anticipate and communicate the expected trajectory of the patient's hospitalization needs and disposition plan;
- to understand the patient's presentation in light of the acute cardiovascular illness and the contributing geriatric impairments;

- to detect acute changes in health status;
- to initiate therapies aimed at counteracting the geriatric impairment;
- to prevent (or detect at an early stage) undesirable downstream complications;
- to consider the geriatric needs of the patient population for resource allocation;
- to report geriatric-risk-adjusted outcome measures for quality control initiatives and comparative effectiveness research.

This study has potential limitations. First, CHD was diagnosed using data obtained from the Medicare claims database one year prior to the 2011 baseline NHATS visit. While this method of studying CHD is widely used in health services research, the severity and degree of coronary artery disease burden could not be ascertained. Despite this limitation, this large study is novel because it is the first to evaluate the *temporal* relationship between frailty and incident cardiovascular disease at five years among those with no documented CHD in the Medicare database. Second, it is plausible that patients with frailty have undiagnosed cardiovascular disease, which in turn lead to higher incidence of cardiovascular events during follow-up.

CONCLUSION

In this large prospective cohort study, we found that patients with CHD and baseline frailty had an accelerated development of geriatric syndromes including impairment in their ADLs, IADLs, disability, mobility disability, loss of independence, and incident dementia at five-year follow-up. We also found that among patients without known CHD, frailty was associated with development of major adverse cardiovascular events at five years even after adjusting for traditional cardiovascular risk factors at baseline. In patient with cardiovascular disease in general, and CHD in particular, studies that evaluate interventions to prevent or slow

the progression of physical frailty syndrome are needed as the United States older population continues to expand in the years to come.

Table 1. Characteristics of the study population of patients with history of coronary heart disease enrolled in the National Health and Aging Trends Study by physical frailty phenotype.

Characteristics	Total	No Frailty	Frailty*	*p*-value
	(n=1,397)	(n=998)	(n=399)	
Age, mean (SD)	77.5	76.7	80.0	<0.001
Age, %				<0.001
65-69	15.7	16.9	11.8	
70-74	24.1	26.0	18.3	
75-79	21.7	23.6	16.1	
80-84	19.3	18.5	21.8	
85-89	12.7	10.2	20.5	
90+	6.5	4.8	11.5	
Gender, %				0.012
Female	48.6	46.4	55.5	
Male	51.4	53.6	44.5	
Race, %				<0.001
Non-Hispanic white	85.6	87.4	80.2	
Non-Hispanic black	6.4	5.9	7.9	
Hispanic	5.2	3.6	10.1	
Other	2.9	3.2	1.9	
BMI, mean	27.8	28.0	27.1	0.044
Smoking status, %				0.056
Smoke at least 1 cigarette/day	58.6	60.3	53.4	
Self-reported disease, %				
Arthritis	58.6	53.4	74.5	<0.001
Diabetes mellitus	34.2	32.5	39.2	0.069
Any cardiac disorder	62.7	61.2	67.3	0.056
Hypertension	74.6	73.1	79.1	0.025
Lung disease	20.6	18.4	27.3	0.008
Osteoporosis	21.8	20.0	27.3	0.012
Stroke	17.3	14.8	24.8	<0.001
Dementia	5.7	3.5	12.4	<0.001
Number of chronic diseases, %				

				<0.001
0-1	14.1	15.8	8.8	
2-3	52.2	56.9	37.8	
4+	33.7	27.3	53.4	
Hospital stay past 12 months, %	39.3	32.1	61.2	<0.001
Any fall past month, %	37.0	29.6	59.6	<0.001
Self-care disability, %				<0.001
No difficulty	64.4	77.0	25.8	
Difficulty but no help	13.9	11.4	21.7	
Help	21.7	11.6	52.5	
Mobility disability, %				<0.001
No difficulty	57.4	70.3	18.1	
Difficulty but no help	21.6	19.4	28.2	
Help	21.0	10.3	53.7	
Household activities disability, %				<0.001
No difficulty				
Difficulty but no help	52.4	63.9	17.4	
Help	12.4	12.8	11.0	
	35.2	23.2	71.7	
Overall disability level, %				<0.001
No difficulty	39.2	50.0	6.1	
Difficulty but no help	20.6	22.7	14.1	
Help	40.3	27.3	79.8	
Depression, %				
PHQ2 score>=3	20.6	12.8	44.5	<0.001
Anxiety, %				
GAD2 score>=3	17.9	12.1	35.5	<0.001
No. ED visits, %				<0.001
0	58.8	65.5	38.5	
1	21.3	20.3	24.2	
>=2	19.9	14.2	37.3	
No. Hospitalizations, %				<0.001
0	66.3	72.3	47.9	
1	20.9	19.5	25.2	
>=2	12.8	8.2	27.0	
Total LOS in hospital, mean	3.6	2.2	8.2	<0.001

No. physician visits, mean	13.2	12.2	16.3	<0.001
No. ADL impairment, %				
0	51.8	64.2	14.0	<0.001
1-2	25.2	24.8	26.4	
>=3	23.0	11.0	59.6	
No. IADL impairments, %				<0.001
0	53.6	65.1	18.4	
1-2	26.0	25.0	29.1	
>=3	20.4	9.8	52.5	
Cognitive impairment, %	7.3	4.8	15.8	<0.001
AD8 Dementia, %	5.3	2.2	14.9	<0.001
Dementia (probable), %	12.4	7.7	26.7	<0.001

*Frailty was assessed by the physical frailty phenotype paradigm that is grounded in five criteria: exhaustion, low physical activity, weakness, slowness, and shrinking (www.nhats.org). Claims-based frailty index (CFI) is a validated frailty tool against the physical frailty phenotype that utilize claims data. **Abbreviations:**; PHQ2 = patient health questionnaire-2; GAD2 = generalized anxiety disorder 2-item; ED = emergency department; LOS = length of stay; ADL = activities of daily living; IADL = instrumental activities of daily living; AD8 = AD8 dementia screening interview; CFI = claims based frailty index.

Table 2. Five-year geriatrics outcomes by physical frailty phenotype among older adults with history of coronary heart disease outcomes in the National Health and Aging Trends Study.

Characteristics	Total	No Frailty	Frailty*	*p*-value
	(n=1,397)	(n=998)	(n=399)	
ADL, %	67.0	57.8	94.9	<0.001
IADL, %	59.7	51.0	86.2	<0.001
Dementia, %	21.2	15.0	40.3	<0.001
Loss of Independence*, %	52.5	41.9	84.9	<.0001
Disability, %	77.3	70.7	97.4	<0.001
Mobility disability, %	61.5	51.2	92.7	<0.001

*Frailty was assessed by the physical frailty phenotype paradigm that is grounded in five criteria: exhaustion, low physical activity, weakness, slowness, and shrinking (www.nhats.org). **Abbreviations:** ADL = activities of daily living; IADL = instrumental activities of daily living. * Loss of independence was defined as "never/rarely go outside or use devices to go outside.

Table 3. Proportional hazards regression model evaluating the influence of physical frailty status on five-year geriatric outcomes among older adults with history of coronary heart disease in the National Health and Aging Trends Study.

Characteristics	Incident Dementia	Loss of Independence	Impairment in ADL	Impairment in IADL	Mobility Disability
	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)
Model 1 (Unadjusted)*					
Frailty	3.77(2.94,4.83)	3.98(3.31,4.78)	3.53(3.06,4.08)	3.21(2.70,3.81)	4.03(3.48,4.65)
Model 2**					
Frailty	2.98(2.36,3.75)	3.47(2.92,4.14)	3.19(2.78,3.66)	2.84(2.41,3.34)	3.67(3.18,4.23)
Model 3***					
Frailty	2.91(2.25,3.77)	3.39(2.83,4.06)	3.09(2.65,3.59)	2.75(2.33,3.25)	3.59(3.06,4.22)
Model 4****					
Frailty	2.58(1.98,3.37)	3.02(2.52,3.62)	2.80(2.39,3.27)	2.47(2.08,2.92)	3.18(2.72,3.72)

*Frailty was assessed by the physical frailty phenotype paradigm that is grounded in five criteria: exhaustion, low physical activity, weakness, slowness, and shrinking (www.nhats.org). **Abbreviations:** ADL = activities of daily living; IADL = instrumental activities of daily living.

**Model 2 was adjusted for age and gender.

***Model 3 was adjusted for age, gender, race/ethnicity, BMI and smoking status.

****Model 4 was adjusted for age, gender, race/ethnicity, BMI and smoking status, diabetes, hypertension and number of chronic diseases.

Table 4. Characteristics of the study population of patients without history of coronary heart disease enrolled in the National Health and Aging Trends Study by physical frailty phenotype.

Characteristics	Total (n=3,262)	No Frailty (n=2,741)	Frailty* (n=521)	*p*-value
Age, mean (SD)	75.2	74.6	79.4	<0.001
Age, %				<0.001
65-69	28.6	30.2	17.3	
70-74	24.9	26.1	16.3	
75-79	19.1	19.4	17.0	
80-84	14.3	14.1	15.4	
85-89	9.0	7.2	21.9	
90+	4.1	2.9	12.1	
Gender, %				<0.001
Female	59.4	58.0	69.6	
Male	40.6	42.0	30.4	
Race, %				<0.001
Non-Hispanic white	84.4	85.6	75.9	
Non-Hispanic black	7.7	7.0	12.9	
Hispanic	4.8	4.2	8.7	
Other	3.1	3.2	2.4	
BMI, mean	27.3	27.4	27.1	0.588
Smoking status, %				0.082
Smoke at least 1 cigarette/day	51.0	51.6	46.4	
Self-reported disease, %				
Arthritis	52.6	49.3	75.4	<0.001
Diabetes mellitus	19.4	17.8	31.0	<0.001
Any cardiac disorder	12.4	10.6	25.3	<0.001
Hypertension	60.3	59.2	68.2	0.005
Lung disease	13.6	11.9	25.2	<0.001
Osteoporosis	21.8	19.9	35.2	<0.001
Stroke	8.7	7.2	19.0	<0.001
Dementia	4.5	2.7	17.6	<0.001
Number of chronic diseases, %				

				<0.001
12.10-1	41.0	44.8	13.9	
2-3	46.9	45.9	54.1	
4+	12.1	9.3	32.1	
Hospital stay past 12 months, %	15.1	12.7	32.5	<0.001
Any fall past month, %	30.0	26.7	53.1	<0.001
Self-care disability, %				<0.001
No difficulty	78.7	84.6	36.7	
Difficulty but no help	10.9	9.5	21.4	
Help	10.4	5.9	42.0	
Mobility disability, %				<0.001
No difficulty	72.5	79.8	20.8	
Difficulty but no help	16.1	14.6	26.4	
Help	11.4	5.5	52.8	
Household activities disability, %				<0.001
No difficulty				
Difficulty but no help	67.0	74.0	17.7	
Help	12.7	12.4	14.9	
	20.3	13.7	67.3	
Overall disability level, %				<0.001
No difficulty	56.5	63.1	9.7	
Difficulty but no help	20.1	20.5	17.5	
Help	23.4	16.4	72.8	
Depression, %				
PHQ2 score>=3	12.6	9.3	36.3	<0.001
Anxiety, %				
GAD2 score>=3	10.7	8.3	28.1	<0.001
No. ED visits, %				<0.001
0	78.1	80.4	61.6	
1	14.9	14.4	18.8	
>=2	7.0	5.2	19.6	
No. Hospitalizations, %				<0.001
0	89.4	91.3	76.1	
1	8.3	7.2	16.3	
>=2	2.3	1.5	7.6	
Total LOS in hospital, mean	0.88	0.63	2.62	<0.001

No. physician visits, mean	7.13	6.85	9.06	<0.001
No. ADL impairment, %				
0	68.7	75.6	20.2	<0.001
1-2	19.8	18.5	28.7	
>=3	11.5	5.9	51.1	
No. IADL impairments, %				<0.001
0	68.4	75.2	19.5	
1-2	19.7	18.3	30.1	
>=3	11.9	6.5	50.3	
Cognitive impairment, %	5.9	4.2	20.0	<0.001
AD8 Dementia, %	4.0	1.8	19.7	<0.001
Dementia (probable), %	9.5	6.2	33.0	<0.001
CFI Frail, %	10.3	7.4	30.3	<0.001

*Frailty was assessed by the physical frailty phenotype paradigm that is grounded in five criteria: exhaustion, low physical activity, weakness, slowness, and shrinking (www.nhats.org). Claims-based frailty index (CFI) is a validated frailty tool against the physical frailty phenotype that utilize claims data. **Abbreviations:**; PHQ2 = patient health questionnaire-2; GAD2 = generalized anxiety disorder 2-item; ED = emergency department; LOS = length of stay; ADL = activities of daily living; IADL = instrumental activities of daily living; AD8 = AD8 dementia screening interview; CFI = claims based frailty index.

Table 5. Five-year cardiovascular outcomes by physical frailty phenotype among older adults without history of coronary heart disease outcomes in the National Health and Aging Trends Study.

Characteristics	Total (n=3262)	No Frailty (n=2741)	Frailty* (n=521)	*p*-value
MACE, %	46.9	43.5	70.8	<0.001
Death, %	12.1	9.0	33.7	<0.001
AMI, %	4.4	4.1	6.8	0.037
Stroke, %	18.6	17.6	25.8	<.0001
PVD, %	18.7	17.0	30.4	<0.001
Any CAD, %	25.3	24.2	33.3	<0.001

*Frailty was assessed by the physical frailty phenotype paradigm that is grounded in five criteria: exhaustion, low physical activity, weakness, slowness, and shrinking (www.nhats.org).

Abbreviations: CAD = Coronary Artery Disease; PVD =peripheral vascular disease; AMI = acute myocardial infarction; MACE = major adverse cardiovascular even

Table 6. Proportional hazards regression model evaluating the influence of physical frailty status on five-year cardiovascular outcomes among older adults without history of coronary heart disease in the National Health and Aging Trends Study.

	MACE	Death	AMI	Stroke	PVD	CAD
Characteristics	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)
Model 1 (Unadjusted)*						
Frailty	2.26(1.94,2.64)	4.51(3.43,5.92)	2.03(1.24,3.32)	1.82(1.48,2.23)	2.22(1.79,2.74)	1.72(1.42,2.09)
Model 2**						
Frailty	1.80(1.57,2.07)	3.11(2.39,4.04)	1.70(1.04,2.77)	1.51(1.25,1.83)	1.63(1.32,2.01)	1.49(1.23,1.79)
Model 3***						
Frailty	1.79(1.53,2.10)	3.16(2.38,4.19)	1.68(1.02,2.76)	1.55(1.25,1.92)	1.61(1.29,2.01)	1.41(1.15,1.72)
Model 4****						
Frailty	1.49(1.26,1.74)	2.64(1.95,3.57)	1.46(0.87,2.46)	1.26(1.03,1.53)	1.33(1.05,1.67)	1.12(0.92,1.37)

*Frailty was assessed by the physical frailty phenotype paradigm that is grounded in five criteria: exhaustion, low physical activity, weakness, slowness, and shrinking (www.nhats.org). **Abbreviations:** CAD = Coronary Artery Disease PVD =peripheral vascular disease; AMI = acute myocardial infarction; MACE = major adverse cardiovascular event

** Model 2 was adjusted for age and gender.

*** Model 3 was adjusted for age, gender, race/ethnicity, BMI and smoking status.

**** Model 4 was adjusted for age, gender, race/ethnicity, BMI and smoking status, diabetes, hypertension and number of chronic diseases.

CHAPTER 3

SARCOPENIA AND HEALTH RELATED QUALITY OF LIFE IN OLDER ADULTS AFTER TRANSCATHETER AORTIC VALVE REPLACEMENT

(Damluji A et al. *Am Heart J.* Submitted-in revision)

INTRODUCTION

Transcatheter aortic valve replacement (TAVR) is the standard of care for patients with severe symptomatic aortic stenosis. Although favorable immediate and long-term outcomes have been established[66, 67], geriatric syndromes continue to limit the overall effectiveness of TAVR in clinical practice.[36, 38] Of these, sarcopenia is a progressive and generalized skeletal muscle disorder that is associated with increased likelihood of adverse outcomes including falls, fractures, physical disability, and mortality.[12] Reduced skeletal muscle quantity/mass and strength are clinical characteristics of sarcopenia that can be readily measured. However, the extent to which a reduction in overall skeletal muscle quantity/mass and strength are associated with clinical outcomes remains unknown. Further, whether skeletal muscle quantity/mass and strength can be utilized to stratify older patients undergoing TAVR procedures into those who are most likely to derive benefit from health-related quality of life (HR-QOL) is an area of active investigation.

By providing precise segmentation of individual muscle and adipose tissue components, computed tomography (CT) can be used to assess body composition and quantify skeletal muscle mass and quality.[68, 69]A single cross-sectional image at the third lumbar vertebrae (L3) correlates well with whole-body skeletal muscle and adipose tissue, providing an accurate assessment of whole-body tissue composition.[13, 14] Given that TAVR patients routinely undergo a preoperative CT scan of the chest, abdomen, and pelvis, body composition can be readily assessed. The aim of

this study was to examine the relationship between SMI and both post TAVR length of hospital stay (LOS) and one-year HR-QOL, in a large consecutive cohort of patients.

METHODS

Study Design

The study sample was derived from 346 consecutive outpatients who underwent TAVR at an academic hospital from September 2012 to June 2018. All patients presented with severe symptomatic aortic valve stenosis (aortic valve area of ≤ 1.0 cm^2 and/or mean transvalvular gradient of $\geq$ 40mmHg) and were deemed by the multidisciplinary heart team to be at high or intermediate risk for surgical aortic valve replacement, due a predicted Society of Thoracic Surgery (STS) operative mortality of $\geq$ 3%, major comorbidities/contraindications for surgery and/or frailty. All patients underwent a pre-TAVR CT scan of the chest, abdomen, and pelvis, pulmonary function tests, and standard 2-dimensional echocardiography with Doppler assessment.

Of the 346 consecutive patients treated, 300 (87%) had CT scans with suitable for interpretation of body composition. Baseline patient demographics and clinical characteristics were recorded prospectively. Muscle strength testing included dominant handgrip strength (kg) and 5-m walk test (seconds). Albumin levels (g/dL) were measured prospectively for all study participants. Mitral and tricuspid regurgitation were deemed significant if reported as moderate or severe by transthoracic echocardiography and Doppler assessment. Pulmonary arterial hypertension was defined as an estimated right ventricular systolic pressure of at least 50 mmHg from the baseline echocardiogram. Major complications were recorded using established Valve Academic Research Consortium (VARC II) definitions for death, major bleeding, myocardial

infarction, stroke, vascular complications, valve-related dysfunction, and acute kidney injury.[70] Hospital LOS was defined as the number of days from the date of procedure to the date of being discharged home or to a rehabilitation facility. All patients were evaluated at 30 days and one-year post TAVR.

The Kansas City Cardiomyopathy Questionnaire Score (KCCQ)

The KCCQ is a validated HR-QOL instrument, which was developed to assess the health status among patient with heart failure. [71] The questionnaire is self-administered and can be completed on average within 4-6 minutes. Within each domain of the health status, the questionnaire is scored by assigning each response to an ordinal value, with 1 beginning for the response related to the lowest value.[71] The questionnaire includes 12-items which quantify physical limitation, symptom frequency, and quality of life, and social limitation.[72] Scores are aggregated under an overall summary score. [71] Symptom burden as measured by KCCQ predicts recurrent heart failure, death, and major cardiovascular events in patients with chronic congestive heart failure and a variety of cardiovascular disoders.[72] The KCCQ questionnaire is a scale that measures HR-QOL and overall health status and it has undergone psychometric testing in patients with severe symptomatic aortic stenosis. KCCQ was determined at baseline, 30 days and 1-year post TAVR.

Body Composition Assessment by CT

Using predefined methods, muscle quantity was evaluated from the CT cross-section at the third lumber vertebra (L3).[13] At this level, using Hounsfield units (HU) thresholds, the cumulative area of all abdominal skeletal muscles (psoas and paraspinal muscles, erector spinae, quadratus lumborum, transversus abdominus, external and internal oblique abdominals, and the rectus abdominus) can be quantified in cm^2.[13] The following HU thresholds were used to characterize and differentiate tissue types: −29 to 150 for muscle, −150 to −50 for visceral adipose tissue, −190 to −30 for intermuscular adipose tissue and subcutaneous adipose tissue.[73] All CT images were analyzed by a single trained observer (GR) using Slice-O-Matic software, version 5.0 (Tomovision, Montreal, Quebec, Canada). A brief overview of this technique can be found here: https://www.youtube.com/watch?v=KJrsQ_dg5mM. Examples of CT-assessed body composition are shown in Figure 1. Very low skeletal muscle mass (i.e., sarcopenia) was defined using Baumgartner's previously established sex-specific cutoff values in elderly individuals: <55 cm^2/m^2 for men and <39 cm^2/m^2 for women.[15] These values were converted to CT measurements using previously established prediction equations.[74]

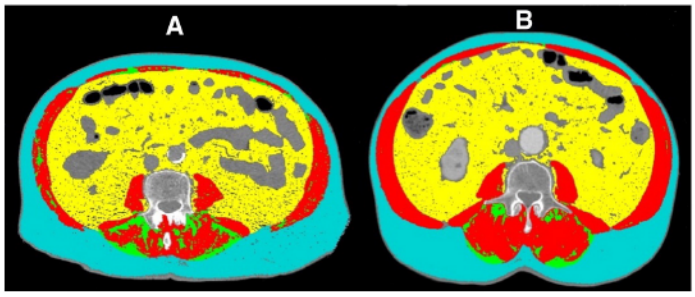


Figure 1. Computed tomographic analysis of body composition. CT images (A and B) using Slice-O-Matic software, version 5.0 (Tomovision). A brief overview of this analysis can be found here: https://www.youtube.com/watch?v=KJrsQ_dg5mM. Skeletal muscle (RED), visceral adipose tissue (YELLOW), subcutaneous adipose tissue (BLUE),

Statistical Analysis

Descriptive statistics for the study population baseline characteristics were presented by quartiles of SMI (cm^2/m^2). Categorical variables were summarized as frequencies and proportions, and continuous variables as means and standard deviations. Differences between the four quartiles of SMI (cm^2/m^2) were compared using the Wilcoxon rank sum, Student's *t*, Pearson X^2, and Fisher exact tests, as appropriate. To determine the distribution of SMI by gender and the prevalence of CT-defined sarcopenia[12], we plotted SMI according to patient gender and used the previously established binary cutoffs (< 55 cm^2/m^2 for men and < 39 cm^2/m^2) to depict those with severely reduced muscle mass (sarcopenia).[12] To examine the relationship between SMI and clinical outcomes and HR-QOL, we compared the following across SMI quartiles: in-hospital mortality, 30-day mortality, hospital LOS and KCCQ at 30 days and at 1-year. To determine the relationship between HR-QOL and SMI, we fitted a linear regression of HR-QOL as assessed by the KCCQ instrument (i.e. Y_i) on indicator variables for quartiles of SMI with the reference is being Q1, i.e. β_0 = mean Y in lowest quartile of SMI). For other quartiles, mean Y is given by:

$$E(Y_i) = \beta_0 + \beta_1 + \beta_2 + \beta_3, \text{j=1, 2, 3,}$$

where j represents the quartile of the ith individual minus 1. Thus, each $\beta_1, \beta_2, \beta_3$ coefficient represents the expected mean difference in one-year HR-QOL (as measured by the KCCQ) between patients within SMI quartiles Q2 to Q4 compared to the lowest quartile (Q1). To address confounding, we constructed the following 4 multiple linear regression analyses: (1) a model adjusting for age, gender, and race, (2) a model including variables in model 1 + body mass index, (3) a model including the variables adjusted for in model 2 in addition to total adipose tissue and (4) a model adjusted for all of these variables in addition to the following cardiovascular risk factors: hypertension, dyslipidemia, diabetes, and prior stroke.

In each of the models above, we evaluated normality by plotting histograms and q-normal plots. Figure 2 represents the q-normal plot for the multivariable linear regression that includes demographic characteristics, body mass index, total adipose tissue, hypertension, dyslipidemia, diabetes mellitus, and prior stroke.

We then reproduced the same results with SMI as a continuous variable. In a similar fashion, normality was evaluated using histograms, q-normal plots, and residual plotted against each continuous covariate. Using an adjusted variable plot, we visualized the multiple linear regression coefficient of SMI. Using a forward stepwise additive approach, multivariable linear regression was used to determine the independent predictors of 1-year QOL. All statistical analyses were performed using STATA version 15 MP (State Corp., College Station, Texas). We considered a p-value < 0.05 as significant and all tests were two-sided.

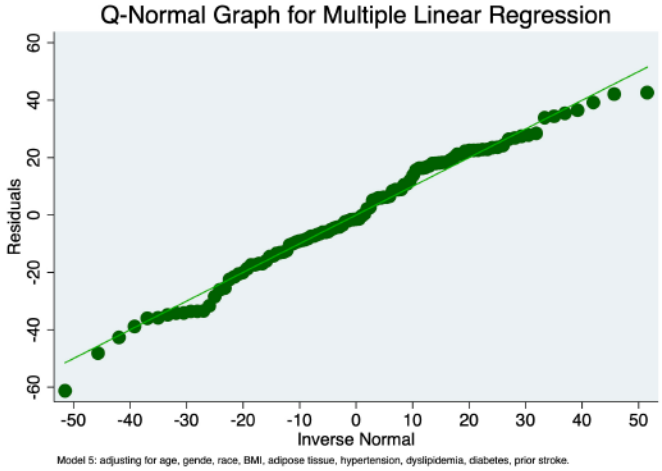


Figure 2. The q-normal plot for multivariable linear regression.

