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Bajracharya. R., Orwig. D., Guralnik. J., Shardell. M., Rathbun. A., Yamashita. T., Magaziner. J. (2021). *Long-term Sex Differences in All-cause and Infection-specific Mortality. (November 10-14). In GSA 2021 Annual Scientific Meeting. Gerontological Society of America.*

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Bajracharya. R., Orwig. D., Guralnik. J., Shardell. M., Rathbun. A., Yamashita. T., Magaziner. J. (2021). Examining Post-Hip fracture Characteristics to explain sex differences in short- and long-term Hip fracture Mortality.

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Abstract

Title of Dissertation: Examining Post-Hip Fracture Characteristics to Explain Sex Differences in Short- and Long-term Hip Fracture Mortality

Rashmita Bajracharya, Doctor of Philosophy, 2021 Dissertation

Directed by: Denise Orwig, Professor, School of Medicine, Department of Epidemiology and Public Health, Division of Gerontology

Abstract (Word count: 350)

Men die at a higher rate than women up to two years after a hip fracture. Moreover, the number of hip fractures among men is expected to increase over the next 30 years with potential sex differences in long-term trajectories of recovery. Therefore, Aim 1 assessed whether male sex was a significant risk factor of all-cause and infection-specific mortality after hip fracture; Aim 2 determined if sex moderated the association between physical performance at 2 months post-fracture and mortality; and Aim 3 evaluated the mediating role of depressive symptoms (at 2 months post-fracture) on the association between TNFα-R1 and mortality and if sex moderated the inflammation-depressive symptoms-mortality link.

Data were from the Baltimore Hip Studies (BHS) 7th cohort (168 men,171 women) that recruited participants in eight hospitals within the BHS network. Women were frequency-matched (1:1) to men on timing of admission. Cox proportional hazard models evaluated associations between sex and mortality (Aim 1) and the moderating effect of sex between physical performance measures and mortality (Aim 2). An Aalen additive hazard model was created and later stratified by sex to assess the mediating effect of depressive symptoms in the association of TNFα-R1 with mortality (Aim 3).

Participants were average age of 80 years and the median mortality follow-up was 4.9 (Interquartile Range=2.3-8.7) years. Men had significantly higher all-cause [Hazard Ratio (HR)=2.31, 95% confidence interval (CI) 2.02-2.59] and infection-specific [HR=4.43, 95% CI 2.07-9.51] mortality. One-unit higher on each physical performance measure was associated with lower mortality [SPPB (HR=0.91, CI=0.83-0.98); gait speed (in 0.1 meters/second) (HR=0.98, CI=0.97-0.99); and grip strength (in kg) (HR=0.95, CI=0.93-0.98)], but the associations did not differ by sex. TNFα-R1 had stronger association with mortality among men compared to women; there were 161 (95%, CI=36-286) and 16 (95%, CI=-58-89) additional deaths in men and women per 1,000 person-years, respectively in the 3rd TNFα-R1 tertile compared to the 1st tertile. However, depressive symptoms did not mediate the association between TNFα-R1 and all-cause mortality in either sex.

Results show higher long-term mortality in men and that infection and elevated acute TNFα-R1 levels may play a role in the sex difference.

Examining Post-Hip Fracture Characteristics to Explain Sex Differences in Short- and Long-term Hip Fracture Mortality

by
Rashmita Bajracharya

Dissertation submitted to the Faculty of the Graduate School of the
University of Maryland, Baltimore in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
2021

Dedication

To my parents, Dan Laxmi “mummy” and Laxmi Chandra “daddy”

To my tata(s) (Sister in my native language) “Rohita tata, Binita tata and Sajina tata”

&

Last but not the least my husband, love of my life, “Sabin”

Acknowledgements

I would like to thank all my committee members Dr. Denise Orwig, Dr. Jack Guralnik, Dr. Michelle Shardell, Dr. Alan Rathbun, Dr. Takashi Yamashita, and Dr. Jay Magaziner for their continuous support in getting my dissertation to the finish line. My special thank goes to Dr. Denise Orwig, who served as my dissertation chair and mentored me during the challenging times of COVID restrictions.

I would also like to thank my friends Jennifer, Shalini, Haesung, Renusha, Seema, and Rabina for encouraging me to keep going when I struggled most.

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List of Abbreviations

SPPB	Short Physical Performance Battery
TNFα	Tumor Necrosis Factor Alpha
BMI	Body Mass Index
LPADL	Lower-Extremity Physical Activities of Daily Living
3MS	Modified-Mini Mental Status
CES-D	Center for Epidemiological Studies Depression
METS	Metabolic Equivalents
BMD	Bone Mineral Density
CRP	C-Reactive Protein
IL-6	Interleukin-6
IDO	Indoleamine 2,3-dioxygenase
BHFS	Brabant Hip Fracture Score
CCI	Charlson Comorbidity Index
O-POSSUM	Orthopedic version of the Physiologic and Operative Severity Score for the Enumeration of Mortality and Morbidity
AUC	Area under the curve
Hb	Hemoglobin
BHS-7	Baltimore Hip Studies-7th cohort study
AIC	Akaike information criterion
CART	Classification and Regression Tree
ELISA	Enzyme-Linked Immunosorbent Assay

CHAPTER 1- INTRODUCTION

More than 260,000 older adults are hospitalized for hip fracture each year in the United States (U.S.).[1] As the older adult population is a growing proportion of the U.S. population, the incidence of hip fracture is projected to increase to 750,000 per year by 2050.[2] Hip fracture is a major public health issue because of a high economic burden to the health care system with total annual direct medical cost of hip fracture estimated at $5.9 billion to the U.S. health care system.[3] Similarly, long-term disability post hip fracture is high with 72-80% of older adults not able to perform their lower extremity activities of daily living at pre-fracture level 12 months post hip fracture.[4] Mortality rate post hip fracture is also high, and almost 60% of hip fracture patients die within five years post hip fracture surgery.[5]

Extant research shows that the mortality rate is significantly higher in men compared to women for the first two years post hip fracture and little is known about sex difference after 2 years.[6] Aging research has universally shown that men die earlier in life compared to women, where sex differences in mortality rates begin to appear after 45 years of age. [8] However, hip fracture is not a normal part of aging, and therefore, higher mortality among men compared to women after hip fracture may not simply be a consequence of life course differences between biological sexes. Hip fracture is a traumatic event leading to sudden disability and the recovery process entails betterment in physical, psychological, and social characteristics.[7] Inability to recover in these characteristics may explain mortality in hip fracture patients. It is not clear in the literature if there are certain characteristics post hip fracture that can explain sex difference in mortality. According to extant research, higher mortality in men may be

attributed to chronic comorbidities prior to hip fracture and higher likelihood of postoperative complications such as delirium, pneumonia, acute renal failure, and urinary retention in men.[8] Establishing clinical characteristics that account for sex differences in morality after hip fracture has the potential to identify individuals who may be pre-disposed for poor survival.