RESULTS

Baseline clinical characteristics

Baseline patient demographics and characteristics are shown in Table 1 for the overall sample (n=300) and according to SMI quartile. Mean age was 79 years, 49% were women, and mean body mass index (BMI) was 29 kg/m^2. Mean SMI was higher in men compared to women (46 vs. 39 cm^2/m^2; p < 0.001). For most patients, hand grip strength was greater in the right vs.

left hand. The majority of patients had hypertension (86%) and dyslipidemia (62%) and approximately one third had diabetes mellitus. Peripheral arterial disease and prior stroke were present in approximately one quarter of patients and a third had a history of prior percutaneous coronary intervention (PCI) and fewer had prior CABG. The majority of procedures were transfemoral (93%), with lower rates of transapical (7%) and transaortic (<1%) access. Mean aortic valve area was 0.74 cm^2 and mean LVEF 54%. At least moderate mitral and tricuspid regurgitation was present in over half, but only a quarter of patients had significant pulmonary hypertension. Mean creatinine clearance was 40 ml/min and mean STS score 6%. The distribution of SMI [(cm^2)/height^2 (m^2)] based on the gender of the participant is presented in Figure 3. Using preidentified cut points, the prevalence of low muscle quantity, (i.e., sarcopenia), was higher in men than women (Men: 61% vs. Women: 39%, p <0.001). The mean age for patients who did not have SMI [(cm^2)/height^2 (m^2)] data available for analysis (n = 46) was 77 years, 46% were women, and the mean BMI 30 kg/m^2.

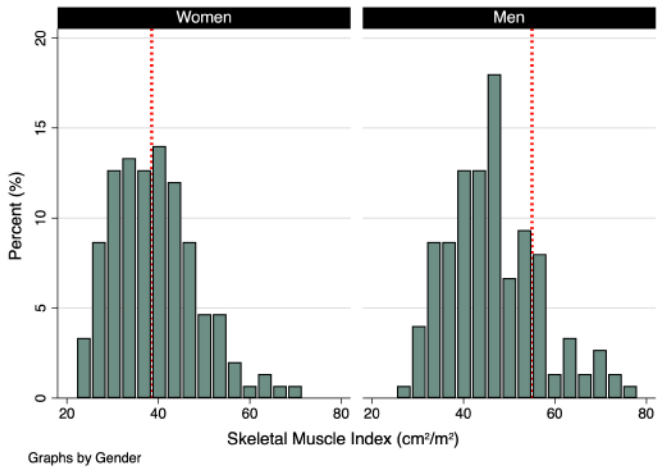


Figure 3. The distribution of SMI [(cm^2)/height (m^2)] based on the gender, which shows the prevalence of sarcopenia by the gender of participant.

Muscle Quantity, Strength, and Performance

Patients with the lowest quartile of muscle quantity/mass (Q1) were older, more likely to be female, have lower BMI and weaker right- and left-hand grip strength and 5m walk time (Table 1). However, cardiovascular

risk factors, comorbidities, renal function, STS-score, and echocardiographic data were similar across all quartiles of SMI. While patients in the lower quartile of SMI were less likely to have had prior PCI, the rate of prior coronary artery bypass surgery and pacemaker insertion was similar across SMI quartiles. Total adipose tissue measured in cm^2 and muscle attenuation measured in Hounsfield Unit (HU) were lowest in patients with lowest quartile of SMI.

Clinical Outcomes, Hospital Length of Stay and Health-related Quality of Life

In-hospital, 30 day and 1-year mortality were low (2%, 7% and 11%, respectively) with no differences across quartiles of SMI. Median hospital LOS was 3 days and there was an inverse relationship between LOS and SMI (SMI Q1 LOS: 5.0 days vs SMI Q4 LOS: 3.9 days, p =0.042). In a multivariable model, for every 10 unit increase in SMI [(cm^2)/height (m^2)], there was a 0.4 day mean reduction in LOS ($\beta = -0.42$, CI -0.75 to -0.09, p = 0.012).

At baseline, the HR-QOL was low (mean KCCQ= 39) consistent with the pre-TAVR state. Health-related QOL was similar across all 4 quartiles of baseline SMI (Pearson p =0.891). Similarly, there was no difference in KCCQ scores at 30-days across all quartiles of SMI (Pearson p = 0.351). However, at 1 year, patients in the highest quartile of SMI had the highest HR-QOL scores in KCCQ post TAVR (Figure 4). When restricting the analysis to only those patients who survived at one-year follow-up, a similar pattern emerged (Figure 5).

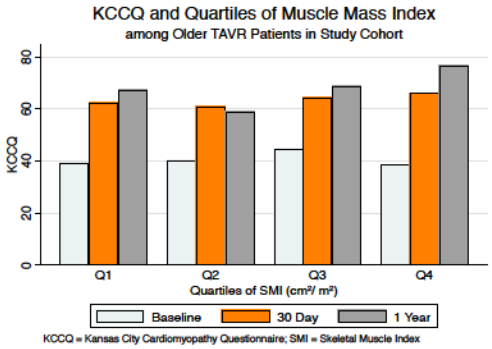


Figure 4

In-hospital, 30 day and 1-year health-related quality of life as measured by Kansas City Cardiomyopathy Questionnaire.

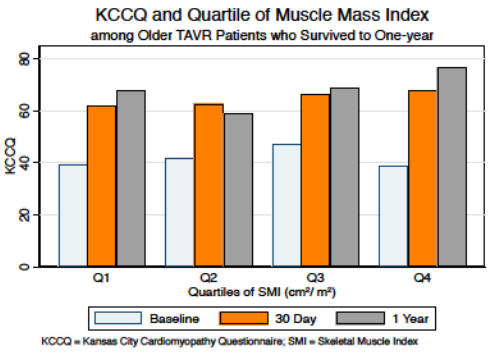


Figure 5

In-hospital, 30 day and 1-year health-related quality of life as measured by Kansas City Cardiomyopathy Questionnaire only among patients who survived to one-year follow-up

In a simple linear regression model with indicator variables for SMI, patients with the highest SMI (Q4) had no difference in KCCQ score at one year compared to the lowest quartile (Q1). After adjusting for age, gender, and race, this difference was larger and statistically significant (18-point difference, p =0.02). After adjusting for BMI, adipose tissue, and other cardiovascular comorbidities (hypertension, dyslipidemia, diabetes mellitus and prior stroke), the KCCQ difference between SMI Q4 vs. Q1 increased to 23 points (p =0.019) (Table 2). In the multivariable model, after adjusting for age, gender, race, BMI, total adipose tissue, and cardiovascular risk factors, there was on average an 8-point increase in KCCQ score per 10 unit increase of SMI [(cm^2)/height (m^2)] (β_1 = 0.81, 95% CI 0.14-1.5, p =0.017) (Figure 6).

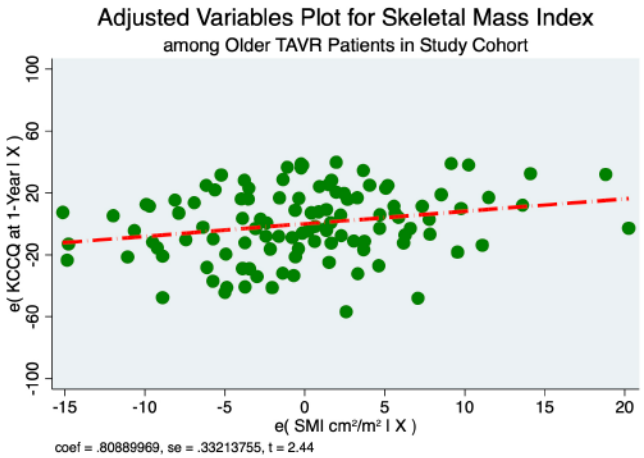


Figure 6. Adjusted variable plot that shows the influence of skeletal muscle index on Kansas City Cardiomyopathy Questionnaire at one-year.

For patients who did not have SMI [(cm^2)/height^2 (m^2)] data available for analysis, in-hospital (2% vs 2%, p = 0.645) and one-year mortality rates were similar (17% vs. 11%, p = 0.241). The median hospital length of stay was also similar (3 vs. 3 days, p = 0.818). Similarly, KCCQ scores at 30-days and one-year did not differ between patients with missing SMI [(cm^2)/height^2 (m^2)] data vs those with available data (30-day KCCQ:

DISCUSSION

In this study, we reported on the prevalence of sarcopenia in a consecutive cohort of older TAVR patients and determined the relationship between CT-derived SMI, hospital length of stay, and 1-year HR-QOL. The key findings include the following: (1) sarcopenia was highly prevalent in the study population, and more common in men vs. women; (2) pre-TAVR muscle strength was positively correlated with SMI; (3) SMI was inversely and independently associated with hospital LOS; and (4) SMI independently predicted 1-year HR-QOL. These findings are relevant as they provide further insight into the factors that govern post-TAVR recovery and QOL and reveal patients in whom nutrition and exercise interventions could have the most impact.

Sarcopenia is widely recognized as a clinical disorder that disproportionately affects older adults[12] and is characterized by low muscle quantity/mass, strength, and quality. For patients undergoing TAVR, muscle strength (often measured as hand grip strength) and CT-derived muscle mass have both been used to assess for sarcopenia.[75] In our study, patients with low muscle quantity/mass were more likely to have low muscle strength and overall muscle strength fell below the gender and age standards. Compared to the frailty AVR study[38], the mean hand grip strength was on average 10 Kg lower in our study.[38] We believe that these differences are due to the fact that our TAVR study population had lower muscle quantity/mass and strength, suggesting a more extensive degree of muscle disorder. Interestingly and despite this finding, the 30-day and 1-year post-TAVR mortality outcomes in our study were favorable and independent of muscle quantity/mass and strength.

In our study, skeletal muscle mass (SMI) predicted both LOS and HR-QOL. These findings are consistent with those reported in other clinical arenas. In a systematic review of the

literature, sarcopenia was associated with worse overall HR-QOL in both older men and women.[76] Furthermore, involuntary weight loss combined with low muscle quantity/mass have been shown to be associated with worse HR-QOL as measured using EuroQol-5 instrument.[77] The natural age-related decline in muscle strength and HR-QOL [78] may be mitigated by exercise, in particular resistance training.[79] In this work, we found that patients with the highest baseline SMI showed the greatest improvement in 1-year HR-QOL and this relationship between SMI and 1-year QOL strengthened after adjustment for age, gender, BMI and other risk factors. In the multivariable model, there was on average an 8-point increase in KCCQ score per 10 unit increase of SMI which translated into a 23-point difference in KCCQ score between the highest and lowest SMI quartiles (p =0.019). Given that as little as a 5 point change in KCCQ is considered clinically meaningful, this magnitude of difference is large and would be associated with major impact on a patient's life, symptoms, and functional status.[80, 81] Taken together, these findings suggest that the intermediate term QOL of an elderly patient with aortic stenosis likely depend not only on successful TAVR, but also on the effective identification and treatment of sarcopenia. Our findings and those of others suggest that sarcopenic patients, who are less likely to note an improvement in HR-QOL following TAVR, may be readily identified from the pre-procedure CT scan.[82, 83] The implication is that these patients could in the future be targeted for either pre- or post-TAVR nutrition and rehabilitation interventions aimed at improving muscle mass and strength.[84] Further studies aimed at improved nutritional protein intake combined with physical therapy, medications to increase muscle mass, prehabilitation or rehabilitation for TAVR are needed to assess the impact on long-term patient reported outcomes in sarcopenic patients (Clinical Trials: NCT03117296 and NCT03522454).

Limitations

There are important limitations to our study. First, the mortality rate in our cohort was quite low (7% at 30 days). However, the primary purpose of our study was to examine the relationship between SMI and HR-QOL rather than mortality. A systematic review of literature has already suggested that sarcopenia may be associated with hospital mortality.[85] Large sample sizes with greater mortality estimates would be needed to unmask any such association with mortality. Second, survival bias can potentially exist in which patients who survived were those on a better HR-QOL trajectory as measured using the KCCQ instrument as compared to those who died. While this is a potential limitation, we found no difference in mortality rate during index admission, 30-day, or one-year follow by different definitions of muscle disorder. We also had a similar KCCQ score trajectories when restricting the analysis to only those patients who survived to one-year follow-up.

CONCLUSION

Sarcopenia is prevalent in TAVR patients, especially among men. Higher SMI is associated with more favorable in hospital LOS and 1-year HR-QOL. To achieve optimal TAVR benefits, further study into how body composition influences post TAVR recovery and long-term improvement is warranted.

IMPACT ON CLINICAL PRACTICE

Measuring skeletal muscle mass among TAVR patients can provide insight into the factors that govern post-TAVR recovery and QOL and reveal patients in whom nutrition and exercise interventions could have the most impact.

FIGURE LEGENDS

Figure 1. Computed tomographic analysis of body composition. CT images (A and B) using Slice-O-Matic software, version 5.0 (Tomovision). A brief overview of this analysis can be found here: https://www.youtube.com/watch?v=KJrsQ_dg5mM. Skeletal muscle (RED), visceral adipose tissue (YELLOW), subcutaneous adipose tissue (BLUE), intramuscular adipose tissue (GREEN).

Figure 2. The q-normal plot for multivariable linear regression.

Figure 3. The distribution of SMI [(cm^2)/height (m^2)] based on the gender, which shows the prevalence of sarcopenia by the gender of participant.

Figure 4. In-hospital, 30 day and 1-year health-related quality of life as measured by Kansas City Cardiomyopathy Questionnaire.

Figure 5. In-hospital, 30 day and 1-year health-related quality of life as measured by Kansas City Cardiomyopathy Questionnaire only among patients who survived to one-year follow-up.

Figure 6. Adjusted variable plot that shows the influence of skeletal muscle index on Kansas City Cardiomyopathy Questionnaire at one-year.

Table 1. Baseline demographic, clinical and echocardiographic characteristics by SMI Quartile.

Variable Name[a]	Total (n=346)	Q1 (n = 75)	Q2 (n = 75)	Q3 (n = 75)	Q4 (n = 75)	P-value
Demographics						
Age, years	79 (9)	83 (8)	81 (9)	79 (9)	75 (9)	<0.001
Female gender	171 (49)	56 (75)	42 (56)	30 (40)	22 (29)	<0.001
BMI, Kg/m^2	29 (7)	26 (6)	27 (6)	29 (6)	33 (6)	<0.001
Baseline KCCQ	39 (23)	39 (23)	40 (23)	45 (23)	39 (23)	0.883
Right grip strength, Kg	15 (12)	12 (6)	14 (7)	15 (7)	20 (7)	<0.001
Left grip strength, Kg	13 (8)	10 (5)	12 (6)	14 (6)	16 (6)	<0.001
5-meter walk test, minutes	9.1 (5)	9.3 (3)	9.7 (4)	8.7 (5)	8.5 (6)	0.208
Albumin, mg/dL	3.5 (0.5)	3.5 (0.6)	3.5 (0.4)	3.6 (0.5)	3.6 (0.5)	0.112
Medical History						
Diabetes Mellitus	121 (35)	24 (32)	25 (33)	26 (35)	33 (44)	0.408
Hypertension	298 (86)	61 (81)	64 (85)	66 (88)	66 (88)	0.611
Dyslipidemia	216 (62)	49 (65)	52 (69)	43 (57)	46 (61)	0.460
Atrial fibrillation/Flutter	116 (34)	25 (33)	24 (32)	26 (35)	27 (36)	0.961
Stroke	31 (9)	11 (15)	5 (7)	3 (4)	9 (12)	0.096
PVD	80 (23)	15 (20)	22 (29)	18 (24)	17 (23)	0.601
COPD	52 (17)	6 (8)	21 (28)	15 (20)	10 (13)	0.008
CrCl, mL/min	40 (18)	38 (14)	40 (17)	44 (17)	39 (17)	0.439
Previous PCI	107(31)	13 (17)	26 (35)	24 (32)	28 (37)	0.037
Previous CABG surgery	71 (21)	12 (16)	17 (23)	15 (20)	16 (22)	0.753
Previous Pacemaker	53 (15)	10 (13)	10 (13)	13 (17)	13 (18)	0.807
Echocardiographic Data						
Mean AV Gradient, mmHg	40 (14)	36 (12)	39 (14)	43 (14)	43 (14)	0.001
AV Area, cm^2	0.74 (0.3)	0.75 (0.3)	0.75 (0.2)	0.75 (0.3)	0.73 (0.2)	<0.001
Ejection Fraction, %	54 (14)	55 (13)	54 (15)	53 (15)	55 (15)	0.823
Pulmonary Hypertension [b]	94 (27)	16 (21)	26 (35)	20 (27)	19 (25)	0.312

Mitral Regurgitation [c]	207 (60)	44 (59)	50 (67)	43 (57)	39 (53)	0.374
Tricuspid Regurgitation [c]	231 (67)	51 (68)	52 (69)	45 (60)	50 (67)	0.632
CT-derived Body Composition						
SMI, cm^2/m^2	42.8 (10)	30.5 (3)	38.9 (2)	45.1 (1.9)	56.7 (7)	<0.001
Muscle attenuation, HU	32.9 (17)	28.8 (12)	30.8 (14)	34.2 (17)	37.9 (21)	0.004
Total Adipose Tissue, cm^2	345 (220)	319 (157)	361 (169)	440 (169)	458 (169)	<0.001
STS Predicted Mortality, %	6 (4)	7 (5)	6 (3)	6 (3)	5 (3)	0.072

[a] Estimates are presented as either mean (SD) or percent (%) of total; missing computed-tomography data = 46 patients.
[b] Defined as right ventricular systolic pressure > 50 mmHg.
[c] Defined as either moderate or severe regurgitation.
% may not add to 100 due to rounding.

Abbreviations: BMI = Body Mass Index; KCCQ = Kansas City Cardiomyopathy Questionnaire; PVD=peripheral vascular disease; COPD = Chronic Obstructive Pulmonary Disease; CrCl = Creatinine Clearance; AV = Aortic Valve; CT = Computer Tomography; SMI = Skeletal Muscle Index; PCI = Percutaneous Coronary Intervention; CABG = Coronary Artery Bypass Graft.

Table 2. Simple and multivariable linear regression of the association between quartiles of skeletal mass index (cm^2/m^2) and Kansas City Cardiomyopathy Questionnaire at one-year post transcatheter aortic valve replacement.

KCCQ	β Coefficient	SD	t	P>|t|	95% Confidence Interval	
Model 1[a]						
Q1	Ref	-	-	-	-	-
Q2	-8.318024	6.012576	-1.38	0.169	-20.23725	3.601206
Q3	1.476674	6.163706	0.24	0.811	-10.74215	13.6955
Q4	9.274805	6.951419	1.33	0.185	-4.505573	23.05518
Model 2[b]						
Q1	Ref	-	-	-	-	-
Q2	-4.616871	6.110662	-0.76	0.452	-16.73454	7.500802
Q3	6.983177	6.70859	1.04	0.300	-6.320209	20.28656
Q4	18.81687	8.028083	2.34	0.021	2.896883	34.73686
Model 3[c]						
Q1	Ref	-	-	-	-	-
Q2	-4.176543	6.230354	-0.67	0.504	-16.53298	8.179894
Q3	7.912338	7.113436	1.11	0.269	-6.195484	22.02016
Q4	20.39908	8.952165	2.28	0.025	2.644569	38.15358
Model 4[d]						
Q1	Ref	-	-	-	-	-
Q2	-3.918549	6.247991	-0.63	0.532	-16.31141	8.474312
Q3	8.35313	7.144687	1.17	0.245	-5.818324	22.52458
Q4	22.49985	9.322309	2.41	0.018	4.009091	40.9906
Model 5[e]						
Q1	Ref	-	-	-	-	-
Q2	-.5522827	6.44249	-0.09	0.932	-13.33884	12.23428
Q3	9.85715	7.39358	1.33	0.186	-4.817058	24.53136
Q4	22.66924	9.464635	2.40	0.019	3.884557	41.45392

Abbreviations: KCCQ = Kansas City Cardiomyopathy Questionnaire; SD = standard deviation; Q = quartile.
[a] **Model 1:** simple linear regression; Q1 is the reference group; Q1 is the quartile with lowest skeletal muscle index.
[b] **Model 2:** adjusted for age, gender, and race.
[c] **Model 3:** adjusted for variables in model 2 + body mass index.
[d] **Model 4:** adjusted for variables in model 3 + total adipose tissue.
[e] **Model 5:** adjusted for variables in model 4 + hypertension, dyslipidemia, diabetes, prior stroke.

CHAPTER 4

HEALTHCARE COSTS AMONG OLDER ADULTS WITH CARDIAC ARREST

(Publication citation: Damluji et al. Circ Arrhythm Electrophysiol. 2018 Apr;11(4):e005689)

INTRODUCTION

An estimated 390,000 out-of-hospital cardiac arrests[2] and 200,000 in-hospital cardiac arrests[86] occur annually in the U.S. Although survival to hospital discharge remains low despite considerable efforts (overall: 11% of those treated by EMS personnel),[87] outcomes have improved over the past 10 years compared to prior decades.[88-91] In the Get with the Guidelines-Resuscitation registry, risk-adjusted survival for in-hospital cardiac arrest improved from 13.7% in 2000 to 22.3% in 2009.[89] Similarly, in the Cardiac Arrest Registry to Enhance Survival, risk-adjusted survival rates for out-of-hospital cardiac arrests improved from 5.7% in 2005 to 8.3% in 2012.[90] Improvement in survival could be attributed to the development of an organized concept of post-cardiac arrest care[92], that includes application of several innovative therapies and technologies, including percutaneous coronary intervention (PCI), antiarrhythmic medication, hemodynamic support, therapeutic hypothermia, metabolic stabilization, and ventilator support.[93-95]

While cardiac arrest research has focused on survival, the financial burden of post-cardiac arrest care and its healthcare associated cost is unknown. Moreover, it is unclear whether hospital profiles or utilization of specific therapeutic interventions linked with survival are associated with cost burden. To address these gaps in knowledge, we aimed to estimate the total healthcare cost associated with post-cardiac arrest hospitalizations. We also examined the secular trends of inflation adjusted cost and its association with patient and hospital level characteristics and implementation of certain therapeutic interventions.

METHODS

Data Source

The U.S. Nationwide Inpatient Sample (NIS) is a part of the Healthcare Cost and Utilization Project (HCUP), sponsored by the Agency for Healthcare Research and Quality (AHRQ). The data is publicly available to any researcher for purposes of reproducing the results. NIS is a large all-payer publicly available database of inpatient stays that contains discharge level data from approximately eight million hospitalizations from about 1,000 hospitals annually. NIS selects 20% of all US hospitals, providing a sample that is geographically dispersed and representative of all inpatient admissions in the United States. The sampling methodology of the NIS dataset allows application of sampling weights to calculate national estimates. Clinical and resource-use data are provided for each hospitalization and are coded using the International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] and Current Procedure Terminology (CPT).

Study Population

We used the ICD-9-CM code 427.5 to identify all hospital admissions associated with the principal or secondary diagnosis of cardiac arrest from 2003 to 2012 and included older patient outcomes of either in-hospital death or discharge alive, independent of neurological function. We obtained patient demographics and hospital level data, the latter includes size based on bed numbers (small, medium and large), location/teaching status (rural, urban non-teaching and urban teaching), and geographic region (Northeast, Midwest, South and West). The definition of these designations is further described by HCUP.[96-101] We used the AHRQ comorbidity software to retrieve baseline comorbidities for each patient. We also used ICD-9-CM codes to assess for baseline comorbidities not included in the AHRQ software (Supplementary Table 1). These

included history of myocardial infarction, coronary artery disease, dyslipidemia, and atrial fibrillation. We also assessed the utilization of selected cardiovascular interventions using CPT codes previously reported in the literature (Supplementary Table 2).

Study Endpoint

The primary endpoint of this study was logarithmic transformation of inflation adjusted hospital cost for index hospitalization after cardiac arrest. The NIS collects hospital charges, which is the amount the hospital billed for services. Total hospital charges were converted to hospital costs using HCUP Cost-to-Charge Ratios based on cost information obtained from hospital accounting reports that were collected by the Centers for Medicare and Medicaid Services (CMS). Hospital costs reflects the actual expenses incurred for hospital services, such as wages, supplies, and utility costs. Annual costs were adjusted for inflation by using the consumer price index inflation multiplier released by the US Bureau of Labor with 2012 as the base year.

Statistical analysis

Using survey analysis methods, we used hospital level discharge weights provided by the NIS to estimate the number of hospitalizations following cardiac arrest. We acquired baseline demographics, baseline comorbidities, hospital characteristics and selected cardiovascular interventions. We calculated weighted frequencies and percentages to present categorical variables. We also presented continuous variables as weighted means and standard deviations. We used Poisson regression to assess trend over time. To adjust for hospital clustering, we used mixed effect generalized linear regression to assess the effect of independent predictors of inflation adjusted hospital cost. The variation in cost was reasonably explained by the model (coefficient of determination = 0.569) and procedural variables improved the model fit. All

statistical analyses were performed using SAS version 9.4 (SAS institute Inc., Cary, North Carolina). We considered *p* value of <0.05 as significant and all tests were two sided. To avoid common errors in the study-design, we followed the checklist developed by Khera and Krumholz to adhere to best research practices and appropriate use of this large administrative database (Supplementary Box 1). [102, 103] This study was exempt from full IRB review because it publicly available and without patient identifiers.

RESULTS

We identified 291,792 unique encounters who were admitted for (or developed) cardiac arrest during their index hospitalization from 2003 to 2012. The number of weighted hospital admissions over that period was 1,387,396. The mean age of the cohort was 66 years, 45% were females and 68% were Caucasian (Table 1). Medicare and Medicaid were the primary payer of 72% of these patients, while 20% had private insurance. Approximately 75% of the admissions occurred during weekdays, with one quarter during the weekend. Of these admissions (n=1.387 million), 31% were in the lower 25th percentile of the median household income and 19% were above the 75th percentile. Large hospitals admitted 66% of patients presenting with cardiac arrest and most these admissions were in urban hospital systems. Of these hospitals, 16% were in the Northeast region, 22% in the Midwest, 41% in the South region, and 21% in the Western region.

There was no noticeable change in patient and hospital characteristics across the study period. Of the encounters who presented with cardiac arrest, 18% had dyslipidemia, 24% had diabetes mellitus, and 44% had hypertension (Table 2). Approximately 30% of the patients had coronary artery disease, 5.5% had prior myocardial infarction and 22% had congestive heart failure. The prevalence of dyslipidemia, diabetes mellitus, hypertension, and coronary artery disease significantly increased during the study period. However, the prevalence of congestive

heart failure and valvular heart disease noticeably decreased over time.

Coronary angiography was performed on 15% of patients and coronary angioplasty was performed in 7% (Table 3). There were small, but significant, increase in the use of most cardiovascular procedures, but not for permanent mechanical support devices or AICD. Although therapeutic hypothermia was performed in only 1% of these admissions, the utilization of hypothermia increased over time. Among all hospital admissions, the use of pacemakers and implantable cardioverter defibrillators was 6% and 3%, respectively. Pacemaker implantation in cardiac arrest patients who survived hospital admission was 10.6%. No significant change in the use of these devices was seen over the study period. Survival after cardiac arrest improved over time; however, the mean hospital length remained constant (~ 9 days) (Supplementary Table 3). Hospital charges and inflation adjusted cost significantly increased throughout the study period (Figure 1). Non-survivors had significant increase in hospital charges, but not inflation adjusted cost (Figure 2 and 3).

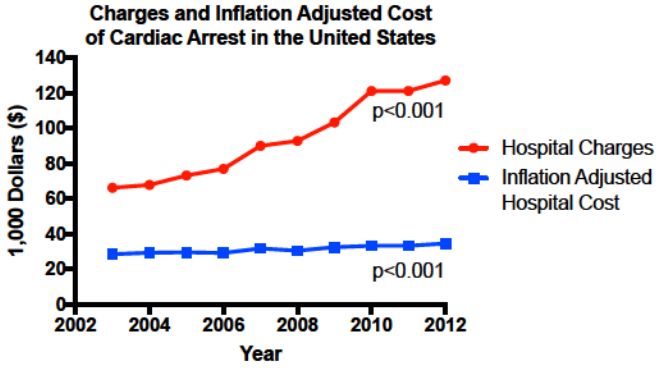


Figure 1. Trends in hospital charge and inflation adjusted hospital cost for patients with sudden cardiac death in the United States NIS, 2003-2012.

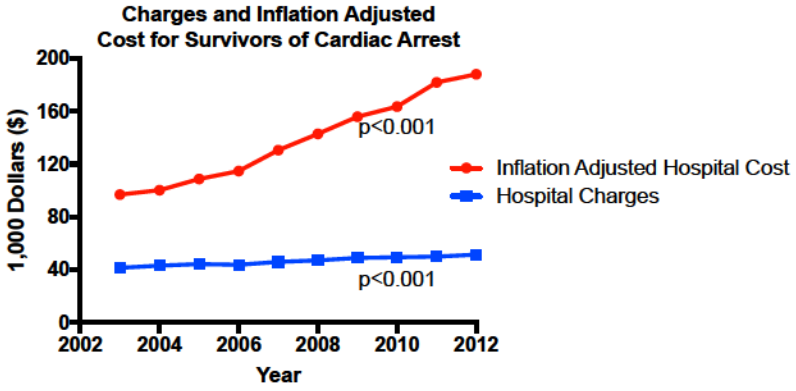


Figure 2. Trends in hospital charge and inflation adjusted hospital cost among patients who survived following sudden cardiac death in the United States NIS, 2003-2012.

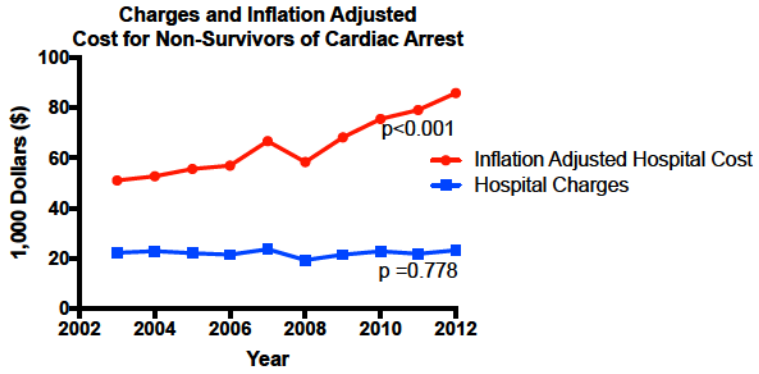


Figure 3. Trends in hospital charge and inflation adjusted hospital cost among patients who died following sudden cardiac death in the United States NIS, 2003-2012.

When stratifying by length of stay, inflation adjusted cost were higher with longer hospital stays (Figure 4). Costs were significantly increased throughout the study period regardless of hospital lengths of stay.

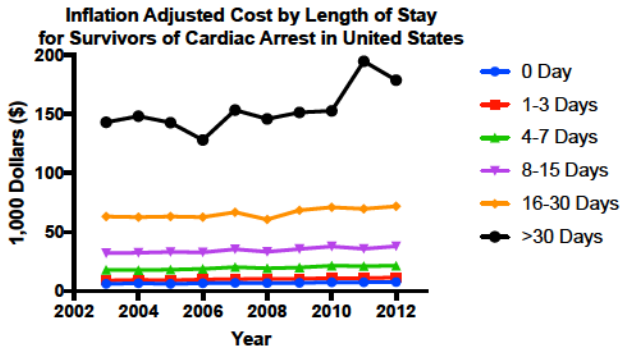


Figure 4. Trends in inflation adjusted cost ($) by hospital length of stay for survivors of cardiac arrest in the United States NIS, 2003-2012.

The inflation adjusted charges and costs had a negatively skewed distribution and logarithmic transformation was used for multivariable analysis, which had a normal bell-curve distribution. After risk adjustment, increasing age, female gender, and Caucasian race were associated with lower rates of inflation adjusted hospital cost (Table 4). Hospitalizations of post-cardiac arrest patients covered by Medicare were associated with higher costs compared to other health insurance coverage. Lengths of stay at hospitals with large and medium bed numbers were associated with greater cost than hospitals with small bed size. Similarly, urban hospital stays cost more than rural counterparts. Compared to hospitals located in the Northeast, Western region hospitals costs were significantly higher while Southern hospitals had significantly lower cost.

Baseline comorbidities had different effects on inflation-adjusted hospital costs. Notably, prior MI, primary diagnosis of MI, and hypertension were associated with lower costs. Conversely, congestive heart failure, atrial fibrillation, electrolyte/fluid imbalances significantly increased cost. Hospitalizations with increased utilization of cardiovascular interventions were associated with significantly higher hospital cost. ECMO, coronary angiography, and ICD and

pacemaker placement were associated with the greatest increase in cost. Of note, patients receiving therapeutic hypothermia had one-fourth increased cost compared to admissions without the utilization of therapeutic hypothermia. Adjusting for patients' demographics, comorbidities, hospital-level characteristics, length of stay, and secular trends, there was an 88% increase in cost ($) for patients who received *any* cardiovascular procedure during index admission, compared to those who did not. The presence of uncomplicated diabetes mellitus and depression were associated with cost savings. When sudden death was restricted to only primary or first secondary diagnoses, the results from the multivariable regression model were similar (Supplementary Table 4).

DISCUSSION

In this study, we analyzed the temporal pattern of healthcare cost for hospitalizations associated with cardiac arrest in the United States from 2003 to 2012. We also presented the effect of patient comorbidity profile, utilization of cardiovascular interventions/devices, and hospital characteristics associated with these admissions on hospital cost. We observed that the inflation adjusted cost associated with hospitalizations in survivors of cardiac arrest consistently increased throughout the study period, regardless of the length of hospital stay. However, hospital cost was stable for those who did not survive the index hospitalization. Patient profiles varied over the study period, and the comorbidities that were associated with greatest increase in cost were history of atrial fibrillation and fluid/electrolyte imbalances. Utilization of cardiovascular interventions and devices remained stable over time and they were consistently associated with significant increase in healthcare cost. We also identified large bed size hospitals, urban teaching hospitals, and Western hospitals as significant contributors to healthcare expenditure.

We observed a rise in hospital costs over the study period. This observation held even after adjusting for length of hospital stay, survival status, and extensive patient and hospital level contributors of cost, which further highlights the economic burden of cardiac arrest. This may be partially explained by several factors. First, the complexity of patients with cardiac arrest and multiple chronic conditions may be associated with higher utilization of hospital resources that we were not able to capture with data available to us in the NIS sample (e.g. utilization of dedicated coronary care units, neuroimaging or renal replacement therapies). Second, the growing adoption of electronic medical records may have increased the accuracy of billing during the later years of the study. Accordingly, this may also have reflected an increase in captured billing and hospital charges.

The patient profile showed increased prevalence of medical comorbidities including conventional cardiovascular disease risk factors such as hypertension, diabetes mellitus, dyslipidemia and obesity. We also observed a decrease in the prevalence of congestive heart disease and valvular heart disease. Despite the changing prevalence of these chronic conditions, it is worth noting that patient comorbidity profile had relatively small effect on hospital cost. In fact, only atrial fibrillation and fluid/electrolyte imbalances were associated with increase in cost over 10%. This may, at least in part, reflect the accumulating experience in management of these chronic conditions as well as the national effort to adhere with therapies associated with improved outcome. This may have decreased hospital length of stay and in turn, associated hospital cost. We also identified utilization of cardiovascular interventions and devices as major contributors to healthcare cost. The increased cost may be attributed to utilization of higher level of care, and specialized personnel to perform these cardiovascular procedures and to operate specialized devices, in addition to the cost of devices themselves. These cardiovascular

interventions and the use of devices may represent reasonable potential for targeted interventions to contain cost, with standardization of care processes and possible regionalization of these services. It is worth noting that our analyses only address healthcare costs associated with the hospitalization and it is reasonable to assume that with increased use of these advanced treatments, downstream cost benefits will be perceived with reduced length of hospitalization, utilization of intermediate facilities, and reduction in readmission.

We also observed noticeable differences in expenditure by hospital characteristics. Larger hospitals, as well as urban teaching hospitals, were associated with higher cost. This may, at least in part, be attributed to the more medically complex patients, socioeconomic mix of the patient population, and the availability of certain advanced treatments in these centers compared to their counterparts. [92] We also observed regional variation in cost with highest resource use in Western hospitals. In a recent national study assessing regional variation of health outcomes of in-hospital cardiac arrest, there was significant differences in the discharge disposition and utilization of post-discharge resources across the U.S.[104] Therefore, regional differences in costs may partly be due to variation in utilization of acute versus post-acute services. It should be noted that the analysis includes a sizable number of patients who had less than one day length of stay. Whether these patients were indeed survivors of cardiac arrest or they were dead on arrival cannot be ascertained.

Our study has several important limitations. First, we used the NIS, which is an administrative claim dataset that depends on ICD-9-CM. Such datasets are prone to coding errors, coding differences across providers and institutions, and change in coding pattern over time. In this study, a potential problem is the inaccuracy of ICD-9 code to identify "true" cardiac arrest patients, or the distinction between out-of-hospital and in-hospital cardiac arrests. Many EMS-

defined cardiac arrest, which would be used to determine 427.5 code for hospital admission, turn out not be cardiac in the first place (i.e. stroke, sepsis, heart failure, or respiratory failure). While the coding may not be optimal, this methodology to identify patients with cardiac arrest has been frequently used in prior studies on cardiac arrest, [88, 105-107] and it has been proposed that more specific coding of cardiac arrest variants be developed for future iterations of ICD coding.[108] Second, a limitation of work such as this is the lack of clinical details on the precise mechanism of the arrest, clinical features prior to the arrest, the details of the responses to cardiac arrest (such as bystander CPR and AED deployment), and the level of neurological and cardiovascular disability associated with the arrest. Clearly, this information is relevant to clinical outcomes data, but the economic burden for society is based on cumulative effects. The latter supports the notion of increasing research support for prediction and prevention of cardiac arrest.[92, 109] For example, in the years 2003-2004 and 2011-2012, the estimated annual inflation adjusted cost post-cardiac arrest in the U.S was $7.3 and $11.1 billion, respectively. The ability of health outcomes research to reduce the incidence of cardiac arrest by 10% (2011-2012) would have saved the healthcare system ~ $1.2 billion. Third, we were not able to ascertain the appropriateness of use of various cardiovascular interventions and devices in patients resuscitated from cardiac arrest, and we were only able to assess the effect of hospital characteristics available to us. As such, we may have missed important systemic patterns associated with cost that may represent valid targets for cost containment interventions. It is possible that other causes for emergency admissions such as those for pneumonia, stroke, sepsis, ST-elevation myocardial infarction, could account for the rising healthcare costs, which was attributed to sudden cardiac arrest in this study. Fourth, because of the large sample size, this study has an enormous statistical power (1-ß), that is able to detect subtle differences in cost. The

interpretation of some of these *statistically significant* results with low strengths of associations may be somewhat challenging. However, patient- or hospital-level characteristics with large strength of association remain important predictor of in-hospital cost after cardiac arrest. Finally, it is also important to note that the study population, which included any inpatient with a ICD-9-CM code of 427.5, did not distinguish between out-of-hospital from in-hospital cardiac arrest. The literature has largely studied these separately and the costs for these events are likely to be substantially different.

In conclusion, hospitalization associated with resuscitated cardiac arrest showed consistent increase in hospital cost over the period of 2003-2012. Utilization of cardiovascular interventions and devices and certain hospital characteristics were the main contributors of rising cost. Post-cardiac arrest hospitalizations represent significant impact burden on healthcare cost. One estimate places the total cost of cardiac arrest in the United States at $33 billion/year,[110] and our data suggests that 17% of that total figure is attributable to index hospitalization post-cardiac arrest with and without survival. Future studies are required to identify targeted interventions best associated with survival outcomes and lowest cost, in addition to supporting the potential economic value of funding research into prediction and prevention of cardiac arrest and sudden cardiac death.[109, 111]

FIGURE LEGENDS

Figure 1. Trends in hospital charge and inflation adjusted hospital cost for patients with sudden cardiac death in the United States NIS, 2003-2012.

Figure 2. Trends in hospital charge and inflation adjusted hospital cost among patients who survived following sudden cardiac death in the United States NIS, 2003-2012.

Figure 3. Trends in hospital charge and inflation adjusted hospital cost among patients who died following sudden cardiac death in the United States NIS, 2003-2012.

Figure 4. Trends in inflation adjusted cost ($) by hospital length of stay for survivors of cardiac arrest in the United States NIS, 2003-2012.

Supplementary Figure 1. Trends in inflation-adjusted log cost ($) by hospital length of stay for survivors of cardiac arrest in the United States NIS, 2003-2012.

Table 1. Demographic and hospital characteristics of patients with cardiac arrest in the United States NIS, 2003-2012.

Variable	Total	2003 - 2004	2005 - 2006	2007 - 2008	2009 - 2010	2011 - 2012	P value*
Number of admissions (Unweighted)	291,792	54,431	53,761	56,047	59,884	67,669	
Number of admissions (Weighted)**	1,387,396	254,460	254,473	265,928	292,098	327,038	
Cardiac arrest as primary diagnosis	5.6	5.9	5.8	5.9	5.5	5.3	
Age, mean (SD), years	65.6 ± 0.2	66.3 ± 0.3	65.7 ± 0.3	65.7 ± 0.3	65.3 ± 0.3	65.3 ± 0.2	0.002
Female	45.4	46.4	46.0	45.4	44.7	44.6	<0.001
Race/Ethnicity, (%)							0.052
Caucasian	68.4	68.3	70.1	68.8	67.8	67.5	
African-American	16.3	16.7	14.5	15.6	16.8	17.2	
Hispanic	9.0	9.4	9.8	8.7	8.6	8.8	
Asian/Pacific Islander	2.7	2.8	2.5	2.8	2.9	2.6	
Native American	0.6	0.3	0.5	0.9	0.7	0.5	
Primary expected payer, (%)							<0.001
Medicare	61.3	63.5	62.2	60.0	59.9	61.3	
Medicaid	10.4	9.6	10.1	9.9	11.0	11.0	
Private insurance	20.3	20.1	20.1	21.7	20.7	19.3	
Self-pay	4.8	4.1	4.7	5.0	5.0	5.2	
No charge	0.4	0.4	0.4	0.6	0.4	0.3	
Other	2.6	2.3	2.5	2.8	2.8	2.7	
Weekend admission, (%)	24.5	23.9	24.5	24.6	24.5	24.9	0.009
Median household income, (%)							0.546
0-25th percentile	31.3	31.5	30.2	31.2	30.9	32.2	
26th - 50th percentile	26.3	27.0	26.0	26.8	26.6	25.2	
51st - 75th percentile	23.4	22.7	24.0	22.7	23.4	24.0	
76th -100th percentile	19.1	18.8	19.8	19.2	19.1	18.6	
Hospital characteristics							

Bed size, (%)							0.612
Small	10.0	10.3	10.3	9.5	9.4	10.4	
Medium	24.0	25.0	25.1	23.9	22.2	24.2	
Large	66.0	64.7	64.5	66.6	68.4	65.4	
Hospital location/teaching status, (%)							0.030
Rural	10.3	12.0	10.6	10.1	10.4	8.9	
Urban non-teaching	42.9	44.1	45.0	44.0	42.3	40.1	
Urban teaching	46.7	43.9	44.4	45.9	47.3	51.0	
Hospital region, (%)							0.999
North east	16.2	16.5	16.0	15.9	15.6	16.7	
Mid west	22.1	21.7	22.2	22.1	22.4	22.3	
South	40.8	40.2	40.7	41.4	40.6	41.1	
West	20.9	21.5	21.2	20.7	21.4	20.0	

Table 1. Demographic and hospital characteristics of patients with cardiac arrest in the United States NIS, 2003-2012.

*p <0.05 were considered significant; *p*-values for linear trends using Poisson regression.
** Statistics, except the first row, were weighted summaries, based on probability sampling methods, so they may approximate national statistics.
***Percent may not add to 100 due to rounding.
*** *Represents % of total population included in the study; ICD-9-CM code 427.5 was used to identify all hospital admissions associated with primary or any secondary diagnoses of cardiac arrest*

Table 2. Clinical characteristics of patients with cardiac arrest in the United States NIS, 2003-2012.

Variable	Total	2003 - 2004	2005 - 2006	2007 - 2008	2009 - 2010	2011 -2012	P value*
Number of admissions (Unweighted)	291,792	54,431	53,761	56,047	59,884	67,669	
Number of admissions (Weighted)	1,387,396	254,460	254,473	265,928	292,098	327,038	
Comorbidities, (%)							
Dyslipidemia	18.4	9.3	11.8	15.8	23.5	28.4	<0.001
CAD	30.1	25.8	25.1	28.3	33.4	36.0	<0.001
Prior MI	5.5	4.3	4.1	4.8	6.4	7.2	<0.001
Atrial fibrillation	23.1	22.5	23.3	20.9	23.0	25.0	<0.001
Alcohol abuse	4.5	4.2	4.7	4.7	4.5	4.5	0.005
Congestive heart failure	22.0	28.5	29.6	21.0	16.0	17.1	<0.001
Chronic pulmonary disease	21.3	22.0	23.2	21.9	19.8	20.1	<0.001
Depression	3.9	2.7	3.2	4.0	4.4	4.7	<0.001
Diabetes mellitus (uncomplicated)	18.8	16.7	16.6	19.3	20.0	20.4	<0.001
Diabetes mellitus (complicated)	5.1	5.1	5.0	5.1	5.0	5.3	0.642
Hypertension	44.3	38.9	41.9	44.6	46.9	48.0	<0.001
Fluid and electrolyte imbalance	43.7	36.0	40.1	43.1	46.4	50.6	<0.001
Obesity	5.8	3.1	3.8	5.3	6.5	9.1	<0.001
Peripheral vascular disease	7.0	6.1	6.0	6.9	7.7	8.2	<0.001
Pulmonary circulation disorder	4.3	3.8	4.1	4.3	4.3	4.7	<0.001
Renal failure (chronic)	19.0	12.7	18.8	20.4	20.3	21.6	<0.001
Valvular heart disease	6.3	9.6	10.5	6.1	3.4	3.4	<0.001
Liver disease	3.2	3.2	3.3	3.1	3.1	3.3	0.368
Primary diagnosis of MI	12.2	14.3	12.7	12.0	11.4	11.0	<0.001

*p <0.05 were considered significant; *p*-values for linear trends.
** Statistics, except the first row, were weighted summaries, based on probability sampling methods, so they may approximate national statistics.
***Percent may not add to 100 due to rounding.
Abbreviations: CAD = Coronary Artery Disease; MI = Myocardial Infarction.

Table 3. Selected interventions of patients with sudden cardiac death in the United States NIS, 2003-2012.

Variable	Total	2003 - 2004	2005 - 2006	2007 - 2008	2009 - 2010	2011 -2012	P value*
Number of admissions (Unweighted)	291,792	54,431	53,761	56,047	59,884	67,669	
Number of admissions (Weighted)	1,387,396	254,460	254,473	265,928	292,098	327,038	
Selected interventions, (%)							
Coronary angiography	15.3	14.0	14.1	15.3	15.7	16.7	<0.001
PTCA	7.3	6.1	6.9	7.6	7.7	8.0	<0.001
Therapeutic hypothermia	1.1	0.0	0.1	0.5	1.5	2.7	<0.001
Short term percutaneous MCS	0.1	0.0 +	0.0	0.0	0.2	0.4	<0.001
Short term non-percutaneous MCS	0.1	0.1 +	0.0	0.1	0.1	0.1	0.040
Permanent MCS	0.1	0.1 +	0.1	0.1	0.1	0.1	0.201
IABP	4.4	3.8	4.3	4.4	4.5	4.8	<0.001
ECMO	0.4	0.2	0.3	0.2	0.4	0.6	<0.001
CIED	8.9	8.5	8.5	9.1	9.2	8.9	0.099
Pacemaker	5.9	5.8	5.6	6.0	6.0	5.9	0.391
AICD	3.3	3.0	3.2	3.4	3.5	3.3	0.038

*p <0.05 were considered significant; *p*-values for linear trends.
** Statistics, except the first row, were weighted summaries, based on probability sampling methods, so they may approximate national statistics.
***Percent may not add to 100 due to rounding.
+ Data from 2003 are not available.
Abbreviations: PTCA = Percutaneous Transluminal Coronary Angioplasty; MCS = Mechanical Circulatory Support; IABP = Itra-aortic Balloon Pump; ECMO = Extracorporeal Membrane Oxygenation; CIED = Cardiovascular Implantable Electronic Device; AICD = Automatic Implantable Cardioverter Defibrillators.

Table 4. Multivariable generalized linear model (GLM) of inflation-adjusted hospital cost in the US NIS database from 2003-2012.

Parameter	Odds Ratio (OR)	P Value*
Age (Unit: 1 year)	0.99	<0.001
Female	0.96	<0.001
Race/Ethnicity		<0.001**
Caucasian	Ref	
African-American	1.08	<0.001
Hispanic	1.10	<0.001
Asian/Pacific Islander	1.11	<0.001
Native American	1.03	0.374
Other	1.07	<0.001
Primary expected payer		<0.001**
Medicare	Ref	
Medicaid	0.93	<0.001
Private insurance	0.98	<0.001
Self-pay	0.89	<0.001
No charge	0.95	0.389
Other	0.88	<0.001
Weekend admission	0.96	<0.001
Median household income		<0.001**
0-25th percentile	Ref	
26th - 50th percentile	1.02	0.001
51st - 75th percentile	1.05	<0.001
76th -100th percentile	1.10	<0.001
Hospital characteristics		
Bed size		<0.001**
Small	Ref	
Medium	1.09	<0.001
Large	1.16	<0.001

Hospital location/teaching status		<0.001**
Rural	Ref	
Urban non teaching	1.18	<0.001
Urban teaching	1.40	<0.001
Hospital region		
North east	Ref	.
Mid west	1.04	0.042
South	0.97	0.191
West	1.29	<0.001
Comorbidities		
Dyslipidemia	1.02	<0.001
CAD	1.00	0.255
Prior MI	0.95	<0.001
Atrial fibrillation	1.11	<0.001
Alcohol abuse	1.03	0.040
Congestive heart failure	1.10	<0.001
Chronic pulmonary disease	1.03	<0.001
Depression	0.88	<0.001
Diabetes mellitus (uncomplicated)	0.95	<0.001
Diabetes mellitus (complicated)	1.01	0.412
Hypertension	0.96	<0.001
Fluid and electrolyte imbalance	1.21	<0.001
Obesity	1.06	<0.001
Peripheral vascular disease	1.06	<0.001
Pulmonary circulation disorder	1.10	<0.001
Renal failure (chronic)	1.04	<0.001
Valvular heart disease	1.03	<0.001
Liver disease	1.06	<0.001
Primary diagnosis of MI	0.93	<0.001
Selected interventions		
Coronary angiography	1.43	<0.001

PTCA	1.26	<0.001
Therapeutic hypothermia	1.28	<0.001
IABP	1.50	<0.001
ECMO	2.38	<0.001
AICD	1.83	<0.001
Pacemaker	1.31	<0.001
Length of stay (Unit: 1 day)	1.05	<0.001
Death	0.73	<0.001
Year		<0.001**
2003	Ref	
2004	1.03	0.152
2005	1.03	0.244
2006	1.04	0.047
2007	1.09	<0.001
2008	1.08	<0.001
2009	1.11	<0.001
2010	1.14	<0.001
2011	1.11	<0.001
2012	1.12	<0.001

*p <0.05
**Represents *p*-value for overall category
***Generalized linear model, family (binomial), link (logit) was used to estimate the difference in log odds of cost on covariates included in the model.
***Missing cost/charge data was 0.199%.
Abbreviations: CAD = Coronary Artery Disease; MI= Myocardial Infarction; PTCA = Percutaneous Transluminal Coronary Angioplasty; IABP = Intra-aortic Balloon Pump; ECMO = Extracorporeal Membrane Oxygenation; AICD = Automatic Implantable Cardioverter Defibrillators.