Current research has assessed the association of characteristics like age, sex, nursing home residence prior to hip fracture, cognitive functioning, and comorbidity with mortality.[9] However, the association of other clinical characteristics like physical performance measures [Short Physical Performance Battery (SPPB), gait speed, and grip strength], tumor necrosis factor α (TNFα) and depressive symptoms has not been evaluated in hip fracture patients. Given the strong association of Short Physical Performance Battery (SPPB),[10,11] gait speed,[12,13],grip strength[14,15], TNFα and depressive symptoms, [16,17] with mortality in the general older adult population; these characteristics may explain mortality outcomes in hip fracture patients.

1.1 Purpose and Overview of Manuscripts

The primary aims of this dissertation are to assess post-operative hip fracture characteristics that may explain sex-differences in short- and long-term mortality that have the potential to identify individuals who may be pre-disposed for poor survival, and more importantly, yield results that can be used to develop more targeted and tailored multi-modal interventions to enhance hip fracture recovery. The aims of this dissertation were addressed in three different manuscripts.

1.2 Sex Difference in All-Cause and Infection-Specific Mortality Post Hip Fracture (Manuscript #1)

Manuscript #1 determined if sex was associated with all-cause mortality and infection-specific mortality up to 10.2 years of follow up controlling for age, cognition, comorbidity, body mass index (BMI), depressive symptoms, and pre-fracture Lower-Extremity Physical Activities of Daily Living (LPADL) limitations. There are inconsistent findings among the few studies that have assessed sex differences in all-cause mortality beyond two years post-hip fracture. [18,19] Past studies have also shown that within two years of hip fracture, men are more likely to experience a respiratory infection (e.g., pneumonia) and die compared to women.[6,20,21] However, it remains unclear if the higher incidence of infectious deaths post-hip fracture in men compared to women persists long-term.

1.3 Determining if Sex Moderates the Association of SPPB, Gait Speed, and Grip Strength with All-Cause Mortality (Manuscript #2)

Manuscript #2 determined if SPPB, gait speed, and grip strength measured at 2 months after a hip fracture was associated with all-cause mortality differently in men and women. Although the association between physical performance measures and mortality in hip fracture patients has not been examined previously, physical performance measures are strongly associated with mortality in the general older adult population.[10–15] The moderating effect of sex on the association of physical performance measures and mortality in non-hip fracture populations has been mixed with stronger association of grip strength with mortality in women compared to men and statistically insignificant sex differences in the association of gait speed and mortality. [14,22,23] It is not clear if there is

an association between physical performance measures and mortality and whether the association is different by sex in hip fracture patients. We also assessed if physical performance measures were better at predicting post hip fracture mortality compared to the previously known predictors of mortality in hip fracture patients like age and comorbidity. A prior study conducted in older adults with acute myelogenous leukemia found that adding SPPB into their model with geriatric assessment measures improved the discrimination of mortality.[24] Similarly, gait speed and SPPB were predictive of mortality among general population older adults, even after controlling for important predictors of mortality like age and comorbidity.[25] It is unclear if physical performance measures alone or in combination with previously known predictors of mortality in hip fracture patients like age, sex, cognition, and comorbidity improves prediction of post hip fracture mortality.

1.4 Determining if Sex Moderates the TNFα-Depressive Symptoms-Mortality Association (Manuscript #3)

Manuscript #3 determined if the mediating role of depressive symptoms in the association of TNFα-R1 and all-cause mortality was different in men and women after a hip fracture. TNFα-R1 is the optimal proxy for TNFα because TNFα-R1 has a long-term bioavailability in the stored serum. TNFα are small proteins that are primarily secreted by helper T cells and macrophages.[26] Although elevation in TNFα levels after hip fracture are important to protect against immediate infections, aging-related decline in immune function and associated 'inflamm-aging' (a progressive rise in proinflammatory status with aging) can render older adults less able to recover from acute injury and infection compared to young adults.[27] Previous research has shown strong associations between

TNFα and depressive symptoms, and both inflammatory activation and major depression increase mortality rates among older adults.[28–31] Women are more likely to experience depressive symptoms associated with inflammation compared to men.[32,33] As such, there may be a stronger mediating effect of depressive symptoms in the association between TNFα and mortality in women. However, it is not clear if depressive symptoms mediate the association of TNFα and mortality and if the association is different by sex.

1.5 Summary of Background

The overarching objective of this study was to evaluate predictors of hip fracture mortality in short-term (1 year) and long-term (up to 10 years) follow-up, specifically focusing on sex differences and the identification of post-operative characteristics with respect to functional and biological predictors of mortality that may explain sex differences in all-cause mortality. The proposed research assessed whether physical performance measures, including SPPB, gait speed, and grip strength alone or in some combination thereof with other known predictors of mortality after hip fracture (e.g., age, sex, cognition, and comorbidity) result in an improved prediction of long-term mortality. Lastly, this research examined if inflammation after hip fracture as measured by TNFα-R1 was differentially associated with all-cause mortality between men and women and whether depressive symptoms partially explain this association and was stronger in women compared to men.

1.6 Specific Aims

Aim 1 (manuscript #1) To determine whether male sex is associated with all-cause mortality and infection-specific mortality after hip fracture over a 10-year follow-up

period controlling for age, depressive symptoms, cognition, comorbidity, BMI, and pre-fracture LPADLs.

Hypothesis 1A Cumulative incidence of all-cause mortality is consistently greater for men compared to women over 10 years of follow up post-hip fracture.

Hypothesis 1B Cumulative incidence of infectious causes of death is consistently greater for men compared to women across 10 years of follow up post-hip fracture.

Aim 2 (manuscript #2)

Aim 2.1 To determine if sex moderates the association between physical performance (measured by SPPB, gait speed and grip strength) at 2 months post-hip fracture and all-cause mortality over 10 years.

Hypothesis 2.1A Poor physical performance at 2 months post-hip fracture predicts poor short-term and long-term (up to 10 years) all-cause mortality.