CHAPTER 5

PERCUTANEOUS CORONARY INTERVENTION IN OLDER ADULTS WITH ST-ELEVATION MYOCARDIAL INFARCTION AND CARDIOGENIC SHOCK

(Publication citation: Damluji A et al. *J Am Coll Cardiol*. 2019 Apr 23;73(15):1890-1900)

INTRODUCTION

The population of older adults is rapidly expanding and is in fact the fastest growing sector of the United States census [6, 112]. Although life expectancy is increasing, and there have been significant therapeutic advances, the burden of cardiovascular disease among older adults remains high. Older patients ≥75 years of age constitute 14-28% of all patients with ST-segment-elevation myocardial infarction (STEMI)—an illness that is among those most associated with death and disability [46, 113-115]. Among older adults with STEMI, more than 10% will develop cardiogenic shock, defined as the presence of hypotension and hypoperfusion—a condition associated with a mortality rate as high as 79% [46].

The two reports from "The SHould we emergently revascularize Occluded Coronaries in cardiogenic shocK?" (SHOCK) Trial failed to find a significant benefit of early revascularization for older patients ≥75 years of age, contrasting with the situation in younger adults [116, 117]. However, a follow-up study from the SHOCK TRIAL Registry, using a larger sample size than the original clinical trial, revealed that PCI in older patients was indeed associated with improved survival, reducing the estimated hospital mortality to 48% [118]. Following these publications, the 2013 American College of Cardiology Foundation (ACCF)/ American Heart Association (AHA) Guideline for the Management of STEMI did not exclude older adults with cardiogenic shock from early revascularization. Consideration of risk factors (including the presence of frailty, multimorbidity, and life expectancy) was advised in decision making about this treatment [119].

Older age is associated with lower rates of early surgical and percutaneous revascularization rates, and higher in-hospital mortality, when compared with younger patients. These figures are based on small-sized studies: National estimates on the use of percutaneous coronary intervention (PCI) during hospital admission in older patients with STEMI and cardiogenic shock have not been examined. Furthermore, the influence of PCI on in-hospital mortality in older adults with STEMI and cardiogenic shock remains controversial [120]. In our present study, we aimed to exploit nationally representative data to: (1) evaluate the rate of utilization of PCI in older adult patients ≥75 years of age with STEMI and cardiogenic shock; and (2) examine the influence of PCI on in-hospital mortality in older patients since the publication of the SHOCK Trial.

METHODS

The National Inpatient Sample (NIS) contains all discharge data from an approximate 20% stratified sample of hospitals in the United States, excluding rehabilitation and long-term acute care facilities. It is part of the Healthcare Quality and Utilization Project (HCUP), which is sponsored by the Agency for Healthcare Research and Quality (AHRQ) [121]. Data are used to identify, track, and analyze national trends in healthcare utilization, access and disparity, and develop measures to improve quality of care. Each individual hospitalization is de-identified and maintained as a unique entry with one primary discharge diagnosis and up to 25 secondary diagnoses. Annual data quality assessments are performed to assure the internal validity of the database. Estimates from the NIS are compared to the American Hospital Association Annual Survey Database, the National Hospital Discharge Survey from the National Center for Health Statistics, and the MedPAR inpatient database from Centers of Medicare and Medicaid.[122] Reports describing these comparisons are published in the NIS website[123] and show that, in most

respects, the data from the NIS resemble the data from typical hospitals in the American Hospital Association. All NIS and National Hospital Discharge Survey estimates agree in overall and regional comparisons, and NIS Medicare measures are consistent with MedPar statistics [124] These reports strengthen the external validity of NIS database. Data on baseline demographics, insurance status, comorbidities, hospital outcome, and length of stay were available in the reports for analysis. Ascertainment for the primary disposition was performed for each encounter and reported as either discharged routinely, against medical advice, transferred to another health care facility, or died. To ensure that the results were accurate, we verified the data against the HCUP standards, available from the HCUP website (http://www.hcupnet.ahrq.gov).

All adult patients ≥ 75 years of age who experienced STEMI and cardiogenic shock during an index hospitalization occurring between 1999 and 2013 were included in our analysis. In order to minimize bias as a result of referral to a PCI-site from non-PCI capable hospital, we only included patients who were admitted from the Emergency Department. Patients who were not admitted to the hospital in whom a decision was made to go for PCI but died on the way to the catheterization laboratory or died while waiting for an available catheterization laboratory in the emergency department were excluded by design of the NIS. STEMI was identified using International Classification of Diseases, 9th Revision, codes (ICD-9) diagnoses codes 410.1x, 410.2x, 410.3x, 410.4x, 410.5x, 410.6x, and 410.8x as a primary or as *any* secondary diagnosis. Cardiogenic shock was identified as an event occurring during the same hospitalization as STEMI, using the ICD-9 of 785.51, and PCI was identified using ICD-9-CM procedure codes of 36.01 to 36.07, 36.09, or 0.66 at any time during the hospitalization (13). As such, PCI could have been performed as either early or late (semi-elective) in relation to hospital admission date.[122] Bleeding was identified using ICD-9-CM diagnosis codes: 430 to 432, 578.X, 719.1X,

423.0, 599.7, 626.2, 626.6, 626.8, 627.0, 627.1, 786.3, 784.7, or 459.0.[125] Death during index hospitalization was the primary outcome of this study. Hospitals enrolled in the program report mortality data as a quality indicator to AHRQ in order to measure and track clinical performance and outcomes. Ascertainment for the primary disposition was performed for each encounter and reported as either discharged routinely, against medical advice, transferred to another health care facility, or died. Comorbid diagnoses such as hypertension, diabetes mellitus with or without complications, obesity, valvular heart disease, peripheral vascular disease, pulmonary circulation disease, chronic obstructive pulmonary disease, renal failure, liver failure, coagulopathy, weight loss, fluid and electrolyte disorder, chronic blood loss anemia and alcohol abuse were pre-identified according to AHRQ definitions. [123].

Statistical analysis

Baseline demographics, comorbidities, hospital characteristics, and inpatient outcomes were compared for older adults ≥ 75 years of age who were treated with versus without PCI. For years 1999 to 2013, we used NIS discharge weights to produce discharge-level estimates for the diagnosis of STEMI and cardiogenic shock.[123] We did not use hospital-level estimates in this analysis because of the new NIS data structure redesign beginning in 2012 thereafter. For years prior to 2012, trend weights were used to create national estimates that are consistent with the data after 2012.[123] Weighted frequencies and percentages were calculated for categorical variables, and weighted means and standard deviations for continuous variables. Annual trends in PCI and mortality rates were assessed, based on discharge weights, using linear regression with calendar year as an independent variable.

To address confounding by comorbidity, we used methods introduced by Rosenbaum and Rubin utilizing propensity scores in observational studies.[126] The propensity score is the

probability of treatment (PCI) given in terms of potentially confounding variables (here denoted by X_2–X_p):

$$Propensity\ Score = \Pr(PCI|X_2 - X_p)$$

Rosenbaum and Rubin showed that, when comparing persons with the same propensity score, the distributions of confounding variables are the same among all treatment groups. This is the "balancing" property: It implies, in an idealized sense, that analyses that compare persons with like propensity scores eliminate confounding by the variables used to construct the scores. Using logistic regression, propensity scores were estimated by modeling the associations of the following covariates with treatment by PCI: gender, race, diabetes mellitus, hypertension, obesity, perivascular vascular disease, pulmonary circulation disorder, chronic lung disease, renal failure, liver disease, coagulopathy, weight loss, electrolyte and fluid disorder, blood loss, and alcohol abuse.

Propensity score distributions were similar between the PCI vs. non-PCI groups (**Figure 1**), indicating control for confounding to be possible across the entire range of the propensity score. The balancing properties of the covariates distribution between the PCI and non-PCI group were assessed within each subclassification of the propensity score, and the balancing properties were

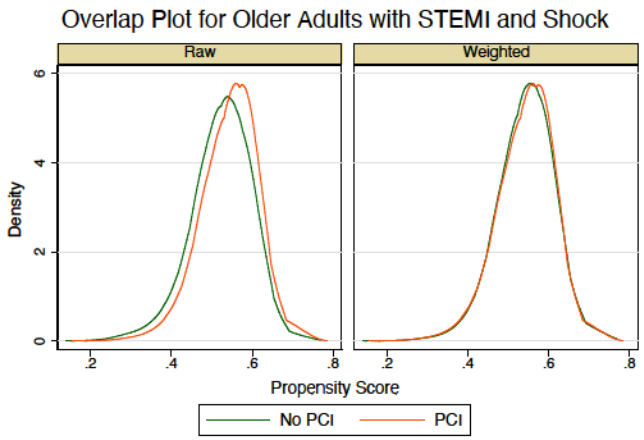


Figure 1. Overlap plot for propensity score. Overlap plot for the estimated density of the propensity scores among older adults presenting with ST-elevation myocardial infarction (STEMI) and cardiogenic shock treated with versus without percutaneous coronary intervention (PCI) in (A) raw data (B) weighted data.

satisfied.[127] We observed the log-transformed probability of death to decrease sharply after an estimated propensity score of 0.4 for being exposed to treatment with PCI, however . For these reasons, we chose to model the propensity score in two ways. First, as described by Rubin and colleagues[128], the propensity score for receiving treatment with PCI was subclassified into five groups (i.e. quintiles), and analyses comparing mortality by treatment status were performed within each group. Second, the propensity score was treated as continuous variable in a regression of mortality on treatment, with a spline term at a propensity score of 0.4.

To compare older adults with STEMI and cardiogenic shock by treatment with PCI, we performed a logistic regression to examine the association of hospital mortality with treatment by PCI (versus non-PCI) within each of the five quintiles of the propensity score. We generated the Mantel-Haenszel odds ratio estimate for in hospital mortality controlling for propensity block for those treated with versus without PCI. We failed to reject the test for homogeneity of odds ratio, indicating a good model fit ($p = 0.508$). Mindful of tradeoffs between accuracy and precision when applying weighting in regression analyses, we estimated the association between treatment with PCI and in hospital mortality within propensity score subclassifications using both unweighted and discharge-weighted analyses. Because the parameters between the unweighted and the weighted data were similar, we have elected to present the estimates derived from the unweighted sample as they are generally more efficient.[129] Because ischemic and bleeding risk coexist in this high-risk cohort, and it might be influenced by PCI and consequent antithrombotic therapies, we performed a sensitivity analysis including bleeding events during hospital admission in the propensity score models. In order to address immortal-time bias that could favor survival for the PCI group, we performed 2 additional sensitivity analyses. First, we repeated the propensity score analysis after excluding patients who died within the first 48 hours of hospital

admission. Second, we repeated the propensity score analysis of PCI on hospital mortality after excluding patients who died within the first week of hospital admission.

We then aimed to estimate the association between treatment with PCI and in-hospital mortality by United States census bureau regions. Accordingly, we performed region-specific logistic regression analyses. We presented the estimated treatment effects in older adults with STEMI and cardiogenic shock using survey analysis methods. We reproduced the results using inverse probability treatment weighting, which is defined as the inverse of the estimated propensity score for PCI patients and the inverse of one minus the estimated propensity score for non-PCI patients [127]. All statistical analyses were performed using STATA version 15 MP (Stata-Corp, College Station, TX). We considered p value of <0.05 as significant, and all tests were two sided. To avoid common errors in the study-design, we followed a checklist that was developed to highlight best research practices and appropriate use of this large administrative database [102, 103]. This study was exempt from full IRB review because it is publicly available and without patient identifiers.

RESULTS

We identified 64,766 unique encounters who were admitted with STEMI and cardiogenic shock from 1999 to 2013. Using survey analysis methods, the number of weighted hospital admissions nationally over the same period was estimated as 317,728 encounters, of whom 111,901 (35%) were for patients age 75 years or older. The baseline characteristics for older adults with STEMI and cardiogenic shock were derived from weighted data and presented in **Table 1**. Among these older adults, those who did not receive PCI were older in age and more likely to be female and belong to an underrepresented minority. The differences in the prevalence of most cardiovascular risk factors and non-cardiovascular diagnoses achieved

statistical significance, commensurate with the very large sample size, but a difference of ~ 20% or more was observed for obesity (higher prevalence for those PCI-treated) and valvular heart disease and congestive heart failure (lower prevalence for those PCI-treated). Older patients who received PCI had significantly lower disease burden compared to those who did not receive PCI as estimated by the Charlson comorbidity index. Medicare was the primary payer for more than 90% of older patients. Most patients were cared for by large hospital systems in urban locations (Table 1). Older adults who were not treated with PCI had shorter mean hospital length of stay, lower mean total hospital charges, and higher crude mortality rate (**Table 1**). The proportion of older patients admitted with STEMI and cardiogenic shock decreased over time following the SHOCK trial, and moreover, this decline in hospital admissions was observed in all regions of United States (Figure 2). While there is a consistent decline in rates of STEMI and cardiogenic shock in older patients, the rates of utilization of PCI in STEMI and cardiogenic shock since the publication of the SHOCK trial results increased progressively during

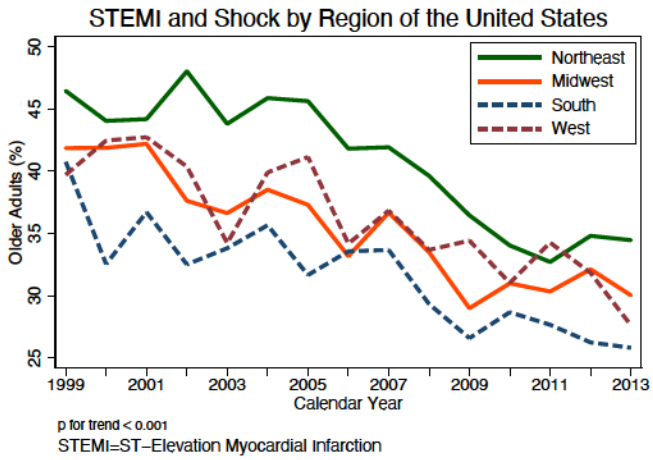
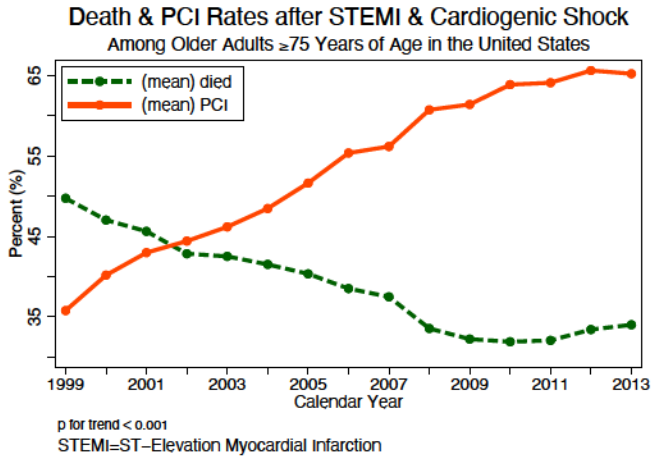


Figure 2. Older adults with ST-elevation myocardial infarct (STEMI) and cardiogenic shock by regions of the United States over the study period (1999-2013). Note that the percent older adults (y-axis) is calculated as the number of admissions for older patients divided by the total number of admissions for STEMI and cardiogenic shock by region of the U.S. overtime.

the study period, and this was paralleled by a substantial reduction in the crude unadjusted mortality rates (**Central Illustration**). The association of PCI with mortality in older adults with STEMI and cardiogenic shock is presented in Table 2, by propensity score subclass for unweighted analyses. In both unweighted and discharge-weighted analyses there was consistent survival benefit of roughly 50% decreased mortality odds associated with treatment by PCI in all subclassification of the propensity score (unweighted Mantel-Haenszel OR: 0.48, 95% CI 0.45-0.51; no weighted estimate differed from its unweighted counterpart by more than 0.02 in any propensity score stratum). When the propensity score was treated as continuous variable with a spline term at 0.4, there remained significant improvement in mortality in the PCI group adjusting for the propensity score (OR 0.47, CI 0.44-0.50). The improvement in mortality in the PCI group was also observed when the propensity score was treated a continuous variable without a spline term. The overall mean probability of death in older patients after STEMI and cardiogenic shock by treatment status with PCI adjusted for the propensity score is presented in Figure 3. When



Central Illustration. Percutaneous coronary intervention in older adults with ST-elevation myocardial infarction and cardiogenic shock (1999-2013). The rates of utilization of percutaneous coronary intervention (PCI) in older patients with ST-elevation myocardial infarction (STEMI) and cardiogenic shock since the publication of the SHOCK trial results between 1999 and 2013.

discharge weights were applied to the logistic regression, there was a consistent survival benefit associated with treatment by PCI in the 5-propensity score subclassification (Table 3). Of the total study population, 5,455 (8.4%) patients had a bleeding event during the hospital encounter. The overall mortality rate in the PCI group was higher if the patient had a bleeding event (unadjusted mortality in PCI group: no-bleeding 29% vs. bleeding 34%, *p*-value <0.001). In order to account for the excess death observed in the bleeding group, an additional sensitivity analysis was performed to include bleeding in the model. PCI remained significant associated with survival within each quintile of the propensity score. To address immortal-time bias that could favor survival for the PCI group, we excluded patients who died within the first 48 hours of hospital admission. After the exclusion, there was a similar and consistent survival benefit associated with treatment with PCI within each subclassification of the propensity score. Similar effects were observed if patients who died within the first week of admission were excluded. Similar survival benefits associated with PCI were observed across the four regions of the United States census bureau (Table 4; unweighted analyses adjusting for

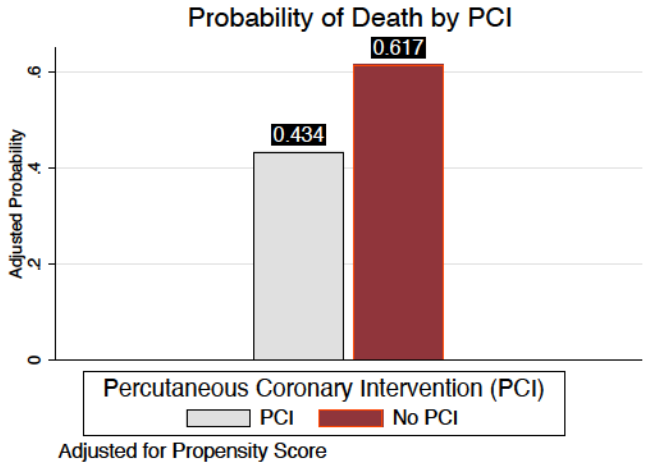


Figure 3. Adjusted probability of death in older patients with ST-elevation myocardial infarction (STEMI) and cardiogenic shock by treatment with percutaneous coronary intervention (PCI). The probability of death was adjusted for hypertension, diabetes mellitus with or without

propensity score with spline).

DISCUSSION

This large and contemporary observational study described the current utilization of early revascularizations with PCI in older adults with STEMI and cardiogenic shock in the United States. To our knowledge, this study is the largest to examine clinical outcomes for this older population. We evaluated the treatment effect associated with PCI for patients aged 75 years or older admitted to the hospital with STEMI and cardiogenic shock from 1999 to 2013. The major findings of this study are: (1) Older adults who were not treated with PCI had worse comorbidity burden, shorter hospital length of stay, and higher crude mortality rates after STEMI and cardiogenic shock than those treated with PCI; (2) In the United States, the rate of utilization of PCI for older adults increased significantly since the publication of the SHOCK trial; (3) The crude mortality rates after STEMI and cardiogenic shock for older adults improved over the past decade; (4) Using propensity score methods, treatment with PCI appears to be associated with significant improvement in hospital mortality in older patients.

Recent evidence suggests that there has been an increase in utilization of PCI in older adults with ACS, including those with ST-elevation myocardial infarction. [130, 131] For example, in a large registry, the proportion of adults 80 years or older with STEMI who underwent PCI increased from 9.2% in 2001 to 31.2% in 2010. [132] These trends were similar in the United States and Europe. [133-135] The Acute Myocardial Infarction in Switzerland Plus Registry examined hospital admission in older adults (≥75 years of age) with STEMI and shock from 1997 to 2006. [136] The rate of utilization of PCI or thrombolysis was significantly lower in older adults (older adults: 15.1% vs. younger adults 39.7%) but there was a parallel decrease in mortality rate between 1997 and 2006 from 82.8% to 75.6%. Dzavik and colleagues reported results from the

SHOCK registry and showed that early revascularization resulted in a decrease in in-hospital mortality in older adults with STEMI and cardiogenic shock (early revascularization: 48% vs. late or no revascularization: 79%; relative risk 0.45, p=0.001). [137] While the SHOCK trial showed little or no benefit of early revascularization on mortality in adults age 75 years or older, our study shows that the rates of utilization of PCI in older patients with STEMI and cardiogenic shock is rising. This rise has been paralleled by an equivalent decline in unadjusted mortality rates over the study period. While it is plausible that older adults in more recent years are healthier in later years than those in earlier years, improvements in optimal medical therapies and revascularization strategies can explain higher longevity after cardiovascular illness in more recent years.

Despite the improvement in survival associated with early revascularization as reported by these studies[136, 137], many older adults with multiple chronic conditions, worse disease burden, and possibly limited life expectancy as assessed by interventional cardiologists, do not receive early revascularization with PCI.[138] This study was aimed to address this important selection bias by implementing different methods of propensity matching to understand the influence of early revascularization adjusting for demographic, clinical, and hospital characteristics between older adults with early revascularization versus those without revascularization. Independent of the propensity methods used, early revascularization in the setting of cardiogenic shock and STEMI was associated with a reduction of in-hospital mortality risk (Absolute Risk Reduction = 21%; Relative Risk Reduction = 41%).

While the mortality rate in older patients is improving since the publication of the SHOCK trial, complexities in management of older adults with STEMI and cardiogenic shock represent a major challenge. The aging process is associated with worse kidney function,

presence of comorbidities, frailty, and predilection to medication induced adverse events. These complexities result in delays in care, and often many older adults with STEMI are not offered early revascularization when their presentations are complicated by cardiogenic shock.[138] In 2007, Alexander and colleagues reviewed the scientific evidence and published an AHA Scientific Statement on Acute Coronary Care in the Elderly focusing on STEMI. Based on the available evidence at the time, it was recommended that older adults with shock selected based on clinical judgement may derive benefit from early revascularization. [46] Clinical judgement remains a critical aspect of acute cardiovascular care in older patients. However, we also believe that the result of this study provides additional important evidence that PCI with early revascularization may be associated with improved mortality risk in older patients, but the risk is higher in older patients with underlying multiple coexisting conditions or high weight of disease burden.

Strengths and Limitations

There are important strengths to this study. First, this study utilized a large nationally representative sample of older patients with STEMI and cardiogenic shock since the publication of the SHOCK trial results. Second, this study used a rigorous application of a state of the art methodology to address measured confounding associated with invasive vs. non-invasive therapies. Third, this study fills an important gap in knowledge regarding the benefit of invasive therapy among older adults presenting with STEMI and cardiogenic shock with varying degree of multimorbidity.

There are several limitations for this study. First, NIS is an administrative dataset with comorbidities identified as ICD-9-CM codes. Such datasets are prone to coding errors by providers or institutions (e.g. over coding of cardiogenic shock by providers and coders). While

this is an important inherent limitation associated with research using administrative datasets, this method in identifying patients with STEMI and shock has been used in prior research. [139] Further, it allows studying large populations with a specific diagnosis or a procedure with the aim to (1) improve healthcare delivery and utilization; (2) identify and eventually eliminate inequalities of care in vulnerable subgroups of the community; (3) maximize benefit associated with pharmacotherapy or invasive care for patients. Second, older adults with STEMI and cardiogenic shock are a high-risk patient population for short term mortality. Operators may identify older patients who are not suitable for early revascularization at the time of STEMI and shock (i.e. active bleeding, very limited life expectancy with end-stage disease process, severe neurocognitive decline), and include patients' preferences or advance directives in decision making process. While these variables are difficult to capture in administrative database and represent a limitation in this study, the large sample size along with the application of different propensity score methods attempt to make the two groups of older adults with and without PCI more comparable. In fact, a comparison between propensity score in older patients treated with and without PCI showed significant overlap in propensity to treatment with PCI (Figure 1). Third, the temporal relationship between the occurrence of STEMI and cardiogenic shock and the decision to attempt PCI was not available in this claims-based dataset. Although this is an important limitation, most cases of cardiogenic shock in older adults occur secondary to STEMI and not as a result of PCI. As such, the bias of cardiogenic shock secondary to failed PCI procedure is minimal, but the key temporal relationship lies between the occurrence of STEMI and cardiogenic shock on the one hand and the decision to perform PCI. The influence of "immortal-time" bias occurs at the beginning of the trajectory and at the end. Patients who don't make it to the cardiac catheterization laboratory because they die while waiting for PCI can

potentially be counted in the no-PCI group. The patients who receive late (semi-elective) PCI (i.e. > 12 hours of presentation) after they have survived their medically treated episode of cardiogenic shock could have been counted in the PCI group. These patients, by definition, are associated with survival, because it can only be performed in patients who have already survived the episode of cardiogenic shock. In randomized trials, survivors with late PCI could be counted as survivors in the 'no-PCI' group (i.e. intention to treat analysis). In observational studies, these fatalities can be misclassified as having occurred in the PCI group. However, we tried to mitigate this problem by the sensitivity analysis excluding early (< 48 hours & < 7 days) fatalities. While this bias may not have been completely eliminated, most patients with STEMI complicated by cardiogenic shock receive PCI early after diagnosis to adhere with national quality metrics of door-to-balloon time as set by the ACC/AHA/ESC. For example, in the National Cardiovascular Data Registry's (NCDR's) Acute Coronary Treatment and Intervention Outcomes Network Registry-Get With The Guidelines (ACTION Registry-GWTG) national database, 11,406 patients presenting with STEMI and cardiogenic shock were studied. [140] Of the 92.3% who underwent coronary angiography, 79% underwent PCI (median [IQR] age of population was 65 [56-76] years). The median time from hospital arrival to PCI for STEMI patients with cardiogenic shock was 1.2 hours (~ 72 minutes). In another cohort from Europe of 1,333 consecutive patients with STEMI complicated by cardiogenic shock (mean age = 63.9 ± 12.6 years), the mean (SD) time between symptom onset to start of PCI was 272 ± 267 mins (~ 4.5 ± 4.45 hours).[141] Two standard deviations of the time between symptom onset to the start of PCI were < 12 hours (i.e. > 95 % of the cohort receive PCI in < 12 hours from onset of symptoms). While this limitation is important, the design of the NIS excluded patients who did not survive into hospital admission from both the PCI and no-PCI groups. Because of this issue of immortal-

time bias, the observed benefit of 'PCI during hospitalization' (Odds Ratio = 0.49) could potentially be exaggerated. Although the design of the NIS and the exclusion of early fatalities did not eliminate the bias completely, the benefit of PCI cannot be explained only by misclassification of fatalities that occurred in patients waiting for PCI, especially that most patients in "real world" clinical practice receive PCI early after diagnosis.