Hypothesis 2.1B The strength of the association of SPPB and gait speed with all-cause mortality is stronger for men compared to women for both short-term and long-term (up to 10 years) follow up. The strength of the association of grip strength with all-cause mortality is stronger for women compared to men for both short-term and long-term (up to 10 years) follow up.

Exploratory Aim 2.2 To determine cut points for physical performance measures that best discriminate post-hip fracture mortality in men and women and to determine if physical performance measures (SPPB, gait speed, and grip strength) alone or in combination with

sex, cognition, depressive symptoms, age, BMI, and LPADLs improve discrimination of post-hip fracture mortality.

Aim 3 (manuscript #3)

Aim 3.1 To determine the mediating role of depressive symptoms (at 2 months post-hip fracture) on the association between TNFα-R1 and all-cause mortality over 10 years.

Hypothesis 3.1A Higher TNFα-R1 is associated with a greater risk of mortality.

Hypothesis 3.1B Depressive symptoms partially explain the association of TNFα-R1 and all-cause mortality.

Aim 3.2 To determine if sex moderates the inflammation-depressive symptoms-all-cause mortality link.

Hypothesis 3.2A The association of TNFα-R1 and mortality is stronger for men compared to women.

Hypothesis 3.2B Depressive symptoms partially explain the association of TNFα-R1 and all-cause mortality better in women compared to men.

1.7 Contribution of Research

Foremost, study findings have the potential to be used by clinicians to characterize older hip fracture patients who at increased risk of mortality, and such information can facilitate the optimization of treatment protocols in future studies, where targeted clinical and functional interventions are tailored towards each sex and post-operative characteristics. In addition, the critical step to developing any preventive

strategies to improve survival, is the early identification of those at increased risk for mortality. Therefore, the characteristics identified in this dissertation can also be used by researchers to create precise risk prediction models to predict older adults at need of intervention to improve survival. A more targeted and closer surveillance of high-risk patients in the recovery period post hip fracture has the potential to lower mortality.

CHAPTER 2- BACKGROUND AND SIGNIFICANCE

2.1 Mortality Post Hip Fracture

Hip fracture is a disabling condition with a high mortality rate. The age-adjusted death rate for hip fracture in the year 2017 in the US was 3.4 per 100,000 people.[34] The all-cause 30-day mortality rate post hip fracture is on average 6-8% and about 64% of the deaths occur in-hospital.[35–37] Furthermore, almost 50% of hip fracture patients die within the first 5 years post hip fracture. On average, all-cause 3-month, 1-year, 2-year, 3-year, 5-year and 10-year mortality rates are 14.5%, 16-22%, 24-32%, 36.6%, 55-75%, and 81.5%, respectively.[5,19,36,38,39] Three out of four hip fractures occur in women, and extant research has mainly focused on women.[40] However, the number of hip fractures among men is projected to increase by 51% from 2010 to 2030, while the number of hip fractures is expected to decrease in women by 3.5%.[2] Men with hip fracture are frailer and have more comorbid conditions than women, yet are paradoxically younger (on average) at the time of fracture, but die at a higher rate in the first two years after fracture compared to women.[6]

2.1.1 Sex Difference in All-Cause Mortality Post Hip Fracture

Literature consistently shows sex as a significant risk factor for all-cause mortality in 60-day, 3-month, 6-month, and 1-year follow up after hip fracture.[41] Even after adjusting for other variables that might impact mortality post hip fracture, including age, pre-existing dementia, and other comorbidities, men are two times more likely to die within one year post hip fracture compared to women.[35,42] There are discordant findings among the few studies that have assessed sex differences in all-cause mortality beyond two years post-hip fracture. Men had a higher risk of all-cause mortality in a 3-year and

5-year follow-up study, but the association was not statistically significant.[18,19] Thus, there is a gap in our understanding of sex as a risk factor of all-cause mortality over longer periods of follow up. This gap will be addressed by *hypothesis 1A.*

2.1.2 Sex Difference in Infectious-Specific Mortality Post Hip Fracture

Infections post hip fracture have been identified as the major cause of death in this population.[35,43] Thirty-day risk of all-cause mortality is almost three times more likely in patients who suffered an infection post-hip fracture surgery compared to those who did not suffer an infection. [44] Pneumonia was the most common infectious cause of death after hip fracture; specifically, risk of mortality was almost 8 times and 4 times higher in those who suffer from systemic sepsis and pneumonia, respectively, compared to those who did not have them.[35–37,44] Past studies show that within four months of hip fracture, men were more likely to suffer from respiratory infection like pneumonia and die because of these infectious causes compared to women.[20,21] There is some information from the available evidence that mortality due to infectious causes is higher in men compared to women for at least first two years post hip fracture.[6] It is not clear if the higher risk of infectious deaths persist in men compared to women beyond two-years of hip fracture. [6] This gap in the literature will be addressed by *hypothesis 1B.*

2.2 Physical Function Indicators as Predictors of Mortality

Performance based measures are used as a standard criterion to measure health status in older adults because of their ability to predict future health outcomes and also because of concerns of self-report bias.[45] The following section describes three physical function measures, namely short physical performance battery (SPPB), gait speed, and

grip strength, which are most frequently used in older adults to predict future health outcomes like morbidity and mortality.

2.2.1 Short Physical Performance Battery (SPPB)

The Short Physical Performance Battery (SPPB) is a composite measure of lower extremity function and strength and has three components: balance, gait speed, and chair stand.[46] Aging-related loss of muscle mass and gain of intermuscular and subcutaneous fat[47] have been associated with lower SPPB score.[47] Poor SPPB scores can also be due to poor functioning of the respiratory and cardiovascular systems in older adults.[47,48] Therefore, there is a potential to use SPPB as a surrogate marker for decline in function of multiple body systems. As such, some studies have used SPPB as a predictor of frailty in older adults and poor SPPB score has also been associated with increased hospitalization, falls, and mortality in older adults.[49–51]