While other analytic methods were proposed to address "immortal-time" bias in observational studies, they are not free of limitations.[142-144] Randomization to early vs. late PCI can address "immortal-time" bias, but in the context of STEMI and cardiogenic shock, a condition with high mortality rate, randomization can be challenged by ethical consideration.[145] Because we used a claims-based dataset to identify diagnoses and procedures, the optimal timing of intervention (early versus late), measures of severity of shock, and burden of illness, revascularization technology and related pharmacotherapy were not available to us for analysis. However, the results of this study remain informative from public health perspective to highlight the influence of PCI on hospital mortality in geriatric population with STEMI and cardiogenic shock.

CONCLUSION

Given that most older adults have atypical symptoms, varying degrees of coexisting disease burden, and higher risks of mechanical complications, they are more likely to be denied early revascularization or have delays in reperfusion therapy.[138] In a landmark manuscript endorsed by ACC, AHA, American Geriatric Society, Rich and colleagues identified critical *knowledge gaps* in cardiovascular care of the older adult populations. [146] The panel of experts pointed out that studies are needed to evaluate the benefits of invasive care in older patients with

ACS (i.e. STEMI and non-STEMI) in the setting of multimorbidity and varying degrees of disease burden. [146] We believe that this study fills important gaps in addressing the influence of invasive care for older adults with multimorbidity. From a public health perspective, early revascularization should not be denied for older adults in the absence of absolute contraindications (i.e. active bleeding, severe neurocognitive decline, and very limited life expectancy with end-stage disease processes).

CLINICAL PERSPECTIVE

Competency in Medical Knowledge: In the United States, the rate of utilization of PCI for older adults presenting with STEMI and cardiogenic shock increased significantly since the publication of the SHOCK trial.

Competency in Patient Care: The crude mortality rates after STEMI and cardiogenic shock for older adults improved over the past decade and treatment with PCI in older patients with STEMI and cardiogenic shock appears to be associated with significant improvement in hospital mortality in older patients. From a public health perspective, early revascularization should not be denied for older adults based on age alone.

FIGURE LEGENDS

Figure 1. Overlap plot for propensity score. Overlap plot for the estimated density of the propensity scores among older adults presenting with ST-elevation myocardial infarction (STEMI) and cardiogenic shock treated with versus without percutaneous coronary intervention (PCI) in (A) raw data (B) weighted data.

Figure 2. Older adults with ST-elevation myocardial infarct (STEMI) and cardiogenic shock by regions of the United States over the study period (1999-2013). Note that the percent older adults (y-axis) is calculated as the number of admissions for older patients divided by the total number of admissions for STEMI and cardiogenic shock by region of the U.S. overtime.

Central Illustration. Percutaneous coronary intervention in older adults with ST-elevation myocardial infarction and cardiogenic shock (1999-2013). The rates of utilization of percutaneous coronary intervention (PCI) in older patients with ST-elevation myocardial infarction (STEMI) and cardiogenic shock since the publication of the SHOCK trial results between 1999 and 2013.

Figure 3. Adjusted probability of death in older patients with ST-elevation myocardial infarction (STEMI) and cardiogenic shock by treatment with percutaneous coronary intervention (PCI). The probability of death was adjusted for hypertension, diabetes mellitus with or without complications, obesity, valvular heart disease, peripheral vascular disease, pulmonary circulation disease, chronic obstructive pulmonary disease, renal failure, liver failure, coagulopathy, weight loss, fluid and electrolyte disorder, chronic blood loss anemia and alcohol abuse.

Table 1. Baseline characteristics for older adults with ST elevation myocardial infarction and cardiogenic shock.

Variable	Overall	No PCI	PCI	*p*-value*
Unweight No. (%)	22,774 (100)	13,165 (57.8)	9,609 (42.2)	-
Weighted No. (%)	111,901 (100)	64,682 (57.8)	47,213 (42.2)	-
Age, mean ±SE	82.0 ± 0.04	82.6 ± 0.6	81.2 ± 0.05	<0.001
Female (%)	53.5	54.5	52.2	<0.001
Minority (non-white) (%)	16.1	16.2	16.0	0.739
Cardiovascular Risk Factors (%)				
Hypertension	45.8	43.9	46.9	<0.001
Diabetes without Chronic Complications	18.8	19.2	18.2	0.047
Obesity	2.0	1.7	2.5	<0.001
Valvular Heart Disease	13.0	15.4	9.7	<0.001
Peripheral Vascular Disease	8.7	8.9	8.7	0.308
Congestive Heart Failure	37.7	43.7	29.6	<0.001
Non-Cardiovascular Diagnoses (%)				
Chronic Pulmonary Disease	17.2	17.7	16.4	0.014
Renal Failure	13.3	13.7	12.8	0.045
Coagulopathy	9.1	8.4	9.9	<0.001
Weight Loss	4.4	4.5	4.3	0.556
Fluid and Electrolytes Disorder	35.2	36.1	33.9	0.001
Chronic Blood Loss Anemia	1.7	1.5	2.0	0.004
Alcohol Abuse	0.7	0.7	0.8	0.446
No. of Chronic Conditions, mean ±SE	7.7 ± 0.05	7.7 ± 0.07	7.7 ± 0.07	0.729
Charlson comorbidity index, mean ±SE	2.8 (1.6)	2.9 (1.6)	2.7 (1.6)	<0.001
Expected Primary Payer, (%)				0.076
Medicare	91	91	91	
Medicaid	1.3	1.3	1.3	
Private	6	6	7	
Self-pay, no charge, other	1.7	1.7	0.7	
Hospital Characteristics				
Hospital Size (%)				<0.001
Small	9	11	6	

Medium	23	25	20	
Large	68	65	73	
Hospital Location (%)				<0.001
Rural	10	13	6	
Urban	9	9	9	
Hospital Region, (%)				<0.001
Northeast	22	25	18	
Midwest/North Central	23	21	26	
South	34	33	35	
West	20	20	22	
Length of stay, mean ±SE	8.25 ± 0.11	7.77 ± 0.14	8.91 ± 0.12	<0.001
Total Charges, dollars, mean ±SE	88,211± 1,997	69,844 ± 1,971	114,990 ± 2,639	<0.001
Disposition of Patient (%)				<0.001
Home	12	6	19	
Facility/other	34	32	38	
Died	54	62	43	

Abbreviations: CHF = congestive heart failure; No = number.
% may not add to 100 because of rounding; * Significance defined as $p < 0.05$.

Table 2. Estimated treatment effects in older adults comparing percutaneous coronary intervention (PCI) to no PCI on the risk of in hospital mortality after ST-elevation myocardial infarction and cardiogenic shock by propensity score subclass.

Propensity Score Subclass[1]	Treatment	N (%)	Events (%)	OR	95% CI	p-value
1	PCI	1,263 (36)	560 (44)	0.44	0.38 – 0.50	<0.001
	No PCI	2,283 (64)	1,473 (65)	–	–	–
2	PCI	958 (40)	444 (46)	0.53	0.45 – 0.62	<0.001
	No PCI	1,441 (60)	894 (62)	–	–	–
3	PCI	1,627 (41)	748 (46)	0.50	0.44 – 0.57	<0.001
	No PCI	2,374 (59)	1,489 (63)	-	–	–
4	PCI	2,034 (45)	868 (43)	0.47	0.42 – 0.53	<0.001
	No PCI	2,542 (55)	1,557 (61)	–	–	–
5	PCI	4,525 (45)	1,532 (41)	0.47	0.41 – 0.49	<0.001
	No PCI	3,727 (55)	2762 (61)	–	–	–

Abbreviations: OR = Odds Ratio; CI = confidence interval; [1] Propensity Score: Using logistic regression, the propensity score was estimated by modeling the associations of the following covariates with treatment (percutaneous coronary intervention) given the covariates: gender, race, diabetes mellitus, hypertension, obesity, peripheral vascular disease, pulmonary circulation disorder, chronic lung disease, renal failure, liver disorder, coagulopathy, weight loss, electrolyte imbalance, blood loss, and alcoholism.

Table 3. Estimated treatment effects in older adults comparing percutaneous coronary intervention (PCI) to no PCI on the risk of in hospital mortality after ST-elevation myocardial infarction and cardiogenic shock adjusting for propensity score subclass using survey analysis method.

Propensity Score Subclass[1]	Treatment	Subpopulation Size N (%)	Events (%)	OR	95% CI	p-value
1	PCI	21,953 (32)	9,992 (46)	0.45	0.38 – 0.54	<0.001
	No PCI	46,505 (68)	30,064 (65)	–	–	–
2	PCI	25,026 (37)	10,924 (44)	0.50	0.42 – 0.59	<0.001
	No PCI	43,332 (63)	26,379 (61)	–	–	–
3	PCI	27,406 (40)	12,199 (45)	0.51	0.43 – 0.60	<0.001
	No PCI	40,633 (60)	24,889 (61)	-	–	–
4	PCI	28,063 (41)	11,971 (43)	0.45	0.37 – 0.55	<0.001
	No PCI	39,952 (59)	24,955 (62)	–	–	–
5	PCI	32,346 (48)	12,371 (38)	0.45	0.38 – 0.54	<0.001
	No PCI	35,664 (52)	20,566 (58)	–	–	–

Abbreviations: OR = Odds Ratio; CI = confidence interval; [1] Propensity Score: Using logistic regression, the propensity score was estimated by modeling the associations of the following covariates with treatment (percutaneous coronary intervention) given the covariates: gender, race, diabetes mellitus, hypertension, obesity, peripheral vascular disease, pulmonary circulation disorder, chronic lung disease, renal failure, liver disorder, coagulopathy, weight loss, electrolyte imbalance, blood loss, and alcoholism. Survey analysis was performed using a self-weighted, stratified systematic, random sample of discharges from all hospitals in the sampling frame (see Methods section).

Table 4. Estimated treatment effects in older adults comparing percutaneous coronary intervention (PCI) to no PCI on the risk of in hospital mortality after ST-elevation myocardial infarction and cardiogenic shock by region of the United States adjusting for propensity score.

United States Region[α]	Treatment	Sample Size N (%)	Events (%)	OR	95% CI	p-value
Northeast	PCI	1,616 (34)	675 (42)	0.41	0.36 – 0.47	<0.001
	No PCI	3,203 (67)	2,026 (63)	–	–	–
Midwest	PCI	2,441 (47)	1,055 (43)	0.49	0.42 – 0.57	<0.001
	No PCI	2,753 (53)	1,727 (63)	–	–	–
South	PCI	3,389 (43)	1,520 (45)	0.51	0.46 – 0.56	<0.001
	No PCI	4,456 (57)	2,758 (62)	-	–	–
West	PCI	2,163 (44)	904 (42)	0.46	0.41 – 0.53	<0.001
	No PCI	2,753 (56)	1,664 (61)	–	–	–

Abbreviations: OR = Odds Ratio; CI = confidence interval; [1] Propensity Score: Using logistic regression, the propensity score was estimated by modeling the associations of the following covariates with treatment (percutaneous coronary intervention) given the covariates: gender, race, diabetes mellitus, hypertension, obesity, peripheral vascular disease, pulmonary circulation disorder, chronic lung disease, renal failure, liver disorder, coagulopathy, weight loss, electrolyte imbalance, blood loss, and alcoholism.

[α] United States region was categorized according to the census bureau region into 4 group: (1) Region 1 (Northeast): (A) Division 1 (New England): Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, Connecticut; (B) Division 2 (Mid Atlantic) New York, Pennsylvania, New Jersey; (2) Region 2 (Midwest) (Prior to June 1984, the Midwest Region was designated as the North Central Region); (A) Division 3 (East North Central) Wisconsin, Michigan, Illinois, Indiana, Ohio; (B) Division 4 (West North Central) Missouri, North Dakota, South Dakota, Nebraska, Kansas, Minnesota, Iowa; (3) Region 3 (South); (A) Division 5 (South Atlantic) Delaware, Maryland, District of Columbia, Virginia, West Virginia, North Carolina, South Carolina, Georgia, Florida; (B) Division 6 (East South Central) Kentucky, Tennessee, Mississippi, Alabama; (C) Division 7 (West South Central) Oklahoma, Texas, Arkansas, Louisiana; (4) Region 4 (West); (A) Division 8 (Mountain) Idaho, Montana, Wyoming, Nevada, Utah, Colorado, Arizona, New Mexico; (B) Division 9 (Pacific) Alaska, Washington, Oregon, California, Hawaii.

Box 1. Study design checklist to ensure appropriate use of National Inpatient Sample.

Section A: Research Design

- **Does the study consider it can only detect disease conditions, procedure, and diagnostic tests in hospital settings?**
  Yes, this study focused on outcomes for patients with ST-elevation myocardial infarction and cardiogenic shock in hospitalized patients.
- **Does the study acknowledge that it includes encounters, not individual patients**?
  Yes, the Results section clearly indicated that the study population included 64,766 unique encounters.
- **Does the study avoid diagnosis/procedure-specific volume assessments for units that are not a part of the sampling frame of the NIS, and are therefore not representatively sampled? E.g. (a) geographic units, like US states, (b) healthcare facilities (after 2011), and (c) individual healthcare providers.**
  This study examined the proportion of older adults with STEMI and cardiogenic shock out of the total number of STEMI and cardiogenic shock cases that were identified. This proportion was stratified by U.S. region. No specific volume assessments were made.

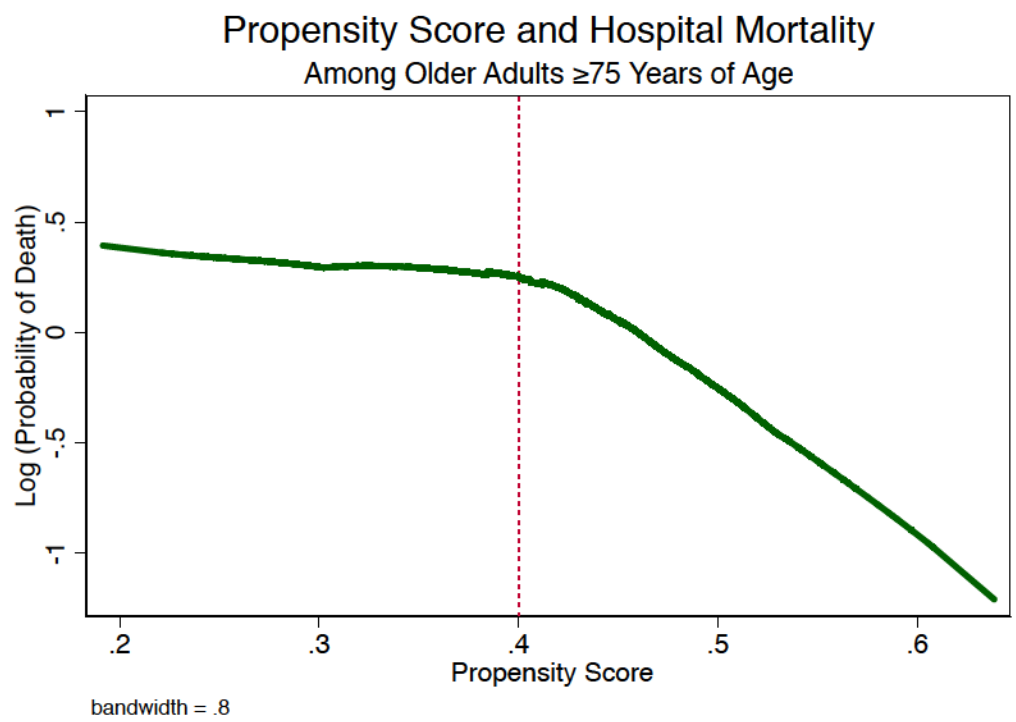
Section B: Data Interpretation

- **Does the study attempt to identify disease conditions or procedures of interest using administrative codes or their combinations that have been previously validated?**
  Yes, these ICD-9-CM codes were obtained from AHRQ data dictionary. *
- **Does the study limit its assessment to only in-hospital outcomes, rather than those occurring after discharge?**
  Yes, only in-hospital mortality was included as an outcome variable. No post-discharge outcomes were available for this analysis.
- **Does the study distinguish complications from comorbidities or clearly note where it cannot?**
  We could not distinguish some complications from comorbidities related to the outcome of in hospital mortality.

Section C: Data Analysis

- **Does the study clearly account for the survey design of the NIS and its components-clustering, stratification, and weighting?**
  Yes, see Methods section.
- **Does the study adequately address the changes in data structure over time (for trends analyses)?**

Yes. In 2012, the data structure for the HCUP National Inpatient Sample was redesigned. We used trend weight to create national estimates in the years prior to 2012. * **Reference:** https://www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp#download



Supplementary Figure 1. Log-transformed probability of death by the propensity score. The graph illustrates a decrease in the risk of death at a propensity score [Pr(PCI) = 0.4]. As such a spline term at Pr(PCI) = 0.4 was chosen.

CHAPTER 6

TEMPORAL TRENDS OF PERCUTANEOUS CORONARY INTERVENTIONS IN OLDER ADULTS WITH ACUTE MYOCARDIAL INFARCTION: AN INCREASING RATE OF UTILIZATION IN VERY-OLD ADULTS

(Publication citation: Damluji A et al. Circ Cardiovasc Interv. 2019 May;12(5):e007812)

The population of older adults in the United States is growing at a rapid pace. It is estimated that adults aged 75 years or older totaled 19 million in 2012, approximately 6% of the total population, and that the number will increase to 46 million, or 11.5% of the population, by 2050.[28] Since aging physiology and lifestyle is associated with increased risks of cardiovascular disease (CVD), it is likely that cardiologists will be treating older adults. Typically, older adults with CVD are prone to worse coronary lesions as well as more comorbidities, and to related risks of adverse outcomes and complications.[6] In this present study, using national data we evaluated the rate of utilization of percutaneous coronary intervention (PCI) during a first admission with the principal diagnosis of acute myocardial infarction (AMI) in patients ≥ 75 years of age to study the utility of revascularization despite the inherent greater age-related risks.

We used the Premier Healthcare Database (Premier, Inc., Charlotte, NC) that includes information from over 750 hospitals and 717 million hospital encounters in the U.S. and is populated with detailed patient-level data.[147] Patient demographic data, billed services including medications, and laboratory, diagnostics, and therapeutic services, in de-identified patient daily service records were available for analysis. Our cohort was all patients aged ≥75 years who were admitted with a first diagnosis of AMI between January 2000 to January 2016. AMI admissions were identified using the primary admission diagnosis based on ICD-9 and ICD-10 Clinical Modification codes (ICD-9: 410-414, 429.2; and ICD 10: I20-I25).

Patients were categorized according to their age at first AMI as follows: (1) young old: age 75-79; (2) middle-old: age 80-84; and (3) old-old: 85-89. We identified those older patients who received PCI using ICD codes. Comorbidities were defined according to the Agency for Healthcare Research and Quality standards. We compared demographic characteristics, clinical conditions, hospital outcomes and utilization of PCI by age category. We then evaluated the influence of PCI as compared to medical therapy on hospital mortality, for each of the three age groups. The absolute risk difference was calculated for PCI vs. medical therapy on hospital mortality for each age category. All statistical analyses were performed using STATA version 15 MP (Stata-Corp, College Station, TX). This study was approved by the Institutional Review Board at the Johns Hopkins University. The data that support the findings of this study will not be made available to other researchers because of restrictions in the data use agreement between Premier Inc. and Johns Hopkins Medicine.

Of 469,827 older patients who were admitted with their first AMI, 157,669 (34%), 143,040 (30%), and 169,088 (36), were young-old, middle-old, and old-old, respectively. The comorbidity burden was highest in the old-old group and the most prevalent disorders were heart failure, valvular disease, stroke, and pulmonary circulation disorders. The overall hospital mortality rate was also highest among the old-old group; (young-old: 8%, middle-old: 10% and old-old: 13%, p-value < 0.001). In the overall cohort, PCI was performed in 38% for the young-old, 33% for the middle-old, and 20% for the old-old age group. Evaluation of secular trends from 2000-2016 revealed an increased rate of utilization of PCIs in the young-old and middle-old groups, which was parallel by a decreased unadjusted mortality rates in the later years of the study (Mortality Rate in 2016: young-old: 5% vs middle-old 7%). For old-old patients with AMI,

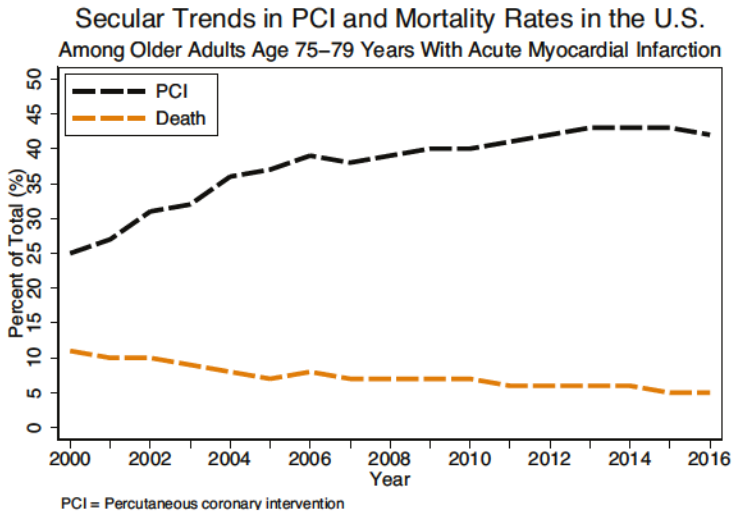
the rate of PCI utilization has increased sharply from 10% to 25% with unadjusted mortality rates declining from 17% in 2000 to 11% in 2016 (Figure 1 A-C).

In the overall cohort, PCI was associated with improved survival in all three age categories compared to medical therapy group (unadjusted OR: Young-Old: 0.47, 95% CI 0.45-0.49; Middle-Old: 0.51, 95% CI 0.53; Old-Old: 0.58, 95% CI 0.55-0.60), but the absolute risk reduction for hospital mortality was highest among the old-old group (Risk-Difference: young-old: 49 per 1,000 cases; Middle-Old: 53 per 1,000 cases; Old-Old 54 per 1,000 cases). In a multivariable model, the use of PCI remained associated with a survival benefit within each age strata.

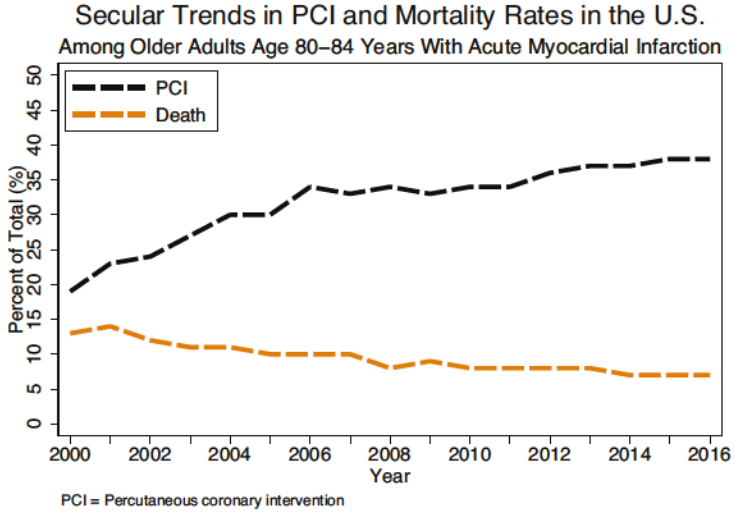
As the population ages, operators are faced with more complex coronary disease anatomy and the decision whether to perform high-risk PCI will become increasingly relevant to daily practice. We found that in the early years of the study period, the majority of PCIs were performed for the young-old. In parallel with the changing population demographics as well as the many recent studies supporting the benefit of PCI in patients with AMI, the use of PCI in older adults has been increasing in recent years. This work has several limitations including the retrospective design of the study, the lack of granularity in regard to the type of myocardial infarction (ST-elevation myocardial infarction vs. non-ST-elevation myocardial infarction) and the type of the procedure (primary PCI vs. non-primary PCI). While imbalances in patients' characteristics and markers of disease severity were included in the multivariable analyses, there are still potential unmeasured confounders that could result in selection bias. However, the results remain valuable to inform physicians treating older patients with AMI, as this group of patients are usually underrepresented in most clinical trials. Our analysis suggests a survival benefit of PCI, even for the very-old, and that revascularization may not be withheld based on

the age of the patient alone at the time of first AMI diagnosis. Future investigations are needed to find ways to improve risk stratification and futility of care at older ages.

A


Secular Trends in PCI and Mortality Rates in the U.S.
Among Older Adults Age 75–79 Years With Acute Myocardial Infarction
PCI
Death
Percent of Total (%)
0
5
10
15
20
25
30
35
40
45
50
2000
2002
2004
2006
2008
2010
2012
2014
2016
Year
PCI = Percutaneous coronary intervention

B


Secular Trends in PCI and Mortality Rates in the U.S.
Among Older Adults Age 80–84 Years With Acute Myocardial Infarction
PCI
Death
Percent of Total (%)
0
5
10
15
20
25
30
35
40
45
50
2000
2002
2004
2006
2008
2010
2012
2014
2016
Year
PCI = Percutaneous coronary intervention

C

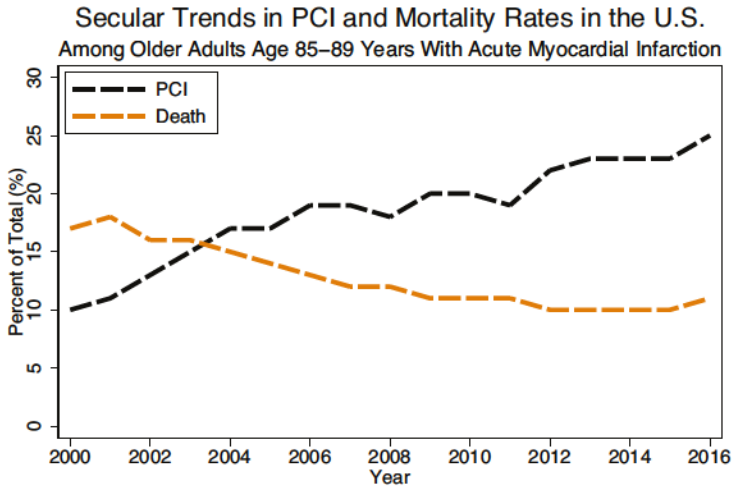

Secular Trends in PCI and Mortality Rates in the U.S.
Among Older Adults Age 85–89 Years With Acute Myocardial Infarction
PCI
Death
Percent of Total (%)
0
5
10
15
20
25
30
2000
2002
2004
2006
2008
2010
2012
2014
2016
Year

FIGURE LEGENDS

Figure 1 (A) Secular trends in PCI utilization and unadjusted mortality rates among adults aged 75-79 years of age admitted with their first AMI in the Premier Healthcare Database from 2000 to 2016. Note that the y-axis represents % of all patients with AMI in age category 75-79; (B) Secular trends in PCI utilization and unadjusted mortality rates among adults aged 80-84 years of age admitted with their first AMI in the Premier Healthcare Database from 2000 to 2016. Note that the y-axis represents % of all patients with AMI in age category 80-84; (C) Secular trends in PCI utilization and unadjusted mortality rates among adults aged 85-89 years of age admitted with their first AMI in the Premier Healthcare Database from 2000 to 2016. Note that the y-axis represents % of all patients with AMI in age category 85-89.

CHAPTER 7

TAVR IN LOW-POPULATION DENSITY AREAS: ASSESSING HEALTHCARE ACCESS FOR OLDER ADULTS WITH SEVERE AORTIC STENOSIS.

(Publication citation: Damluji A et al. *Circ Cardiovasc Qual Outcomes.* Submitted: in-revision).

INTRODUCTION

The relationship between volume and outcomes has long been a focus of surgical research, and recommendations derived from these findings are now appearing in expert consensus statements.[148, 149] Support for the creation of "centers of excellence" and initiatives such as the "take the volume pledge"[148] have been proposed in order to limit certain high-risk surgical procedures to centers and operators with a minimum threshold of case numbers. Similar recommendations have recently appeared in expert consensus statements on the institutional requirements for transcatheter aortic valve replacement (TAVR).[150] These recommendations are based on studies demonstrating a modest but significant improvement in outcomes in high volume TAVR facilities as compared with low volume centers.[151, 152]

Prior work has described the consequences of restricting certain procedures to centers based on volume-outcome relationships and highlighted the creation of access disparities.[149] These disparities are often exaggerated in regions with low-population densities or mixed racial and socioeconomic status, and can be further exaggerated in areas with higher concentrations of older individuals.[153-156] In acknowledgement of these barriers, the Department of Health and Human Services has required individual states participating in managed care plans to set time and distance standards for specialty care services to ensure timely access for specialized healthcare services.[153, 157] This requirement has been especially important in states like Florida, where uninsured and underinsured rates are high, and the costs of care are soaring.[158, 159] While

no standard metrics for access to TAVR procedures (e.g. time or distance) have been established, the recent TAVR consensus statement does recognize that some centers performing less than the annual minimum will need to be maintained in order to meet the needs of underserved populations.[150]

In light of these expert statements and the inherent challenges of delivering healthcare across states like Florida, the maintenance of optimal procedural outcomes without compromising healthcare access remains an active area of debate. This is an especially difficult issue for cardiovascular procedures like TAVR that require a high degree of technical expertise and a multidisciplinary team of healthcare professionals. To further explore these relationships, we examined (1) differences in both travel time and distance, (2) TAVR utilization rates and (3) in-hospital TAVR mortality rates across the broad spectrum of Florida county population densities from low to high (i.e. rural vs. urban).

METHODS

Study Population

The population for this study was derived from data provided by the Florida Agency for Health Care Administration inpatient database. The Florida Agency for Health Care Administration was created in 1992 to set standards for health policy and healthcare planning in the state of Florida. To achieve this goal, an inpatient database was created, and a mandatory reporting system was established for all participating hospitals, which was required to maintain the license to provide healthcare services in the state.[160, 161] The reporting system consists of 72 data elements, which are captured in a deidentified fashion, including zone improvement plan (ZIP) codes for each patient's primary residence and TAVR center, primary and secondary diagnostic codes, current procedural terminology (CPT) codes, and outcome measures including

in-hospital mortality, length of stay, and healthcare costs during each inpatient visit. For the purposes of this study, all consecutive adult patients who underwent TAVR procedures from 2011 to 2016 in the state of Florida were identified using ICD-9 (35.05 and 35.06) and ICD-10 codes (02RF3).

For each TAVR patient, demographic data including age, gender, race/ethnicity, primary residency, and TAVR center ZIP codes were recorded. Quality metrics including time from hospital admission until TAVR procedure were collected, hospital length of stay, and discharge status were reported. For each patient, the time (minutes) and distance (miles) from primary residence to the TAVR center where the procedure was performed were calculated using the patient's home ZIP code and TAVR facility ZIP code (see below for details). Census data for the county of each patient's primary residence were obtained from the Bureau of Economic and Business Research at the University of Florida in Gainesville. Each county in the state was then categorized according to 5 different levels of population density (population per square mile) from the lowest to the highest quintile.

Definitions of Population Density

To examine multiple descriptors of population densities, four different definitions were examined according to the standards set by the Bureau of Economic and Business Research at the University of Florida.[162] The most common way to examine population density is by dividing the total number of the population of an area by the total land area, but because the state of Florida has large uninhabited blocks of land (forests, parks, wetlands, and nonresidential land), the appropriate method to examine population densities in different counties is an area of debate. To account for these complexities, 4 definitions for population densities have been described:[162]

(1) total population census for each county per square mile; (2) total population census for each county per square mile after excluding zero population census blocks (i.e. uninhabited land including forests, parks, wetlands, and nonresidential land); (3) median population census for each county per square mile of total land (i.e. this is a measure of an average population density at the smallest level of census geography); and (4) 95% population census for each county per square mile of total land (i.e. this is a measure of how dense the urban cores are).[162]

Using data from the 2010 United States census, and the published standards on land areas for each county, Rayer and Wang calculated and displayed the population density for every county using each of the four methods. The investigators then assigned each county to the appropriate population density quintile from lowest to highest. A color-coded map for each method was created displaying each county in one of five colors based on the specific quintile of population density (Figures 1). Each of these 4 definitions allowed potential comparisons in demographic characteristics and social determinates of health in vulnerable populations residing in the state of Florida.

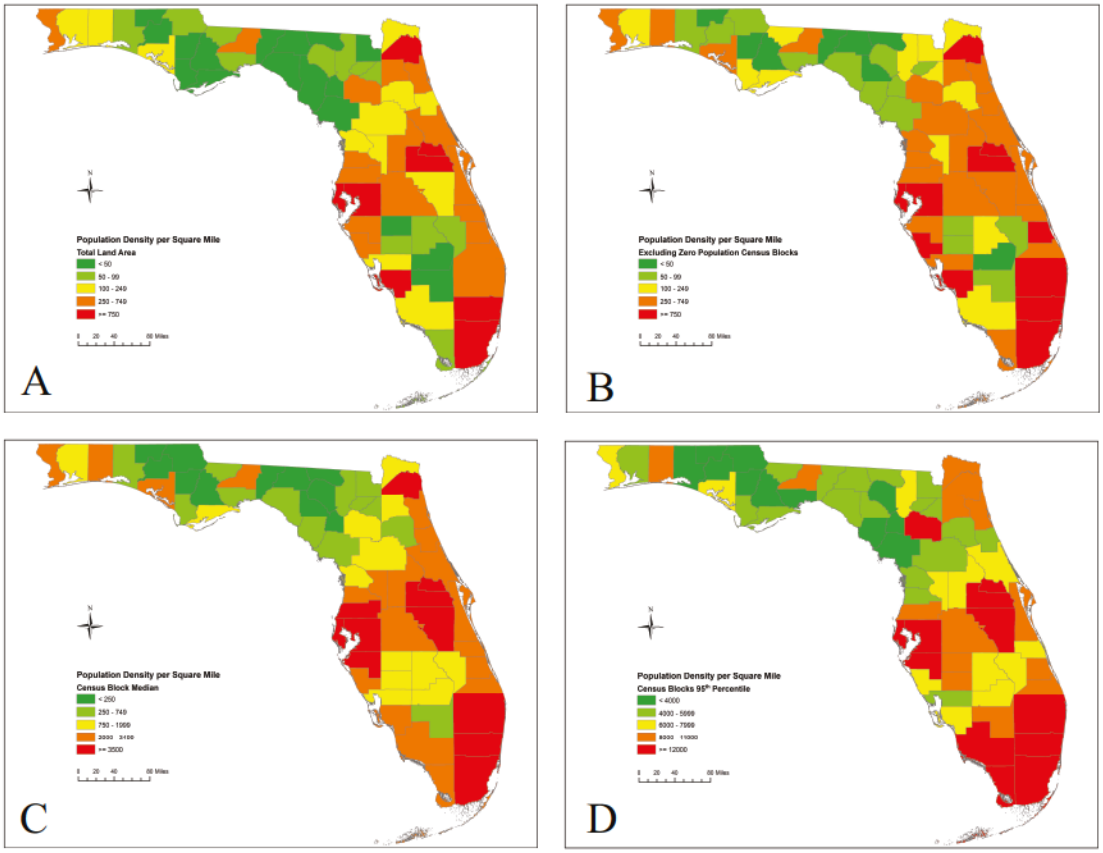


Figure 1. A. Population density per square mile for Florida counties using total land area, 2010. Population data was derived from the 2010 United States Census.
Figure 1. B. Population density per square mile for Florida counties excluding census blocks with zero population, 2010. Zero population land was defined as uninhabited land including forests, parks, wetlands, and nonresidential land.
Figure 1. C. Population density per square mile for Florida counties using median census block density, 2010. The median census block density is a measure of an average population density at the smallest level of census geography.
Figure 1. D. Population density per square mile for Florida counties using 95th percentile census block density, 2010. The 95th percentile census block is a measure of how dense the urban cores are.

Calculation of Driving Times and Distances

The average driving time (minutes) and distances (miles) were calculated using the Google Distance Matrix application programming interface (API) (https://developers.google.com/maps/documentation/distance-matrix/start; Accessed July 3,

2019). The Distance Matrix API is a service that provides travel distance and time based on the recommended route (based on historical data) between the start and end destination, which in this case was the global positioning system coordinates corresponding to the ZIP code of the patient's primary residence and facility's street address, respectively (https://www.census.gov/geo/maps-data/data/gazetteer2016.html; Accessed July 3, 2019). The application allows for developers to code for the computation of travel distance and time for multiple points within Google Maps, such as ZIP codes. Routes used for distance and time did not consider real-time traffic conditions. Both time and distance were used for comparison; however, some evidence shows time comparisons is a better measure over straight-line distances in areas with increased rurality.[163]

Statistical Analysis

The population density was first examined using the simplest definition, the total number of the population of the county area by the total land area in Florida (Figure 1). Baseline demographics, year of the procedure, hospital level-data, and inpatient outcomes were compared for all patients who underwent TAVR in Florida from 2011 to 2016 based on population density quintiles. Descriptive statistics, including frequencies and proportions for binary and categorical variables, and mean with standard deviation for continuous data were presented. Comparisons were performed using either chi-squared test, or analysis of variance, as appropriate.

Utilizing a linear trend estimation, the distance from the patient's primary residence to the TAVR center was compared for each quintile of total land population density relative to the area with highest population density in the state. These comparisons were repeated for each of the four definitions of the population density. The multivariable linear regression model was adjusted for age, gender, and Elixhauser comorbidity index.[164] In a similar fashion, the difference

in the travel time by car (minutes) was estimated for each category of population density as compared to people residing in areas with the highest population densities adjusting for age, gender, and Elixhauser comorbidity index. We then plotted the mean number of TAVR procedures per 100,000 people according to population density defined as: (1) the total number of people per square mile of total land; and (2) the total number of people per square mile of land after excluding uninhabited territories (i.e. forests, parks, wetlands, and nonresidential land).

To examine the time and distance required for participants to reach high volume TAVR centers, a sensitivity analysis excluding low volume facilities that performed on average <50 TAVR procedure/year over two consecutive years was performed. In similar fashion, a linear trend estimation was used to compare the differences in travel distance (miles) and travel time (minutes) between each category of population density and those residing in the highest population density areas adjusting for age, gender, and Elixhauser comorbidity index.[164] To illustrate where each TAVR center is located in relation to population densities in the state of Florida, we plotted the hospital that offer TAVR procedures according population density defined as total number of people per square mile of land after excluding uninhabited land. The analyses described above were then repeated using the alternative population density definitions as a sensitivity analysis. A two-sided p-value of <0.05 was considered statistically significant. All analyses were performed using STATA 15MP (StataCorp, College Station, Tx). No extramural funding was used to support this work.

RESULTS

During the study period from 2011 to 2016, 6,559 discharges following TAVR procedures were identified. There were 28 duplicate entries that were identified and excluded,

rendering a final sample size of 6,531 TAVR patients. Demographic characteristics of the study population were examined and compared by quintile of total land area population density (Table 1). The mean (SD) age was 82 (9) years, 96% were ≥65 years of age, 83% ≥75 years of age, 43% were female, and 91% Caucasian. The majority of patients who received TAVR in areas with population density of 100-249 and 250-749 people/square mile were Caucasians, while ethnic minorities resided in either highly populated areas or regions with the lowest population densities. Compared to the highest quintile of population density, patients residing in the lowest quintile were younger (mean age: 78 vs 81 years old, $p<0.001$), more likely to be men (male gender: 62% vs 53%, $p<0.001$) and less likely to be a member of a racial minority group (racial minority: 10% vs 11%, $p<0.001$). Of the 6,529 TAVR procedures performed during the study period (data on 2 procedures were missing), the majority were performed in 2015 and 2016 with a rapid increase in the utilization rate since 2011 (Table 1). While all quintiles of population density showed a rapid increase in the later years of study, patients residing in the lowest quintiles had fewer TAVR procedures compared to those in the highest population density counties (Table 1). The majority of patients in low population density regions were treated in large hospital systems (mean hospital beds = 752 beds) and most TAVR centers were located in the areas with the highest population density (Central Illustration).

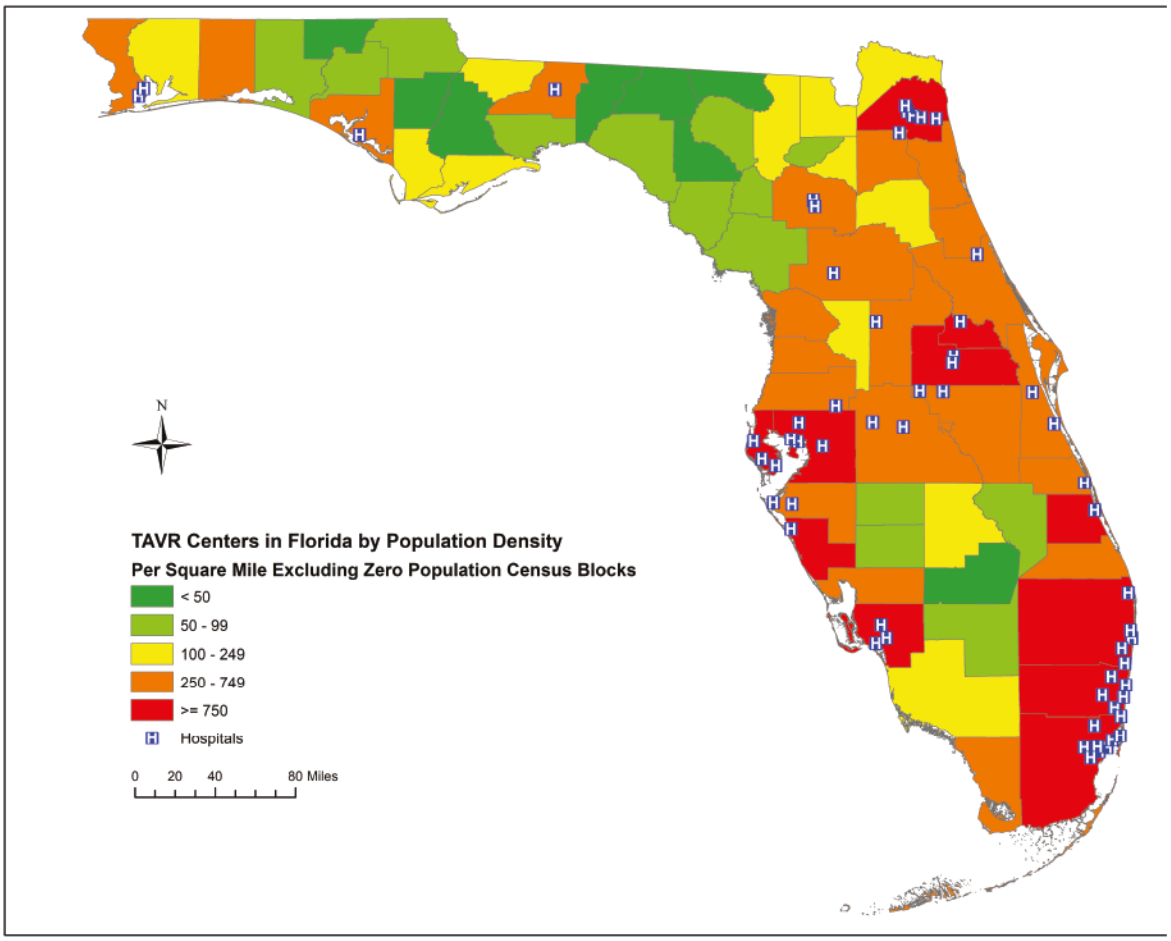


Figure 2 (Central Illustration). Transcatheter aortic valve replacement centers in Florida by population density. Population density per square mile for Florida counties excluding census blocks with zero population, 2010. Zero population land was defined as uninhabited land including forests, parks, wetlands, and nonresidential land.

On average, the mean distance traveled for the entire cohort was 33 miles for an average travel time of 42 minutes. Patients residing in low population density areas had significantly longer travel distances and times compared with those who lived in higher density areas. Overall, unadjusted in-hospital TAVR mortality rate was low (Hospital Mortality: 2.66%; 95% CI: 2.2 to 3.1), however the higher mortality was observed in for patients who lived in low-density areas

(Table 1). The age- and sex-adjusted hospital mortality among patients residing in the low population density areas remained higher than those residing in high population density areas (Mortality: <50: 5% (95% CI: 0.1-10.2) vs. high-population density area 1% (95% CI: 0.7-7.4), *p*-value=0.015). More patients were discharged home and patients were less likely to go to rehabilitation or acute care facility when they resided in low population density areas.

As compared to the highest population density areas, patients living in low population density areas had an average adjusted travel distance 39.4 (95% CI: 31.8 to 47.0) miles further and 31.8 (95% CI: 34.6 to 49.0) minutes longer (Table 2). Comparing patients in intermediate density areas to those who reside in low density areas, these travel distances and times were smaller. These differences in the estimated travel distance and time from the patient's primary residence to the TAVR center were consistent regardless of the definition of population density (Table 2). When the analysis was limited to only high-volume centers (defined as centers performing over 50 procedures/year), the same trends were observed across the definitions of population density (Table 3). The rate of TAVR utilization is presented by two definitions of population density: (1) the total number of the population divided by the total land area of county; and (2) the total number of population divided by total land after excluding uninhabited blocks of land (i.e. zero land: forests, parks, wetlands, and nonresidential land) (Figure 2). After excluding uninhabited land, the rate of utilization of TAVR procedures per 100,000 people was lowest in areas with low population density areas with a substantial increase as the population density increases (TAVR utilization low [<50] vs. high [≥750] population density: 7 vs. 45 TAVR procedures/100,000 people, *p*-value < 0.001) (Figure 3).

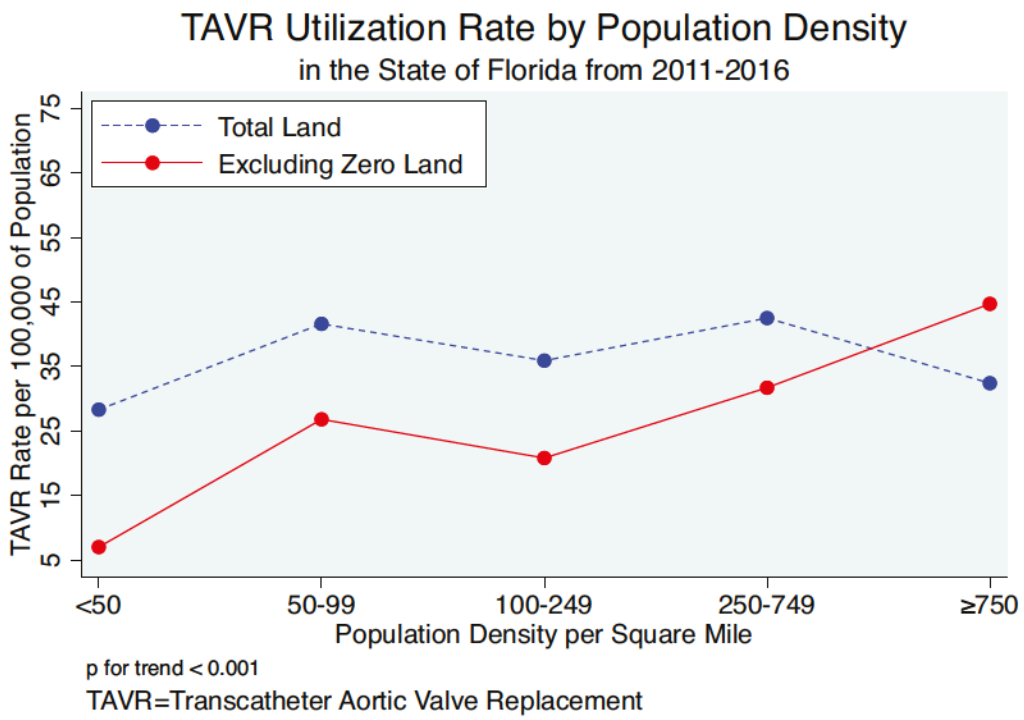


Figure 3. Transcatheter aortic valve replacement utilization rate by population density in Florida from 2011 to 2016. Population density was defined as (1) Total land: population per square mile for Florida counties using total land area, 2010; (2) Population density per square mile for Florida counties excluding census blocks with zero population, 2010. Zero population land was defined as uninhabited land including forests, parks, wetlands, and nonresidential land. Population data was derived from the 2010 United States Census.

DISCUSSION

In this study, we compared TAVR travel times and distances, TAVR utilization rates and TAVR mortality across the spectrum of population densities in the state of Florida from 2011 to 2016. The main findings of this study are: (1) the majority of TAVR centers in the state of Florida were located in high population density areas; (2) there were stark differences in travel time and distance for TAVR patients residing in the lowest population density counties

compared to the highest, (3) after excluding uninhabited land in the state of Florida, TAVR utilization rates varied 7-fold according from low to high population density areas; (4) TAVR mortality varied minimally for patients who are living in low versus high population density regions; and (5) higher proportion of low population density patients are discharged directly home, which may also reflect lack of geographic access to rehabilitation center/skilled nursing facility.

In previous work evaluating healthcare utilization among older patients, travel distances exceeding 10 miles from the patient's residence to healthcare facility or centers located outside the patient's "activity space" were associated with reduced rate of healthcare utilization.[156] In this context, an additional increase in the drive time from the patient primary residence to the healthcare facility of 45-60 minutes for patients residing in the lowest population density areas, likely represent a significant access barrier for the older patients typically considered for TAVR procedures. Although the rate of growth of TAVR utilization over the study period was rapid and comparable to national estimates, the rate of adoption was slowest in the lowest population density areas in Florida.[165, 166] Combined with the lower overall rate of TAVR procedures/100,000 of populations, these findings may speak to a broader issue of underdiagnosing and undertreating diseases like severe symptomatic aortic stenosis in lower population density areas. We have shown that there are differences in racial and ethnic distribution of older patients who received TAVR across different areas of population density. Rural communities with low-population densities or poor underserved urban areas may have a lack of high-quality primary care, which results in underutilization of specialized cardiac care and cardiovascular imaging. These problems in disease detection or diagnosis can in part explain the racial and ethnic differences observed in older patients undergoing TAVR procedures.[167]

The location of TAVR centers when it comes to population densities is critical to serve populations at risk for restricted healthcare access. We determined that highly specialized cardiac centers that provide TAVR services are located mainly in high population density areas. While relatively large healthcare systems exist in low population density areas, proper planning on how to distribute these highly specialized cardiac centers is lacking. The American Association for Thoracic Surgery, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons have suggested a minimal standard for TAVR procedures to maximize quality outcomes and minimize procedure related complications. The rapid growth of TAVR centers in areas of high population density relative to low population density areas can create an imbalance in healthcare services by regions and geography. This imbalance in cardiac care was previously shown in centers offering percutaneous coronary interventions.[168] For example, the state of Nevada has a high prevalence of coronary artery disease burden, but the number of PCI centers in proportion to the population is significantly lower than a comparable states with a similar population.[168]

Financial barriers to establish TAVR programs in low-population density areas exist. While surgical aortic valve replacement has great financial benefits for most hospitals,[169] there are financial disincentives for smaller, rural hospitals to establish TAVR programs. Diagnosis-related group payments vary widely, and these payments are lowest for more rural, non-teaching hospitals.[170] With lower reimbursement rates for TAVR in rural regions, the “halo effect” associated with structural heart disease procedures cannot make up for this financial disincentive. It should be noted that many rural hospitals in the United States are designated as "critical access hospitals". These hospitals are not reimbursed via the inpatient prospective payment systems, but

rather paid according to what Centers for Medicare and Medicaid Services deem to be 101% of reasonable costs

The costs associated with opening a TAVR programs (e.g. hybrid operating room or high-quality computed tomography) also weigh heavily on hospitals above other needs for their community. Other financial factors that preclude TAVR centers in low-population density areas include the competitive healthcare market and the emergence of large healthcare system that aim to consolidate high-end cardiovascular service lines in urban hospital systems in high population density areas. The differential utilization of TAVR procedures may not only be TAVR-specific, but the concept can potentially be applied to all procedural care. Future research should study this differential utilization of other cardiovascular procedures (e.g. coronary artery bypass graft surgery) by population density. If similar findings are found, this will point out to the overall lack of medical and advanced procedural resources in areas of low population densities.