2.2.1.1 SPPB and Mortality

The score range of the SPPB is 0-12, with 12 being the highest functioning. Low SPPB scores have been shown to be a good predictor of increased risk of mortality in several older adult populations including older adults 75 years and older, older adults with cancer, and hospitalized older adults.[10,11,52,53] A study that followed individuals for a little more than a year found that those who scored 5 to 8 on the SPPB had almost double the risk of mortality compared to those who scored 9-12.[53] Similarly, every one unit increment in SPPB score was associated with 36% (HR= 0.64) lower risk of premature mortality in a two-year follow-up study.[11] Another study with 10 years of follow up found that among older adults 75 years and older, the hazard of dying among those with

an SPPB score <7 was 1.37 compared to those with SPPB >7.[10] One study that followed cancer patients for 18 years found that individuals who scored 7-9 and ≥10 on SPPB saw a 43% (HR=0.57) and 50% (HR=0.50) lower risk of death compared to those scoring 6 or less.[11] The association of SPPB score with mortality has not been studied in a hip fracture population. This gap in the literature will be addressed in *hypothesis 2.1A.*

2.2.1.2 Sex Difference in SPPB

Women on average score lower on the SPPB compared to men.[54,55] Poorer performance on the SPPB among women, specifically post hip fracture, can be attributed to various factors. One is that physical performance is impacted by involvement in day-to-day physical activity and there is evidence that men engage in physical activity more than women.[56,57] Although there is no evidence of sex-based difference in physical activity post-hip fracture, men (in general) may be more active prior to hip fracture and men may feel more comfortable engaging in physical activity post- hip fracture compared to women.[58,59] Similarly, another reason for poorer SPPB performance can be attributed to higher rate of depression in women compared to men.[55] Depressive symptoms can hinder involvement, leading to less physical activity and negatively impact physical performance.[60] Given these sex differences in physical activity and depression, the association of SPPB with mortality may be different based on sex. It is clear in the literature that SPPB is a strong predictor of mortality in older adults in both short- and long-term follow up; however, the moderating effect of sex on the association of SPPB and all-cause mortality is not clear. This gap in the literature will be addressed in *hypothesis 2.1B.*

2.2.2 Gait Speed

Gait speed is a measure of how well one can walk and there is evidence showing that gait speed predicts the survival of human beings. [61,62] Walking requires energy; for example, two Metabolic Equivalents (METS) is required to walk at a speed of 0.67 m/sec; and three METS is needed to walk at a speed of 1.1 m/sec. [63] Walking also requires a coordinated effort from all the biological systems, including the cardiovascular, respiratory, musculoskeletal, and nervous systems, in order to control and balance the body while walking. [61] Proper functioning of these body systems is crucial for survival as well as to be able to maintain gait speed. As such, gait speed is a physical performance metric used to predict survival in older adults.

2.2.2.1 Gait Speed and Mortality

Slower gait speed is associated with higher mortality among community-dwelling older adults and older adults with chronic conditions.[12,13] Although the association of gait speed with mortality has not been explored in hip fracture patients, this measure predicts recovery of activities of daily living post-hip fracture.[64] Compared to participants who did not perceive an improvement in walking ability post hip fracture, those who did perceive a substantial improvement in walking ability had a 0.13 m/s increase in gait speed.[65] Gait speed has also been found to predict future fractures in hip fracture patients.[66,67] Moreover, past research has found that an increase of 0.17 to 0.26 m/sec in gait speed was required for a substantially meaningful improvement in self-reported mobility. [65] Given that slower gait speed is associated with higher risk of future fracture and poor recovery in basic activities of daily living in hip fracture patients, it is likely that

slow gait speed will predict increased mortality in older adults after hip fracture. The association of gait speed with all-cause mortality will be assessed in *hypothesis 2.1A*.

2.2.2.2 Sex Difference in Gait Speed

Although rate of decline in gait speed with aging is consistent in both women and men, women usually have slower gait speed compared to men.[68,69] Sex differences in gait speed are likely due to difference in body composition (i.e., height, weight, etc.). Women are more likely to have higher total body fat and intermuscular fat which has been associated with slower gait speed and physical performance.[70] Similarly, women are more likely to be obese, and evidence suggests that association of BMI with gait speed is stronger for women compared to men, such that higher BMI lowers gait speed in men only when BMI exceeds the threshold of obesity (BMI of >30 is considered obese).[71] Men on average are taller than women and might have gait speed advantage; however, the gait speed advantage because of height is lost at older age.[72] Additionally, women are more likely to suffer incident disability, measured by activities of daily living limitations, and remain disabled for a longer duration compared to men.[68] Inability to perform activities of daily living is strongly associated with slower gait speed.[65]

2.2.2.3 Sex Difference in the Association of Gait Speed and Mortality

Little information is available with regards to sex differences in the association of gait speed and mortality. A study conducted among middle-aged adults (aged 35–55 years) found that the association of gait speed with all-cause mortality is stronger in men compared to women but the difference was not statistically significant.[73] Additionally,

there is only one study that assessed if the interaction between gait speed and sex predicts mortality in older adults.[23] The interaction effect was not significant, suggesting that the association between gait speed and mortality does not vary by sex. However, no studies have assessed sex differences in the association between gait speed and mortality in a hip fracture population. Given the effect of sex on the relationship between gait speed and mortality post-hip fracture is unknown and the effect of sex on this association in the general population of older adults is unclear, it is important to further investigate these sex differences. The gap in our understanding of the association of the moderating effect of sex on the association between gait speed and mortality will be addressed by *hypothesis 2.1B.*

2.2.3 Grip strength

Grip strength is used as a marker of overall and upper body muscle strength.[74] Although grip strength is not directly required for lower limb function, poor grip strength is associated with a slower gait speed.[75] Similarly, there are studies linking poor grip strength to poor cognitive functioning, greater difficulty performing activities of daily living, and lower survival rates.[76–78] In hip fracture patients, poor grip strength has been associated with worse outcomes post hip fracture like worse functional recovery.[79–81]

2.2.3.1 Grip Strength and Mortality

Literature consistently shows a strong association of lower grip strength with an increased risk of mortality in older adults.[14,15] With increasing age the number and size of muscle cells is reduced.[82] As skeletal muscles take up the largest amount of glucose in the

body through surface membrane sugar transport proteins, decrease in muscle size and number can lead to hyperglycemia.[83,84] Hyperglycemia can have several consequences including reduced ability of the muscle cells to contract and relax.[85] This can lead to a reduced muscle strength as measured by grip strength. As such, there are studies that have linked poor grip strength to type 2 diabetes and metabolic syndrome in older adults.[84] Higher incidence of these chronic conditions can increase mortality risk. Similarly, poor grip strength is also associated with lower bone mineral density (BMD).[86] One of the explanations for the low BMD associated with poor muscle strength is that the bone requires mechanical force produced by muscles to maintain its BMD. Supporting this argument is the positive association of exercise and bone mass.[87] As such individuals with low grip strength are more likely to have a fall and are at a higher risk of fragility fracture associated with the fall.[88,89] This also increases their risk of early mortality in individuals with poor grip strength.

2.2.3.2 Sex Difference in Grip Strength

Mean grip strength is lower in women compared to men. A grip strength of <27 kg in men and <16 kg in women is considered weak grip strength. [75] The lower grip strength in women does not necessarily mean poor functional recovery and mobility compared to men. An individual's muscle strength is highly correlated with body size, as such men have stronger grip strength as men on average have higher body weight and height compared to women.[90] In hip fracture patients, higher grip strength at baseline is predictive of better function at 3 months and 6 months post-hip fracture in both men and women.[81]

2.2.3.3 Sex Difference in the Association of Grip Strength and Mortality

In studies done among community-dwelling older adult population, there are sex differences in the association between grip strength and mortality.[22,78] In both studies, grip strength was classified into categories based on tertiles/quartiles. The lowest level of grip strength was compared to the highest level of grip strength in each of these studies. Compared to the highest category, those in the lowest category were at a greater risk of mortality. The association of poor grip strength with higher mortality was stronger for women compared to men.[14,22] However, the interaction of sex and grip strength was not significant.[78]

2.3 TNFα as a Predictor of Mortality

After an orthopedic trauma, the inflammatory biomarkers that are most important to assess proinflammatory activity are the cytokines such as IL-6 and tumor necrosis factor α (TNFα).[91] Although post fracture inflammation is a response to the trauma and is important to protect against infections and immediate threat, inflammation post trauma/injury has also been linked to devastating outcomes such as multiple organ failure and lung injury.[92] Additionally, among other cytokines, TNFα is most strongly associated with sarcopenia (muscle wasting) and patients with sarcopenia after hip fracture are at two times more risk of mortality over seven years follow up compared to hip fracture patients without sarcopenia.[94,95]

2.3.1 Tumor Necrosis Factor Alpha (TNFα)

TNFα are small proteins that are primarily secreted by helper T cells and macrophages. Helper T cells and macrophages are components of the immune system.

TNFα can act locally (nearby cells) or on distant cells. TNFα is involved in modulating activities of immune cells by helping them communicate and act on infectious agents/injury.[26]

2.3.1.1 TNFα and Mortality

TNFα was associated with mortality in older adults even after controlling for other covariates including other inflammatory biomarkers like C-reactive protein (CRP) and Interleukin-6 (IL-6).[96] One of the mechanisms through which TNFα is associated with an increased risk of mortality is the inflammatory response, specifically in older adults, is also accompanied by muscle catabolism and insulin resistance.[91] Insulin resistance is a condition when the body is not able to utilize available insulin hampering glucose absorption and energy regulation by the body. Insulin resistance can initiate a cascade of devastating outcomes, which includes accelerated atherosclerosis and hypertension, ultimately increasing mortality risk.[97,98] Moreover, in older adults 'inflamm-aging' (a progressive rise in proinflammatory status with aging) may worsen the challenge posed to the immune system by acute infection during the injury. As such, for vulnerable older adults, recovery from inflammation may be difficult. [99,100]

2.3.1.2 Sex Differences in Association of TNFα and Mortality

Women are more likely to have higher levels of inflammatory biomarkers in response to an infection or injury, in general.[101–103] However, higher TNFα levels are associated with mortality only in men but not women.[28] The mechanism of sex difference in the association of TNFα and mortality in men but not women is not well-understood. One of the reasons is that men have more underlying chronic conditions compared to

women at the time of hip fracture, which can make men more susceptible to poor survival.[28] Another explanation for increased mortality in men is that men are more susceptible to cardiovascular disease at a lower threshold of inflammatory biomarkers compared to women.[104] The moderating effect of sex on the association of TNFα and mortality is not known in hip fracture patients. Understanding the association of TNFα and mortality is critical in older adults with hip fracture because, elevated levels of proinflammatory mediators take longer to return to normal after an inflammatory response compared to young adults.[105,91]

2.3.2 Depressive Symptoms

Depressive symptoms are a persistent feeling of sadness and inability to experience pleasure that can have several consequences on well-being of an individual such as poor physical performance and increased health care use.[106] More than 85% of patients post-hip fracture (during hospital stay) present with incident mild depressive symptoms. [107] Another study found that, 40% of hip fracture patients experience moderate to severe depression within one month post-hip fracture.[108] For 10% of the hip fracture patients, the depressive symptoms can reach a threshold of depression between 1 to 8 weeks.[108]

2.3.2.1 Depressive Symptoms and Mortality

Depressive symptoms are an important predictor of mortality in older adults.[16,17] Although evidence is scarce, depressive symptoms after hip fracture are associated with increased mortality.[109,110] There are several studies that have linked higher depressive symptoms in hip fracture patients to poor physical performance like SPPB and functional

recovery, like walking independently.[111–113] Past evidence shows that older adults with depressive symptoms are more likely to be less interested in self-care activities like exercise and medication adherence, which can contribute to poor survival .[114,115] Similarly, depressive symptoms are also associated with poor nutrition, and social isolation and loneliness increasing risk of mortality.[116–118]

2.3.2.2 Sex Differences in Association of Depressive Symptoms and Mortality

There are well-established sex differences in the prevalence and presentation of depressive symptoms.[119] Women in every age category are more likely to report depressive symptoms compared to men.[119,120] Women are ten times more likely to report somatic symptoms like fatigue, insomnia, and loss of appetite, compared to men.[119,120]

Greater severity of depressive symptoms increases the risk of mortality in both men and women. Women with > 5 depressive symptoms were two times more likely to die compared to women with ≤ 5 depressive symptoms on an average six years of follow up.[121] Similarly for men, those in the highest quantile of depressive symptoms as measured by Center for Epidemiological Studies Depression (CES-D) were 15% more likely to die compared to those in the highest quantile of depressive symptoms in an 18 years follow up study.[122] With respect to the moderating effect of sex, evidence suggests that the association of depressive symptoms and mortality is stronger in men compared to women.[29,123] Higher mortality in men than women can be explained by the evidence that women with depressive symptoms are also more likely to seek professional help compared to the men with depressive symptoms.[119] Similarly, men are more likely to

participate in unhealthy behaviors like drinking alcohol to cope with their depressive symptoms.[119]