As TAVR guidelines aim to establish minimum standards to achieve the highest quality through volume thresholds these disparities in access to care can be exaggerated by imposing limits on expansion. In states with high health care costs, large uninsured patient populations, and access barriers, such as Florida, limiting care to specific centers has been controversial as reflected in current concerns over Certificate of Need (CON) laws.[158, 159, 171] Supporters of CON repeal, which already has minimal CON requirements, cite inflated costs and limited access as reasons for repealing these types of laws and recommendations. Expanding access by appropriate planning of TAVR centers targeting low density areas can mitigate problems related to disparity and healthcare access. The recent Centers for Medicare and Medicaid Services coverage determination for hospitals without TAVR experience included a minimum of 50 surgical aortic valve replacement operations in the prior year. For surgeons without TAVR experience, the

volume threshold is at least 100 career open heart surgeries and that for interventional cardiologist include a minimum of 100 structural heart disease procedures in a lifetime or 30-left sided structural procedures per year. While we believe that these quality metrics are important to ensure safe outcomes, it may restrict access for certain patients in low-population density areas. From health policy perspective, healthcare access should be discussed to decrease healthcare disparities created by volume requirements.

It should be noted that despite the differences in the distribution of TAVR centers by population density, racial, and ethnic factors, the U.S. has more TAVR programs per population than any other country. This expansion of TAVR programs was driven by different factors including industry, hospitals/physicians, and patient advocacy groups. While there were real efforts to extend TAVR services to cover populations in need, concerns were raised regarding large profit margins and market acquisition, hospital requesting accreditation without meeting the minimum quality metrics for establishment of TAVR programs, and industry funding for advocacy groups that makes the appropriate planning for TAVR centers more challenging. The National Coverage Decisions are needed to establish a network of treatment centers that meet reasonable standards to provide high-quality care and healthcare access that is equivalent to other specialized services. Guidelines should reflect the balance between quality standards and healthcare access for communities at risk for under diagnosis and under treatment of aortic valve disease. While creative solutions like ride-sharing platforms could be used to improve access, this approach has produced mixed results in the primary care setting.[172] Other creative solutions to address healthcare access include the establishment of local primary valvular heart disease care centers in low-population density areas to promote and improve screening, diagnosis, and prognostication of valvular heart disease and that will ultimately lead to higher referral to

specialized TAVR centers in urban areas. If pre-procedural work-up and post-procedure care can be done competently at the local level and if telemedicine can allow meetings with TAVR center personnel for those living in low-population density areas, then the need to travel to a TAVR center may become a one-time occurrence.

Limitations

There are limitations to this retrospective analysis. First, calculating travel times with applications like the Google Matrix distance does not take into consideration potential traffic congestion, which may not represent the traffic conditions at the time the patient is traveling for their procedure. For this reason, we considered both distance and time in our analyses.[173] Second, we used the population density estimates derived from 2010 census data that were validated by Rayer and Wang and reported previously.[162] The population has grown in the years between 2010 and 2016. While the updated census data can produce slightly different population estimates, the relative population density of the counties in the state of Florida did not change substantively over that time interval. Further, the method used to examine population density in the state of Florida is an area of debate because of the large uninhabited land in the state. In order to avoid this limitation, we presented the data utilizing all 4 definitions of population that were previously described. Third, it plausible that sophisticated patients who need TAVR procedures may travel many miles to get to a TAVR program that is nationally "ranked". While this can result in bias, many patients from this socioeconomic status likely reside in urban area rather than rural counties with low-population densities. These socioeconomic factors (e.g. education levels and income) could be major determinants of TAVR outcomes. However, current and future planned generation of risk-adjustment algorithms do not include these factors in risk calculation and future studies should consider these factors when evaluating health outcomes in

older patients after TAVR procedures. It should be noted that while there was a difference in the unadjusted mortality rate by population density, clinical and socioeconomic variables that confound the relationship between population density and mortality may still exist. Fourth, we assume that TAVR was "appropriate" in everyone who received the procedure. Setting minimal standards for institutions can theoretically result in "overutilization" of TAVR procedures, an important problem when evaluating healthcare access versus quality. Fifth, CPT codes are frequently used in outpatient datasets to identify procedures. In this inpatient dataset, ICD-10 could not be validated against CPT codes for TAVR (33361-69) because patients are deidentified and linkage with outpatient data was not possible. Lastly, TAVR utilization data available for analysis include only those patients who received TAVR. Data on patients who should receive TAVR, but did not, are not available in the inpatient database. Examination of underutilization of TAVR in low-population density areas should be addressed in future research.

CONCLUSION

Floridians living in more rural counties face significantly longer travel distances and times for TAVR, much lower TAVR utilization rates and higher unadjusted TAVR procedural mortality. This is of particular importance for vulnerable elderly for whom these phenomena may create disparities in care. The inherent trade-offs between access to TAVR, its rate of utilization and procedural mortality are all important considerations when determining institutional and operator requirements for TAVR across the country.

FIGURE LEGENDS

Figure 1. A. Population density per square mile for Florida counties using total land area, 2010. Population data was derived from the 2010 United States Census.

Figure 1. B. Population density per square mile for Florida counties excluding census blocks with zero population, 2010. Zero population land was defined as uninhabited land including forests, parks, wetlands, and nonresidential land.

Figure 1. C. Population density per square mile for Florida counties using median census block density, 2010. The median census block density is a measure of an average population density at the smallest level of census geography.

Figure 1. D. Population density per square mile for Florida counties using 95th percentile census block density, 2010. The 95th percentile census block is a measure of how dense the urban cores are.

Figure 2. Transcatheter aortic valve replacement centers in Florida by population density. Population density per square mile for Florida counties excluding census blocks with zero population, 2010. Zero population land was defined as uninhabited land including forests, parks, wetlands, and nonresidential land.

Figure 3. Transcatheter aortic valve replacement utilization rate by population density in Florida from 2011 to 2016. Population density was defined as (1) Total land: population per square mile for Florida counties using total land area, 2010; (2) Population density per square mile for Florida counties excluding census blocks with zero population, 2010. Zero population land was defined as uninhabited land including forests, parks, wetlands, and nonresidential land. Population data was derived from the 2010 United States Census.

Table 1. Demographic characteristics of patients who received transcatheter aortic valve replacement by total land population density per square mile in the state of Florida from 2011 to 2016.

		Total Land Population Density per Square Mile					
Variable [a]	**Total** (n=6,531)	**<50** (n=101)	**50-99** (n=242)	**100-249** (n=740)	**250-749** (n=2,704)	**≥750** (n=2,744)	***P value*** [f]
Demographics							
Age, years, mean (SD)	82 (9)	78 (10)	81 (8)	81 (8)	82 (8)	81 (8)	<0.001
Female gender, (%)	2,829 (43)	38 (38)	115 (48)	295 (40)	1,102 (41)	1,279 (47)	<0.001
Race, (%)							<0.001
Caucasian, (%)	5,936 (91)	91 (90)	215 (89)	686 (93)	2,494 (92)	2,450 (89)	
Black, (%)	201 (3)	4 (4)	13 (5)	12 (2)	65 (2)	107 (4)	
Other [b], (%)	394 (6)	6 (6)	14 (6)	42 (6)	145 (5)	187 (7)	
Year of Procedure, (%)							<0.001
2011	32 (0)	0 (0)	0 (0)	1 (0)	10 (0)	21 (1)	
2012	406 (6)	6 (6)	11 (5)	35 (5)	159 (6)	195 (7)	
2013	592 (9)	14 (14)	31 (13)	59 (8)	257 (10)	231 (8)	
2014	897 (14)	16 (16)	42 (17)	92 (12)	373 (14)	374 (14)	
2015	1,707 (26)	27 (27)	60 (25)	193 (26)	698 (26)	729 (27)	
2016	2,895 (44)	37 (37)	97 (40)	360 (49)	1207 (45)	1,194 (44)	
Hospital-level Data, (%)							
Hospital beds	631 (236)	752 (170)	716 (243)	579 (248)	595 (239)	668 (222)	<0.001
Distance, miles [c]	33 (43)	61 (48)	82 (49)	57 (49)	36 (49)	17 (49)	<0.001
Time, minutes [c]	42 (40)	73 (42)	95 (47)	67 (47)	44 (47)	27 (47)	<0.001
Time until procedure, days [d]	2 (4)	2 (6)	2 (4)	2 (4)	1 (4)	2 (4)	<0.001
Hospital Outcomes							
Hospital mortality, % (95% CI)	2.7 (2, 3)	7.4 (3, 15)	1.4 (0, 4)	2.0 (1, 3)	2.0 (1, 3)	3.4 (3, 4)	<0.001
Discharge home or self-care, % (95% CI)	33 (31, 34)	46 (36, 56)	42 (36, 49)	39 (36, 43)	37 (35, 38)	26 (24, 27)	<0.001

Discharge to acute care facility [e], % (95% CI)	26 (25, 27)	17 (10, 26)	18 (13, 23)	24 (21, 27)	27 (26, 29)	27 (26, 29)	<0.001
Length of hospital stay, days, mean (95% CI)	7 (6.9, 7.3)	7 (6, 9)	7 (6, 7)	6 (6, 7)	6 (6, 7)	8 (8,8)	<0.001

Abbreviations: CI = confidence interval.

[a] % may not add to 100 due to rounding.
[b] Includes American Indian, Alaskan Native, Asian, Native Hawaiian or Pacific Islander, and other racial minorities.
[c] Distance (miles) is defined as the distance from the patient's home zip code to the TAVR center where patient received the TAVR procedure. Time (minutes) is defined as the time needed to travel from the patient's home zip code to the TAVR center where patient received the TAVR procedure.
[d] Time until procedure is the mean number of days from admission date to procedure date.
[e] Discharged to home care, skilled nursing facility, or rehabilitation center.
[f] *p*-values were obtained from generalized linear model.

Table 2. The mean difference in distance (miles) and time (minutes) from patient's home to transcatheter aortic valve replacement center by population density in Florida from 2011 to 2016. Note that the reference group is the highest quintile of high-population density areas.

	Distance to TAVR Center (Miles) [a]				Time to TAVR Center (Minutes) [b]			
	β Coefficient [g]	*P Value*	95% CI		*β* Coefficient [h]	*P Value*	95% CI	
Total Land [c]								
<50	42.1	<0.001	34.2	50.0	44.1	<0.001	36.9	51.4
50 - 99	64.7	<0.001	59.5	69.9	67.3	<0.001	62.6	72.1
100 - 249	39.2	<0.001	35.9	42.4	39.7	<0.001	36.7	42.6
250 - 749	18.9	<0.001	16.8	21.0	17.6	<0.001	15.6	19.5
Zero Block [d]								
<50	49.4	<0.001	33.9	64.9	44.4	<0.001	30.2	58.6
50 - 99	52.7	<0.001	46.4	59.0	54.7	<0.001	48.9	60.5
100 - 249	42.8	<0.001	38.9	46.8	45.5	<0.001	41.9	49.1
250 - 749	29.1	<0.001	27.0	31.2	29.6	<0.001	27.6	31.5
Median [e]								
<250	54.4	<0.001	45.4	63.5	49.9	<0.001	41.5	58.2
250 - 749	36.6	<0.001	30.9	42.3	39.3	<0.001	34.1	44.6
750 - 1,999	33.0	<0.001	29.8	36.2	35.1	<0.001	32.1	38.1
2000 - 3,499	32.6	<0.001	30.5	34.8	32.6	<0.001	30.6	34.6
95th % [f]								
<4000	47.4	<0.001	40.0	54.8	48.4	<0.001	41.6	55.2
4000 - 5,999	37.7	<0.001	34.2	41.2	39.1	<0.001	35.8	42.3
6000 - 7,999	23.9	<0.001	21.2	26.8	26.2	<0.001	23.7	28.8
8000 - 11,999	25.3	<0.001	22.6	27.9	23.9	<0.001	21.4	26.3

Abbreviations: CI = Confidence interval.
[a] Distance (miles) is defined as the distance from the patient's home zip code to the TAVR center where patient received the TAVR procedure. Reference group is patients in highest population density area (>750 people per square mile). [b] Time (minutes) is defined as the time needed to travel from the patient's home zip code to the TAVR center where patient received the TAVR procedure. (Reference: >750 people per square mile). [c] Total land area of the state of Florida by population density measured as people per square miles; [d] excluding uninhabited land (i.e. excluding blocks with zero inhabitants) (Reference: >3,500 people per square mile); [e] Median population density per square mile of land; [f] 95th percentile of population density per square mile of land (Reference: >12,000 people per square mile); [g] The additional distance in miles travelled compared with the population density area. The models were adjusted for age, gender, and Elixhauser comorbidity index; [h] The additional time in minutes travelled compared with the population density area. The models were adjusted for age, gender, and Elixhauser comorbidity index.

Table 3. The mean difference in distance (miles) and time (minutes) from patient's home to transcatheter aortic valve replacement center by population density in Florida from 2011 to 2016 only among high volume centers defined as a center performing > 50 procedures per year. Note that the reference group is high-population density areas.

	Distance to TAVR Center (Miles) [a]				Time to TAVR Center (Minutes) [b]			
	β Coefficient [g]	*P Value*	95% CI		β Coefficient [h]	*P Value*	95% CI	
Total Land [c]								
<50	39.4	<0.001	31.8	47.0	41.8	<0.001	34.6	49.0
50 - 99	60.7	<0.001	55.5	66.0	63.3	<0.001	58.4	68.3
100 - 249	38.8	<0.001	35.5	42.2	39.8	<0.001	36.6	42.9
250 - 749	18.5	<0.001	16.2	20.7	17.1	<0.001	14.9	19.2
Zero Block [d]								
<50	51.3	<0.001	36.5	66.2	45.6	<0.001	31.7	59.5
50 - 99	48.7	<0.001	42.4	54.9	51.0	<0.001	45.2	56.9
100 - 249	42.0	<0.001	38.0	46.0	45.8	<0.001	42.1	49.6
250 - 749	32.2	<0.001	29.9	34.4	33.1	<0.001	31.0	35.2
Median [e]								
<250	55.9	<0.001	47.2	64.6	51.2	<0.001	43.0	59.4
250 - 749	33.1	<0.001	27.6	38.7	36.7	<0.001	31.4	41.9
750 - 1,999	31.6	<0.001	28.3	34.8	33.8	<0.001	30.7	36.8
2000 - 3,499	34.9	<0.001	32.6	37.2	35.6	<0.001	33.4	37.8
95th % [f]								
<4000	47.0	<0.001	40.0	54.0	48.4	<0.001	41.8	55.0
4000 - 5,999	38.0	<0.001	34.5	41.5	39.7	<0.001	36.4	43.1
6000 - 7,999	26.2	<0.001	23.4	28.9	28.9	<0.001	26.3	31.5
8000 - 11,999	30.6	<0.001	27.6	33.5	29.5	<0.001	26.7	32.3

Abbreviations: CI = Confidence interval.

[a] Distance (miles) is defined as the distance from the patient's home zip code to TAVR center where patient received TAVR procedure. Reference group is patients in highest population density area (>750 people per square mile). [b] Time (minutes) is defined as the time needed to travel from the patient's home zip code to TAVR center where patient received TAVR procedure. (Reference: >750 people per square mile). [c] Total land area of the state of Florida by population density measured as people per square miles; [d] excluding uninhabited land (i.e. excluding blocks with zero inhabitants) (Reference: >3,500 people per square mile); [e] Median population density per square mile of land; [f] 95th percentile of population density per square mile of land (Reference: >12,000 people per square mile). [g] The additional distance in miles travelled compared with the population density area. The models were adjusted for age, gender, and Elixhauser comorbidity index; [h] The additional time in minutes travelled compared with the population density area. The models were adjusted for age, gender, and Elixhauser comorbidity index.

OVERALL CONCLUSIONS

Geriatric Syndromes and Cardiovascular Disease

In **Chapter 1**, we conducted a large retrospective cohort study which examined the prevalence and impact of frailty among older patients admitted with AMI. Our study suggested that frailty is not uncommon during AMI hospitalization (Prevalence Rate ~ 19%). Similar to findings obtained from small single center studies, we demonstrated that frail older patients were less likely to receive revascularization strategies as a treatment for AMI, as compared to non-frail adults. With improvement in the overall cardiovascular care for AMI, the rate of PCI utilization for frail older patients have increased substantially and this increase was associated with decrease in the overall morality rate of frail patients over the past decade, although this association was stronger in non-frail patients, highlighting the potential for effect measure modification.

In **Chapter 2**, we aimed to differentiate the influence of frailty from the influence of coronary artery disease on five-year clinical outcomes in a prospective cohort using the National Health and Aging Trends Study. We demonstrated that among patients with coronary heart disease, the presence of baseline physical frailty led to higher incidence of geriatric syndromes during follow-up. These geriatric syndromes were incident dementia, loss of independence, ADL and IADL disability, and mobility disability as compared to non-frail patients. We have also demonstrated that among patients without coronary heart disease, the presence of physical frailty was a risk factor for major adverse cardiovascular events and all-cause mortality at five-year follow-up. This work is the first to disentangle the effect of frailty from the effect of underlying cardiovascular disease process on health outcomes. Frailty is a risk factor for adverse cardiovascular and geriatric risks. Because of these strong associations, routine assessment of

frailty as part of the cardiovascular care for older adults is needed and measures to prevent or reverse the development of frailty are critical gaps in knowledge in cardiovascular aging research that need to be addressed in future investigation.

In **Chapter 3**, we evaluated the prevalence of the geriatric syndrome sarcopenia and its influence on health-related quality of life in older adults with severe symptomatic aortic stenosis as part of a retrospective study with *de novo* data collection. We demonstrated that the prevalence of sarcopenia is high among older adults being considered for TAVR. While TAVR procedures are generally safe and prolong life for older adults with severe aortic stenosis, we found that the presence of muscle mass disorder had lower health-related quality of life metrics at one-year follow-up. As a next step, our team has put together a research proposal to investigate the influence of protein supplementation combined with resistant exercise training on health-related quality of life, frailty, and muscle mass during follow-up after TAVR procedure. This effort is instrumental in evaluating outcomes beyond hard clinical cardiovascular endpoints among older adults with valvular heart disease to focus on geriatric health for the elderly.

Healthcare Utilization and Cost in The Older Populations with Cardiovascular Disease

In **Chapter 4**, we examined the healthcare utilization and cost among older patients presented with sudden cardiac death from 2003 to 2012. With improvement in cardiovascular care for older patients in the cardiac intensive care units, we observed that the inflation adjusted cost associated with these hospitalizations was consistently increasing, regardless of the length of hospital stay. The concomitant presence of multiple chronic conditions (i.e. multimorbidity) with sudden cardiac death resulted in the greatest influence on healthcare cost. The post-cardiac arrest hospitalizations for older adults result in significant burden on healthcare system and the society

as a whole. Research that evaluates targeted interventions best associated with survival at low healthcare cost is needed. Further, the results of **Chapter 4** highlights the economic value of funding research into prevention of cardiac arrest in the older patient population.

In Chapter 5, we demonstrated that similar to cardiac arrest, the survival associated with STEMI-complicated by cardiogenic shock among older patients is improving in the years between 1999 to 2013. In a propensity matched analysis (n=64,766 patients), we showed that revascularization with PCI is increasing among these high-risk older patients. Further, PCI was associated with improvement in survival, as compared to patients who were not offered percutaneous revascularization. This can be explained by the improvement in procedural techniques, advancement in cardiovascular technologies, and better patient selection, which allow successful high risk coronary interventions in older complex patients. Despite these promising results, the overall mortality rate for older adults with STEMI-complicated by cardiogenic shock remains high. The aging process complicates the cardiovascular management because older patients have worse kidney function, presence of geriatric syndromes including frailty and multimorbidity, and predilection to medication induced adverse events. Studying geriatric syndromes in the context of acute cardiovascular illness remains a research priority highlighted in a recent Scientific Statement by the American Heart Association.[174]

In **Chapter 6**, we extended our evaluation of older adults with acute myocardial infarction to those in the very old age group (≥85 years: n =169,088). While this age group had high comorbidity burden and excessive mortality as compared to the young-old group (patients with age 75-79 years), the overall rate of utilization of percutaneous revascularization in very old age group was close to 20%. There was a sharp increase in the proportion of PCI use during AMI admission from the year 2000 to 2016. In a population of older adults that carries less risk than

that presented in **Chapter 5**, PCI utilization is on the rise. With such substantial increase in percutaneous revascularization among older patients, which is expected to further increase overtime, geriatric complexities highlighting best management strategies will be important areas for future investigations.

In **Chapter 7**, we studied the healthcare access and TAVR utilization rates for older adults with severe symptomatic aortic stenosis. We found that TAVR procedures for older patients are common in areas with high population density and that older patients who reside in low population density areas have significantly higher travel time and travel distance to receive TAVR. While the mortality rate varied minimally for patients who are living in low versus high population density regions, TAVR utilization rates was 7-fold in high population density areas, as compared to low density areas. Vulnerable older patients face obstacles in healthcare access when as it relates to specialized cardiovascular procedures that may create disparities in care. The inherent trade-offs between healthcare access and procedural mortality are important considerations for the care of the elderly.