2.3.3 Mediating Effect of Depressive Symptoms on the Association between TNFα and Mortality

There is no study that has examined the mediating effect of depressive symptoms in the association between TNFα and mortality. However, there is evidence showing that in the 12 months after hip fracture, those in the highest IL-6 and TNFα group had greater risk of reporting higher depressive symptoms.[31] One of the mechanisms for this association can be that inflammatory mediators have been associated with inability to feel pleasure leading to reporting of greater depressive symptoms.[124] Another mechanism can be the link of inflammatory biomarkers with higher level of fear and anxiety leading to an individual reporting higher levels of depressive symptoms.[124] Similarly, the evidence also suggests that cytokines like TNFα can activate indoleamine 2,3-dioxygenase (IDO).[125] IDO activation decreases tryptophan bioavailability leading to a decrease in serotonin, which creates depressive-like behavior. [125] IDO is any enzyme that is responsible for first step in the cleavage of tryptophan.[126] Tryptophan is an amino acid that is responsible for the formation of neurotransmitter serotonin, which is associated with regulation of mood.[127] This gap in the literature will be filled by *Hypothesis 3.1B*.

2.3.4 Sex Differences in the Pathway TNFα-Depressive Symptom-Mortality

Evidence suggests that the combined effect of increased levels of inflammatory biomarkers (C Reactive protein in the cited study) and depressive symptoms increases mortality risk only in men but not women. [128] One of the explanations for increased mortality in men is that men are more susceptible to cardiovascular disease at a lower

threshold of inflammatory biomarkers compared to women.[104] Similarly, women are more likely to experience depressive symptoms associated with inflammation compared to men.[32,33] As such there may be a stronger mediating effect of depressive symptoms in the association between TNFα and mortality in women. However, the moderating effect of sex on the TNFα→Depressive Symptom→Mortality pathway is unclear. TNFα-R1 is the optimal proxy for TNFα because TNFα-R1 has a long-term bioavailability in the stored serum; therefore, we used the TNFα-R1 assay. We hypothesize that a larger portion of the association between TNFα-R1 and mortality will be explained by depressive symptoms in women compared to men but the total effect and direct effect of TNFα-R1 on mortality will be stronger for men compared to women (*Hypothesis 3.2B*).

2.4 Theoretical Model

The covariates selected for the models in aims 1, 2, and 3 are based on risk scoring models for the prediction of post-operative hip fracture mortality. Several models are available in the literature that can be used to predict post-operative hip fracture mortality such as Nottingham Hip Fracture Model, Brabant Hip Fracture Score model – 30 (BHFS-30), Brabant Hip Fracture Score (BHFS-365), Charlson Comorbidity Index (CCI, not specific to hip fracture population), Orthopaedic version of the Physiologic and Operative Severity Score for the Enumeration of Mortality and Morbidity (O-POSSUM).[129] Area under the curve (AUC) for any of these models was significantly different and almost all of them performed reasonably well with AUC > 0.70.[129] Most of these models predict 30-day post-hip fracture mortality. Only one model, Brabant Hip Fracture Score (BHFS-365), predicted 1-year mortality. [9,130] Therefore, we will use the risk factors identified in the BHFS-365 as covariates while assessing the association of

clinical indicators (physical performance measures, TNFα and depressive symptoms) with mortality. Based on BHFS-365, the factors that can predict post-hip fracture mortality are age, sex, nursing home residence prior to hip fracture, cognitive functioning, Hb, respiratory disease, renal insufficiency, diabetes and malignancy.[9] Instead of using comorbid conditions such as Hb (hemoglobin, proxy for anemia), respiratory disease, renal insufficiency, diabetes and malignancy separately as suggested by BHFS-365, the Charlson Comorbidity Index (CCI) will be used since it is a strong predictor of post-hip fracture mortality.[129] Based on the exposure for each proposed aim, we will add other variables to the models in aim 1, 2, and 3. The covariates are described in detail in **chapter 3, 4, 5, and 6**. A summary of outcome, exposures, and covariates of interest in aim 1, aim 2, and aim 3 are provided as a conceptual framework in **Figure 2.1**.

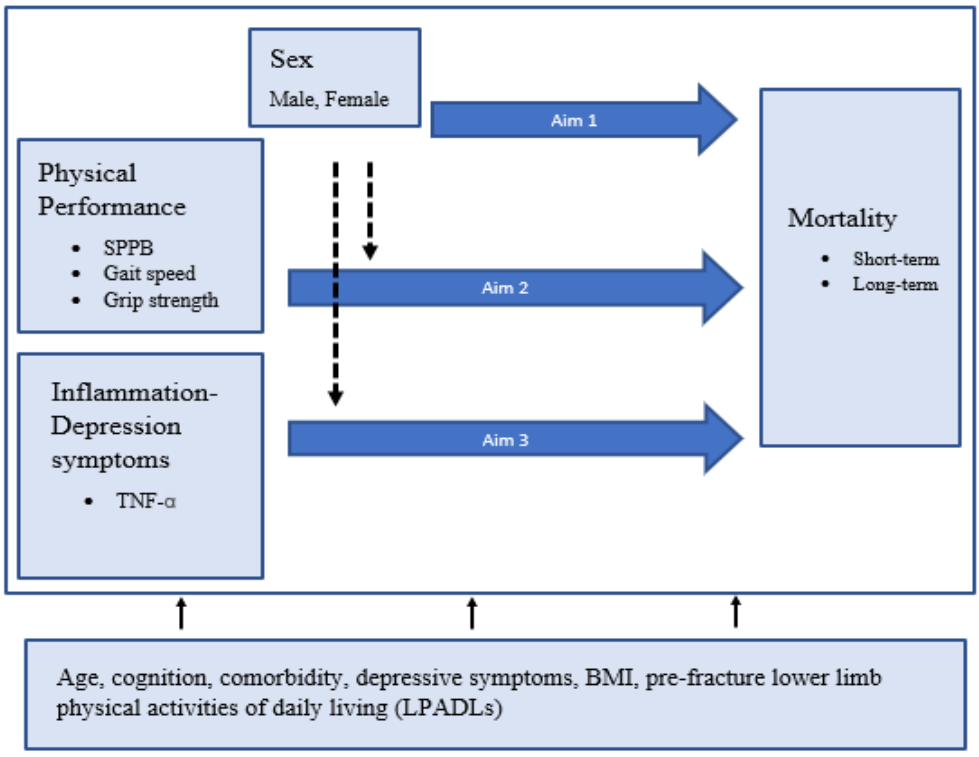


Figure 2. 1: Conceptual framework

2.5 Summary of Gaps in Sex Differences in Post Hip Fracture Mortality Research

There are several gaps in the current research.