In Conclusion, coronary heart disease, valvular heart disease, and sudden cardiac arrest are mainly diseases of older adults, and as this population grows, the prevalence of CVD worldwide continues to increase. However, many of the trials that have been conducted do not include older adults with typical geriatric complexities such as frailty, sarcopenia, multimorbidity, polypharmacy, and neurocognitive impairment. Thus, data pertaining to therapies best suited to this age group are lacking. Furthermore, health outcomes in older adults need to be tailored to improve symptoms, health-related quality of life, and functional status that incorporate aging complexities and move beyond an exclusively disease-centered approach.[6] The rising costs of healthcare and the increasing prevalence of cardiovascular disease drive the need

for preventative cardiovascular care for older adults. Basic science and translational research focused on cardiovascular aging as well as clinical trials that include representative populations of complex older patients will help develop better treatment insights with greater potential to improve quality of life, to reduce adverse side effects, and to reduce cardiovascular mortality and morbidity among CVD patients.[6]

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CURRICULIM VITAE

Abdulla Al Damluji

I. Personal

Academic Rank	Assistant Professor of Medicine (Part-Time) Johns Hopkins University
Primary Appointment	Interventional Cardiology Inova Heart and Vascular Institute
Secondary Appointment	Structural Heart Disease Inova Heart and Vascular Institute
Email	Abdulla.Damluji@jhu.edu
Twitter Handle	@DrDamluji
LinkedIn	linkedin.com/in/drdamluji

II. Higher Education

2000-2006	**Bachelor of Medicine and Surgery, MBChB** University of Baghdad, Baghdad, Iraq
2006-2007	**Master of Public Health, MPH** Johns Hopkins Bloomberg School of Public Health Johns Hopkins University, Baltimore, MD
2016-2020	**Doctor of Philosophy, PhD** Graduate Training Program in Clinical Investigation Johns Hopkins University, Baltimore, MD

III. Post Graduate Training

2009-2010	**Internal Medicine Internship** Department of Medicine, Penn State Hershey Medical Center Penn State University College of Medicine, Hershey, PA
2010	**Critical Care Medicine Research Fellowship** Division of Pulmonary and Critical Care Medicine Johns Hopkins University, Baltimore, MD

2010-2012	**Internal Medicine Residency** Department of Medicine, Hershey Medical Center Penn State University College of Medicine, Hershey, PA
2012-2015	**General Cardiology Fellowship** Division of Cardiovascular Diseases, Jackson Memorial Hospital University of Miami Miller School of Medicine, Miami, FL
2015-2016	**Interventional Cardiology Fellowship** Division of Cardiovascular Diseases, Jackson Memorial Hospital University of Miami Miller School of Medicine, Miami, FL

Board Certifications

2012	**ABIM, Internal Medicine, Diplomat** ABIM ID: 322626
2014	**American Board of Nuclear Cardiology, Diplomat** Eligibility ID: NC18936
2015	**National Board of Echocardiography, Diplomat** NBE ID: 00027776
2015	**ABIM, Cardiovascular Disease, Diplomat** ABIM ID: 322626
2018	**ABIM, Interventional Cardiology, Diplomat** ABIM ID: 322626

Certifications and Licensure

2004	**Certificate, Frontiers in Intestinal and Colorectal Diseases** St Mark's International Congress, St. Mark's Hospital
2007	**Certificate, Epidemiology and Biostatistics** Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
2007	**Certificate**, **Research Program Coordination** Johns Hopkins University, Baltimore, MD
2009	**Pennsylvania Medical Training License** MT 194380
2012	**Florida Medical License** ME 112629

2014-Current	**Basic Life Support, BLS** **Advanced Cardiovascular Life Support, ACLS**
2015	**Nuclear Cardiology Training Program** Level II Certification
2015	**Cardiac Echocardiography Training Program** Level II Certification
2015	**Vascular Ultrasonography Certification** Cleveland Clinic, Weston, Florida
2015	**National Board of Echocardiography, Testamur** NBE ID: 00027776
2016	**Council for Certification in Cardiovascular Imaging, Diplomat** CBNC ID: 9803
2016	**Maryland Medical License** D0081288
2018	**Virginia Medical License** 0101265563

IV. Experience

Academic Appointments

2012-2016	**Miami Structural Heart Disease Program, Research Fellow** University of Miami Hospital Miller School of Medicine, Miami, FL
2012-2016	**Cardiovascular Module, Instructor** MD, MD/PhD, and MD/MPH Programs University of Miami Miller School of Medicine, Miami, FL
2016-Current	**Assistant Professor of Medicine (Part-Time)** Division of Cardiology Johns Hopkins University, Baltimore, MD

Clinical/Hospital Appointments

2007-2008	**Critical Care Medicine, Research Program Coordinator** Johns Hopkins University, Baltimore, MD
2012-2016	**Clinical Fellow in Medicine**

	Interventional Cardiology, Structural Heart Disease University of Miami Hospital, Miller School of Medicine
2012-2016	**Staff Physician, Department of Emergency Medicine** Miami VA Medical Center, Miami, FL
2016-2019	**General Cardiology Consultation Service** Sinai Hospital, LifeBridge Health Cardiovascular Institute LifeBridge Health, Baltimore, MD
2016-2019	**Interventional Cardiologist, Department of Medicine** Sinai Hospital of Baltimore, Cardiovascular Institute LifeBridge Health, Baltimore, MD
2016-2019	**Structural Heart Disease Operator, Department of Medicine** Beverly and Jerome Fine Cardiac Valve Center LifeBridge Health, Baltimore, MD
2016-2019	**Co-director, Sinai Program in Health Outcomes Research** Department of Medicine, LifeBridge Health, Baltimore, MD
2019-Current	**Director, Inova Center for Outcomes Research (ICOR)** Inova Heart and Vascular Institute, Falls Church, VA
2019-Current	**Interventional Cardiologist, Alexandria Hospital** Inova Heart and Vascular Institute, Alexandria, VA
2019-Current	**Interventional Cardiologist, Inova Fairfax** Inova Heart and Vascular Institute, Falls Church, VA
2019-Current	**Cardiologist, Inova Mt. Vernon Hospital** Inova Heart and Vascular Institute, Alexandria, VA

Honors and Awards

2000	**National Baccalaureate** Average: 93%; Score: 650/700; Nationwide Rank: 29/>100,000 students Baghdad College, Baghdad, Iraq
2004	**Predoctoral Research Scholar** St Mark's Hospital, Harrow, London, United Kingdom
2006	**Distinction, Final Examination, Department of Medicine** University of Baghdad, Baghdad, Iraq
2008	**Research Excellence for Young Physicians Recipient**

	NAAMA, Washington, DC
2010	**J. Lloyd Huck Chair in Medicine Letter of Recognition Recipient** Robert Aber, MD, MACP, Professor and Chair-Department of Medicine Pennsylvania State College of Medicine, Hershey, PA
2010	**Outstanding Intern of the Year** Department of Medicine, Penn State College of Medicine, Hershey, PA
2011	**Research Poster Finalist** Hyponatremia in the Hospitalized Orthopedic Patients American College of Physicians, National Conference, San Diego, CA
2011	**Hepatology Resident of the Year** Division of Gastroenterology and Hepatology Penn State University College of Medicine, Hershey, PA
2011	**Department of Medicine Award for Excellence in Academic Research** Department of Medicine, Penn State University, Hershey, PA
2012	**Award for Best Clinical Research Abstract Recipient** American College of Physicians, Mid-Atlantic Meeting
2013	**Featured Publication Award Recipient, MDLINX.COM/Nephrology** Reversal of End Stage Renal Disease in Patients with TAVR
2013	**Fellows in Training Scholarship Program Award Recipient** Complex Cardiovascular Catheter Therapeutics, Orlando, FL
2013	**Association of Subspecialty Professors Grant Recipient** Council on Cardiovascular Care of Older Adults American College of Cardiology, San Francisco, CA
2013	**Young Investigator Award Poster Finalist** American College of Cardiology, Florida Chapter
2014	**How to Become Cardiovascular Investigator Travel Grant** Heart House, American College of Cardiology, Washington, DC
2014	**Cardiovascular Research Technologies Fellowship Grant** MedStar Washington Hospital Center, Washington, DC
2014	**25th Annual Cardiovascular Interventions Fellowship Award** Scripps Clinic, La Jolla, California
2014	**Robert J Myerburg Outstanding Research Fellow Award**

	Division of Cardiology, University of Miami, Miami, Florida
2015	**Letter of Recognition, *PLOS ONE* Journal** Reference: (2015) PLOS ONE 2014 Reviewer Thank You. PLoS ONE 10(2): e0121093; doi: 10.1371/journal.pone.0121093
2015	**Geriatric Section Editorial Fellow Award** Geriatric Cardiology Section Editorial Board Meeting American College of Cardiology Conference, San Diego CA
2015	**American College of Cardiology/American Geriatric Society/National Institute of Aging Multimorbidity in Older Adults Workshop Planning Committee, Travel Award Recipient** Heart House, American College of Cardiology, Washington, DC
2015	**Robert J Myerburg Outstanding Research Fellow Award** Cardiovascular Division, University of Miami, Miami, Florida
2015	**Cardiovascular Division Research Grant Recipient ($5,000)** University of Miami Miller School of Medicine, Miami, Florida
2016	**Cardiovascular Research Technologies (CRT) Fellowship Grant** MedStar Washington Hospital Center, Washington, DC
2016	**Edwards LifeSciences TAVR Foundation Training Grant** Travel and educational grant, Therapy Development, New York, NY
2017	**Best Scientific Abstract, American College of Cardiology** Selected for Oral Presentation for Geriatric Cardiology Section ACC'17 Washington, DC.
2017	**Johns Hopkins Claude D. Pepper Scholar** Older Americans Independent Center, Johns Hopkins University
2018	**Johns Hopkins Claude D. Pepper Scholar** Older Americans Independent Center, Johns Hopkins University
2018	**Featured Publication "Editor's Picks"** *Circulation: Arrhythmia & Electrophysiology* This research publication was selected as one of the two "Editor's Picks" article, which was distributed free of charge to all readers without regard to institutional or individual subscription.
2018	**Best Research Abstract, The National Pepper Center Conference** On Behalf of the OAIC Center, at Johns Hopkins University Funded by the National Institute on Aging, NIH

2018	**Early Career Reviewer** **Clinical and Integrative Cardiovascular Sciences (CICS) Study Section** National Heart, Lung, and Blood Institute, National Institute of Health
2018	**Mentor, The American College of Cardiology/American Geriatric Society/National Institute on Aging** **(Diagnostic Testing in Older Adults with CVD)** Selected as a "Mentor" to early career investigators by ACC leadership
2018-2019	**Chair, Acute Cardiovascular Care in Older Patients** **The American Heart Association** Chair and Moderate of AHA Scientific Session, Chicago, IL

V. Publications

Peer-Reviewed Publications

Pubmed: https://www.ncbi.nlm.nih.gov/myncbi/1JQ25jftneeAe/bibliography/public/

1. Forbes A, **Al-Damluji A**, Ashworth S et al. Multicentre randomized-controlled clinical trial of Ipocol, a new enteric-coated form of mesalazine, in comparison with Asacol in the treatment of ulcerative colitis. Aliment Pharmacol Ther 2005;21:1099-104.

2. Mendez-Tellez PA, **Damluji A**, Ammerman D et al. Human immunodeficiency virus infection and hospital mortality in acute lung injury patients. Crit Care Med 2010;38:1530-5.

3. Wozney JL, **Damluji AA**, Ahmed F, Zangari M, Loughran TP, Jr., Talamo G. Estimation of daily proteinuria in patients with multiple myeloma by using the protein-to-creatinine ratio in random urine samples. Acta Haematol 2010;123:226-9.

4. **Damluji A**, Colantuoni E, Mendez-Tellez PA et al. Short-term mortality prediction for acute lung injury patients: external validation of the Acute Respiratory Distress Syndrome Network prediction model. Crit Care Med 2011;39:1023-8.

5. **Damluji A**, Gilchrist IC. When size matters: feasibility of using larger diameter radial catheters. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions 2012;79:601-2.

6. Kho ME, **Damluji A**, Zanni JM, Needham DM. Feasibility and observed safety of interactive video games for physical rehabilitation in the intensive care unit: a case series. J Crit Care 2012;27:219 e1-6.

7. **Damluji A**, Gilchrist IC. Teaching old dogs new tricks. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions 2013;82:9-10.

8. **Damluji A**, Zanni JM, Mantheiy E, Colantuoni E, Kho ME, Needham DM. Safety and feasibility of femoral catheters during physical rehabilitation in the intensive care unit. J Crit Care 2013;28:535 e9-15.

9. **Damluji A**, Bilsker MS, Cohen MG. Reversal of end stage renal disease in patient with transcatheter aortic valve replacement. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions 2014;83:482-4.

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22. **Damluji AA**, El-Maouche D, Alsulaimi A et al. Accelerated atherosclerosis and elevated lipoprotein (a) after liver transplantation. J Clin Lipidol 2016;10:434-7.

23. **Damluji AA**, Macon C, Fox A et al. The association between in-hospital hemoglobin changes, cardiovascular events, and mortality in acute decompensated heart failure: Results from the ESCAPE trial. Int J Cardiol 2016;222:531-537.

24. **Damluji AA**, Pomenti SF, Ramireddy A et al. Influence of Total Coronary Occlusion on Clinical Outcomes (from the Bypass Angioplasty Revascularization Investigation 2 DiabetesTrial). Am J Cardiol 2016;117:1031-8.

25. Sager SJ, **Damluji AA**, Cohen JA et al. Transient and persistent conduction abnormalities following transcatheter aortic valve replacement with the Edwards-Sapien prosthesis: a comparison between antegrade vs. retrograde approaches. J Interv Card Electrophysiol 2016;47:143-151.

26. Singh V, **Damluji AA**, Mendirichaga R et al. Elective or Emergency Use of Mechanical Circulatory Support Devices During Transcatheter Aortic Valve Replacement. J Interv Cardiol 2016;29:513-522.

27. Chaudhary R, **Damluji A**, Batukbhai B et al. Venous Thromboembolism Prophylaxis: Inadequate and Overprophylaxis When Comparing Perceived Versus Calculated Risk. Mayo Clin Proc Innov Qual Outcomes 2017;1:242-247.

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29. **Damluji AA**, Cohen ER, Moscucci M et al. Insulin provision therapy and mortality in older adults with diabetes mellitus and stable ischemic heart disease: Insights from BARI-2D trial. Int J Cardiol 2017;241:35-40.

30. **Damluji AA**, Myerburg RJ, Chongthammakun V et al. Improvements in Outcomes and Disparities of ST-Segment-Elevation Myocardial Infarction Care: The Miami-Dade County ST-Segment-Elevation Myocardial Infarction Network Project. Circ Cardiovasc Qual Outcomes 2017;10.

31. **Damluji AA**, Nelson DW, Valgimigli M et al. Transfemoral Approach for Coronary Angiography and Intervention: A Collaboration of International Cardiovascular Societies. JACC Cardiovasc Interv 2017;10:2269-2279.

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33. **Damluji AA**, Al-Damluji MS, Pomenti S et al. Health Care Costs After Cardiac Arrest in the United States. Circ Arrhythm Electrophysiol 2018;11:e005689.

34. **Damluji AA**, Murman M, Byun S et al. Alternative access for transcatheter aortic valve replacement in older adults: A collaborative study from France and United States. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions 2018;92:1182-1193.

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37. **Damluji AA**, Bandeen-Roche K, Berkower C et al. Percutaneous Coronary Intervention in Older Patients With ST-Segment Elevation Myocardial Infarction and Cardiogenic Shock. Journal of the American College of Cardiology 2019;73:1890-1900.

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39. Batchelor W, Dahya V, Tehrani B, **Damluji A**, et al. Radial artery remodeling following transradial percutaneous coronary intervention in men and women: insights from serial ultrahigh frequency ultrasonography. *Cardiovasc Revasc Med.* 2019.

40. Rout A, Madianos E, Pfeffer P, **Damluji AA**. Transcatheter Aortic Valve Replacement in a Sinus of Valsalva Aneurysm: The Evolving Role of Structural Cardiac Imaging. *Circulation: Cardiovascular Imaging.* 2019; In-press

41. **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 Sep 3;8(17):e013686. doi: 10.1161/JAHA.119.013686. Epub 2019 Aug 31. PubMed PMID: 31475601.

42. **Damluji AA**, Forman DE, van Diepen S, Alexander KP, Page RL, 2nd, Hummel SL, Menon V, Katz JN, Albert NM, Afilalo J and Cohen MG. Older Adults in the Cardiac Intensive Care Unit: Factoring Geriatric Syndromes in the Management, Prognosis, and Process of Care: A Scientific Statement From the American Heart Association. *Circulation*. 2019:Cir0000000000000741.

43. Batchelor W, Dahya V, Tehrani B, **Damluji AA**, et al. Radial artery remodeling following transradial percutaneous coronary intervention in men and women: insights from serial ultrahigh frequency ultrasonography. Cardiovasc Revasc Med 2019. *Cardiovasc Revasc Med*. 2020

Peer-Reviewed Electronic Publications

1. **Damluji A**, Forman DE. Secondary Prevention of Atherosclerotic Cardiovascular Disease in Older Adults | Expert Analysis. *http://www.acc.org/*. October 26, 2015. (Last accessed on July 3, 2017) http://www.acc.org/latest-in-cardiology/articles/2015/10/23/08/33/secondary-prevention-of-atherosclerotic-cardiovascular-disease-in-older-adults.

2. **Damluji A**, Forman DE. Secondary Prevention of Atherosclerotic Cardiovascular Disease in Older Adults | Patient Case Quiz. *http://www.acc.org/*. October 26, 2015. (Last accessed on July 3, 2017) http://www.acc.org/education-and-meetings/patient-case-quizzes/secondary-prevention-of-atherosclerotic-cardiovascular-disease-in-older-adults.

3. **Damluji A**, Forman DE. Statin Therapy for Secondary Prevention of Atherosclerotic Disease | Clinical Image. *http://www.acc.org/*. (Last accessed on July 3, 2017) http://www.acc.org/education-and-meetings/image-and-slide-gallery/media-detail?id=1995627319444428c92b4c8db1e814794.

4. Nunez Breton JD, Chongthammakun V, **Damluji A**. Embolic Stroke with Chronic Cluster Headaches: The Role of Three-Dimensional Transesophageal Echocardiography for Surgical Risk Stratification. European Society of Cardiology Clinical Case Galleries. (Last accessed on July 3, 2017) http://learn.escardio.org/clinicalcase/casedetail/edc35400-0872-4b92-8242-e1e6a3fd93d8

5. **Damluji A**, Krishnaswami A, Normand SL. Prasugrel or Clopidogrel Based on Chronological Age Cutoff in Two Older Men after Percutaneous Coronary Intervention. (Last accessed on July 3, 2017) http://www.acc.org/education-and-meetings/patient-case-quizzes/prasugel-or-clopidogrel-based-on-a-chronological-age-cutoff-after-pci

Non-Peer Reviewed Publications (Editorials)

1. **Damluji A**, Sepulveda K & Needham D. Understanding and improving long-term sequelae of ARDS. The Journal of Respiratory Diseases. *The Journal of Respiratory Diseases*. 2008; **29:**198-199.

2. **Damluji A**, Siddiqi F, Dinglass V & Needham D. Long-Term Outcomes after Acute Lung Injury/Acute Respiratory Distress Syndrome. *US Respiratory Disease.* 2008; **2:**89-92.

3. **Damluji A** & Gilchrist IC. When size matters: feasibility of using larger diameter radial catheters. *Catheter Cardiovasc Interv.* 2012; **79:**601-602.

4. **Damluji A**, Gilchrist IC. Teaching Old Dogs New Tricks. *Catheterization and Cardiovascular Interventions.* 2013;82(1):9-10.

5. **Damluji AA**, Cohen MG. Aortic balloon valvuloplasty and severe systolic dysfunction. Is there a danger zone? *Catheterization and cardiovascular interventions* : official journal of the Society for Cardiac Angiography & Interventions. 2014;84:832-3.

6. **Damluji AA**, Moscucci M. Reply: Benefit of Primary Percutaneous Coronary Intervention in Elderly Patients With Cardiogenic Shock. J Am Coll Cardiol. 2019 Aug 13;74(6):824-825. doi: 10.1016/j.jacc.2019.06.016. PubMed PMID: 31395138.

Textbooks and General Books

1. **Damluji A,** Ramireddy A, Forman DE. Management and Care of Older Cardiac Patients. *Encyclopedia of Cardiovascular Research and Medicine.* Publication Date: 2017; Publisher: Elsevier.

Book Chapters/Meeting Proceedings

1. **Damluji A**, Forman D. Secondary Prevention of Cardiovascular Disease in the Elderly; Essentials of Cardiovascular Care in Older Adults (ECCOA) http://www.cardiosource.org/ECCOA

2. **Damluji A.** The influence of frailty and multimorbidity on acute cardiovascular care in the cardiac intensive care unit: A contemporary approach in the management of a growing population. American Heart Association Scientific Sessions. November 10-12, 2018

Acknowledgements

1. Dinglas VD, Friedman LA, Colantuoni E, Mendez-Tellez PA, Shanholtz CB, Ciesla ND, Pronovost PJ, Needham DM. Muscle Weakness and 5-Year Survival in Acute Respiratory Distress Syndrome Survivors. *Crit Care Med* 2017. 45(3):446-453. doi: 10.1097/CCM.0000000000002208

2. O. J. Bienvenu, J. Gellar, B. M. Althouse, E. Colantuoni, T. Sricharoenchai, P. A. Mendez-Tellez, C. Shanholtz, C. R. Dennison, P. J. Pronovost and D. M. Needham Post-

traumatic stress disorder symptoms after acute lung injury: a 2-year prospective longitudinal study. Psychological Medicine, Available on CJO 2013 doi:10.1017/S0033291713000214

3. Needham DM, Colantuoni E, Mendez-Tellez PA, Dinglas VD, Sevransky JE, Dennison Himmelfarb CR, Desai SV, Shanholtz C, Brower RG & Pronovost PJ. Lung protective mechanical ventilation and two year survival in patients with acute lung injury: prospective cohort study. *BMJ* 2012; **344:**e2124.

4. Bienvenu OJ, Colantuoni E, Mendez-Tellez PA, Dinglas VD, Shanholtz C, Husain N, Dennison CR, Herridge MS, Pronovost PJ & Needham DM. Depressive symptoms and impaired physical function after acute lung injury: a 2-year longitudinal study. *Am J Respir Crit Care Med* 2012; **185(5):**517-524.

5. Dinglas VD, Gellar J, Colantuoni E, Stan VA, Mendez-Tellez PA, Pronovost PJ & Needham DM. Does intensive care unit severity of illness influence recall of baseline physical function? *J Crit Care* 2011; **26:**634 e631-637.

6. Dowdy DW, Bienvenu OJ, Dinglas VD, Mendez-Tellez PA, Sevransky J, Shanholtz C & Needham DM. Are intensive care factors associated with depressive symptoms 6 months after acute lung injury? *Crit Care Med* 2009; **37(5):**1702-1707.

7. Dowdy DW, Dinglas V, Mendez-Tellez PA, Bienvenu OJ, Sevransky J, Dennison CR, Shanholtz C & Needham DM. Intensive care unit hypoglycemia predicts depression during early recovery from acute lung injury. *Crit Care Med* 2008; **36(10):**2726-2733.

8. Needham DM, Yang T, and Dinglas VD et al. Timing of low tidal volume ventilation and intensive care unit mortality in acute respiratory distress syndrome. A prospective cohort study. Am J Respir Crit Care Med. 2015 Jan 15;191(2):177-85. doi: 10.1164/rccm.201409-1598OC.

Podium Presentations

1. **Damluji A.** "Iraq: Rebuilding a Nation's Health". Conference: Revitalizing Iraq's Health Infrastructure; Co-organizer and part of a multi-panel conference at the JHSPH Speakers: Iraqi Ambassador to the United Nations, Mr. Faisal Istrabadi and Jordanian; Ambassador to Washington DC, Prince Zeid Ra'ad Zeid Al-Hussein. Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland http://www.jhsph.edu/publichealthnews/articles/2007/iraq_symposium.html

2. **Damluji A.** "External Validation to the ARDSNet Prediction Model for Mortality in ALI"; Department of Medicine Research Conference, June 4, 2010; Pennsylvania State College of Medicine

3. **Damluji A.** "Delirium and Acute Brain Dysfunction: An Unrecognized Epidemic" Grand Rounds: Department of Medicine, March 19, 2010; Pennsylvania State College of Medicine

4. **Damluji A et al.** "Prompt Revascularizations vs. Intensive Medical Therapy for Chronic Total Occlusions of Coronary Arteries: Results from BARI-2D Trial"
Surgical Revascularization for Ischemic Heart Disease Session, Monday November 17, 2014; American Heart Association Scientific Session, Chicago, IL

5. **Damluji A et al.** Insulin Provision Therapy and Increased Mortality in Elderly Patients with Diabetes Mellitus and Stable Ischemic Heart Disease: Insights from BARI-2D Trial; Highlighted Original Research: Stable Ischemic Heart Disease and the Year in Review; Sunday March 15, 2015; American College of Cardiology, San Diego, CA

6. **Damluji A et al.** LV Systolic Dysfunction is Improved by TAVR: Insights from the French American Registry. American Heart Association Scientific Session, Orlando, Florida

7. **Damluji A et al.** The Incidence and Outcomes of Acute Kidney Injury after TAVR. American Heart Association Scientific Session, Orlando, Florida

8. **Damluji A et al.** Percutaneous coronary intervention in adults age 75 years or older with STEMI and cardiogenic shock. American College of Cardiology, Geriatric Section, Washington, D.C. March 2017.

9. **Damluji A et al.** Older On behalf of the Johns Hopkins University's Claude D. Pepper Older Americans Independence Center: "Hot Topics". Pepper Coordinating Centers Conference. May 2018.

10. **Damluji A**, Bandeen-Roche K, Forman DE, Gerstenblith G, Huang J, Moscucci M, Resar R, Varadhan, Walston JD, Segal JB. Frailty among Patients with Acute Myocardial infarction. International Conference on Frailty and Sarcopenia Research, Miami Beach, USA. Feb 20-22 2019.

11. **Damluji A.** Measuring Frailty Status in Older Adults with Acute Myocardial Infarction in Population-based Studies: Feasibility to Capture Prevalence and Effect Measure Modification. International Conference on Frailty and Sarcopenia Research, Miami Beach, USA. Feb 20-22 2019.

VI. Professionalism

Statistical Skills	**Statistical modeling for biomedical research** Package: STATA 15 (STATA Corp LLC, College Station, Texas) • Generalized linear modules. • Inferential statistics.

- Simple & multiple linear regressions.
- Simple & multiple logistic regressions.
- Survival analyses - hazards regression analysis.
- Multiple Poisson regression.
- Fixed and repeated effects analysis of variance.

Other Activities

Iraq Olympic Swimming Team- Butterfly (100m and 200m)
2000, Qualified, Finals-International Regional Swimming Olympics, (Middle East and Africa), Amman, Jordan

Editorial Responsibilities

2014 – Reviewer, PLOS ONE
2014 – Reviewer, Journal of Interventional Cardiology
2016 – Reviewer, American Journal of Cardiology
2016 – Reviewer, Circulation
2017 – Reviewer, European Heart Journal
2018 – Reviewer, Journal of the American Heart Association
2019 – Reviewer, Journal of the American Medical Association
2019 – Reviewer, British Medical Journal
2019 – American Heart Journal
2019 – Circulation: Cardiovascular Interventions

Professional and Honorary Organizations

2009 American College of Physicians, Member (Member ID: 01437419)
2009 Society of Critical Care Medicine, Member
2012 Society of General Internal Medicine, Member
2012 American College of Cardiology, Member
2013 American Society of Nuclear Cardiology, Member
2013 Society of Cardiovascular Computed Tomography, Member
2014 National Lipid Association, Member (ID: 31879)
2014 American Heart Association, Fellow
(Quality of Care and Outcomes Research and Council on Clinical Cardiology)
2015 American Society of Echocardiography, Member (171687)
2015 American Society of Nuclear Cardiology, Member
2016 American College of Physicians, Fellow (Member ID: 01437419)
2016 American College of Cardiology (ACC), (Elected Fellow)

VII. Research Support

Johns Hopkins University **Damluji (PI)** 07/01/2016—06/30/2020
Frailty after Acute Myocardial Infarction

This Johns Hopkins University grant supported acquisition of the Premier Healthcare Database to evaluate the prevalence of frailty in older adults admitted with acute myocardial infarction in the United States.

The Rodbell Family Foundation **Damluji (PI)** 12/01/2017—11/30/2019
Percutaneous Coronary Interventions in Older Adults with STEMI and Cardiogenic Shock
The main premise of this award was to study health outcomes for older patients admitted with ST-elevation myocardial infarction complicated by cardiogenic shock.

Completed Support (past three years)

P30-AG021334 **Walston (PI)** 07/01/2017—06/30/2019
NIH/NIA—Older Americans Independence Center (Claude E. Pepper) Scholar Award
I was awarded the Research and Educational Component (REC) award from the Johns Hopkins Claude E. Pepper center to study older adults with frailty and multisystem dysregulation after the diagnosis of acute myocardial infarction.

LifeBridge Health Cardiovascular Institute **Damluji (PI)** 07/01/2016—06/30/2017
Economic Outcomes After Cardiac Arrest in the United States.
This grant aimed to establish the economic outcomes after sudden cardiac arrest in a nationally representative sample of hospitalizations in the United States

K23HL153771 **Damluji (PI)** 07/01/2020—06/30/2025
NIH/NHLBI—Frailty and Resiliency in Older Adults with Acute Myocardial Infarction
Status: Submitted—pending IRG Review; Impact Score: 31