1) We have satisfactory information from the available evidence that all-cause mortality and infection-specific mortality is higher in men compared to women for at least the first two years post hip fracture. It is still unclear if the higher all-cause mortality and infection-specific mortality post hip fracture in men compared to women after controlling for other risk factors of mortality such as age and comorbidity persist beyond two years of hip fracture.
2) Although literature shows physical performance measures such as SPPB, gait speed, and grip strength predict all-cause mortality in general older adult population, the association of these physical performance measures during the post-fracture recovery period with hip fracture mortality is unclear.
3) The moderating effect of sex on the association of physical performance measures and mortality in non-hip fracture population has been mixed with stronger association of grip strength with mortality in women compared to men and statistically insignificant sex differences in the association of gait speed and mortality. It is not clear if there is a moderating effect of sex in the association of physical performance measures and all-cause mortality in hip fracture patients.
4) The association of TNFα with mortality; the association of TNFα with incident depressive symptoms; and the association of depressive symptoms with mortality is clear in the available literature. However, it is not clear if the association of TNFα with mortality can be explained to some degree by depressive symptoms.

Similarly, it is also unclear if the inflammation-depressive symptoms link (both direct and indirect) with mortality is different in men and women.

CHAPTER 3 - RESEARCH DESIGN AND METHODS

3.1 Parent Study Design

Data comes from the Baltimore Hip Studies 7th (BHS-7) cohort. Participants (≥ 65 years old and community-dwelling) were enrolled from one of eight acute care hospitals in the 25-hospital BHS network and were admitted with a hip fracture diagnosis (ICD-9 codes 820.00-820.9). The enrollment period was from May 2006 through June 2011, and all participants were consented (or proxy provided consent) within 15 days of admission. BHS-7 was designed to assess sex differences in the sequelae of hip fracture, and female patients were frequency-matched (1:1) to males on the timing of admission within each hospital to ensure equal numbers of men and women. Study visits, which include questionnaires, performance assessments and blood collection, were conducted at baseline (within 22 days of admission) and 2, 6, and 12 months post- admission. Further details regarding the study design and methodology are available elsewhere.[40]

3.2 Aim 1 Design and Methods

The complete case analysis sample for Aim 1 included 300 participants (male= 145, female= 155) in the original cohort.

3.2.1 Measures

3.2.1.1 Outcomes

All-cause mortality and infection-specific mortality were the outcomes and death data were obtained from 2006-2018 for a median follow up of 10.2 years. All deaths and cause of deaths were verified through the National Death Index. Deaths were defined as infection-related if one or more contributing conditions or the underlying cause of death

had any of the following ICD-10-CM codes: A04.7, A04.71-2, A41.9, A41.90, A49.0, A49.9, J15.20, J15.211-2, J15.29, J18.0-2, J18.8-9, J44.0, or N39.0.[131]

3.2.1.2 Exposure

Biological sex (male or female).

3.2.1.3 Covariates

Age, baseline Modified Mini-Mental State Examination (3MS), Charlson Comorbidity Index (CCI), Center for Epidemiological Studies Depression scale (CES-D), and body mass index (BMI); and pre-fracture lower-extremity activities of daily living (LPADL) limitations were the covariates. These variables were selected for aim 1 because each of these variables were predictors of mortality based on the past studies and were differently distributed by sex in hip fracture patients. [38,113,132–135] 3MS was used to assess cognitive function.[150] The score ranged from 0-100. Comorbid conditions were evaluated using the Charlson Comorbidity Index (CCI), a weighted index of comorbidities that takes into consideration the number and seriousness of chronic conditions.[151] Higher CCI scores indicate greater comorbidity and are associated with greater mortality.[151] In the current study, CCI score ranged from 0-8 in which only moderate or severe (not mild) liver disease was recorded. The 20-item Center for Epidemiological Studies Depression scale (CES-D) measured depressive symptoms. Questions ask about symptomology occurring in the last week, and responses are scored on a Likert scale that yields a summary score ranging from 0-60.[145] Lower-Extremity Physical Activities of Daily Living (LPADL) function was assessed in the week prior to fracture using a modified form of the Functional Status Index, which measures the ability

to perform an activity and level of difficulty.[152] Response categories included no help, used equipment, used human assistance, used equipment and human assistance, did not perform due to health reasons, and did not perform due to non-health reasons. [152] Participants who responded needing equipment/human help to perform these activities and those who didn't perform because of health reasons were categorized as disabled.[4,7] LPADL score range from 0 to 12 with higher score indicating more disability. Body Mass Index (BMI) was measured as kilograms per meters squared (kg/m^2). The conceptual framework in **Figure 3.1** shows how the covariates are associated with the exposure and outcome.

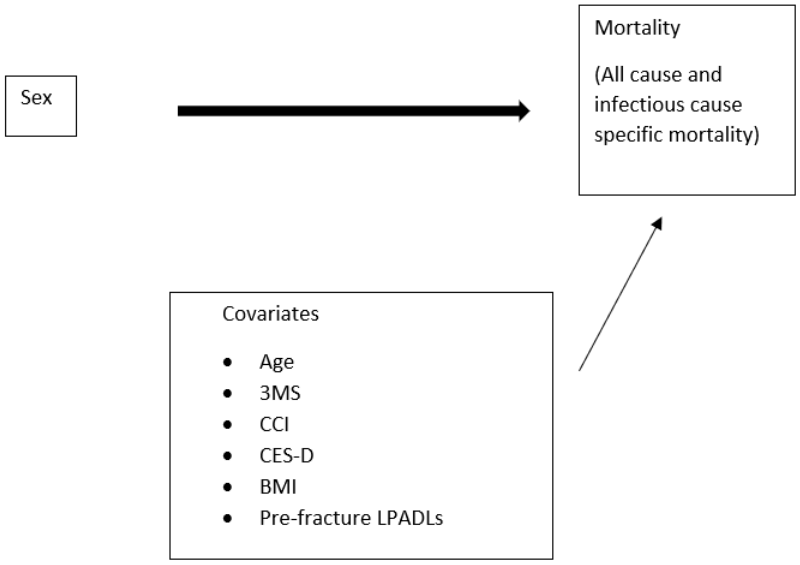


Figure 3. 1: Conceptual framework for Aim 1

3.2.2 Analysis

Separated by sex, percentages and frequencies were estimated for categorical variables, and mean and standard deviations were calculated for continuous variables. Unadjusted associations between sex and all-cause mortality were evaluated using Kaplan-Meier survival curves and log-rank tests.[136] Unadjusted association between sex

and infection-specific mortality was evaluated using Cumulative incidence for competing risk method and Gray's test.[137]

The adjusted association between sex and all-cause mortality was estimated using a Cox proportional hazards model with adjustment for age, cognition, comorbidity, depressive symptoms, BMI, and pre-fracture LPADL limitations (*Hypothesis 1A*). The adjusted association of sex and infection-specific mortality was assessed using a multivariable cause-specific Cox model to account for competing causes of death (*Hypothesis 1B*). [138] The model was adjusted for age, cognition, comorbidity, depressive symptoms, BMI, and pre-fracture LPADL limitations. Secondary analyses assessed whether the relationship between sex and mortality changes over time during hip fracture recovery by including interaction term between sex and time (i.e. sex*time). Model goodness-of-fit was assessed using Akaike information criterion (AIC).[139] Lastly, sensitivity analyses were conducted to assess differences in participant characteristics between those with and without missing data. Statistical significance was defined as $p < 0.05$ or 95% confidence intervals excluding the null, and all analyses were performed using SAS, Version 9.4 (SAS Institute, Inc., Cary, NC).[140]

Model for hypothesis 1A

$$h(t; sex, x) = \lambda_0(t) \exp\{beta_1 Sex + beta_i x_i\}$$

$$h(t; sex, x) = \lambda_0(t) \exp\{beta_1 Sex + beta_2 Sex*time + beta_i x_i\}$$

Model for hypothesis 1B

$$h_{ij}(t; sex, x) = \lambda_0(t) \exp\{beta_1 Sex + beta_j x_i\}$$

h_{ij} (t; sex, x) = $\lambda_0(t)$ exp {$beta_1$Sex + $beta_2$ Sex*time + $beta_j$ x_i}

Where h_{ij} is the hazard ratio for the i^{th} person with j^{th} cause of death and x_i denotes additional variables. Time is operationalized as continuous years.

3.2.3 Power

Two sample log-rank test was used. Given each group (men and women) has at least 145 participants with median survival in men of 43 months and in women of 75 months using a two-sided alpha level of 0.05, a power of 96.8% is estimated. A software nQuery was used for power calculation. [141,142]

3.3 Aim 2 Design and Methods

The BHS-7cohort (n=339, 168 men and 171 women) was restricted to 209 participants (102 men and 107 women) who survived until 2 months post-fracture, had physical performance data at 2 months, and had complete data for all covariates included in the adjusted models. Physical performance measures included SPPB, gait speed, and grip strength, which were evaluated separately using three different models to assess the association between each exposure variable and mortality.

3.3.1 Measures

3.3.1.1 Outcomes

Death data were obtained from 2006-2018 for a maximum of 10.2 years. All deaths were verified through the National Death Index.

3.3.1.2 Exposures

Physical performance measures include Short Physical Performance Battery (SPPB), 3-meter gait speed, and grip strength obtained at 2 months after a hip fracture admission. The SPPB measures balance, gait, strength, and endurance.[46] Standing balance was measured through timed side-by-side, semi-tandem, and tandem stands. Gait speed was assessed by a 3-meter gait speed test, where participants were instructed to walk at their usual speed from standing start and to walk past the finish line. Finally, participants were assessed for their ability to rise from a chair 5 times as fast as possible. The participants were timed from first sitting to final standing position. Each task was scored from zero to four, based on established cut points [46] and a summary score was calculated (0-12, with 12 the highest functioning) by combining all three component scores. Grip strength was measured in kilograms using a JAMAR Hydraulic Hand Dynamometer.[143]

3.3.1.3 Covariates

Potential confounders were selected a priori based on literature review and are the same as those used in Aim 1: age, CCI, 3MS, CES-D, BMI, and pre-fracture LPADL limitations collected at baseline. These variables were selected as covariates because prior research has shown them to be predictive of mortality in older adults with hip fracture.[38,113,132–135] The conceptual framework in **figure 3.2** shows the association of the exposures, outcome, and covariates diagrammatically.

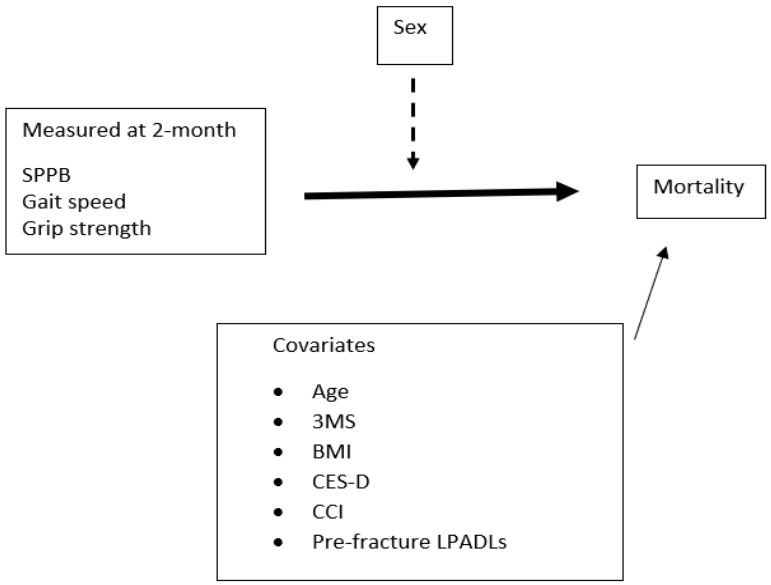


Figure 3. 2: Conceptual framework for Aim 2

3.3.2 Analysis for Aim 2.1

Variable distributions were described by sex to assess the characteristics of the complete-case analysis samples at baseline (immediately post-fracture or two months follow-up). Percentages were estimated for the categorical variables; means and standard deviations were calculated for continuous variables. Bivariate associations between categorical variables and all-cause mortality were evaluated using Kaplan-Meier survival curves and log-rank tests.[136] Unadjusted Cox proportional hazard models were used to estimate associations between continuous variables and all-cause mortality.

In *hypothesis 2.1A*, the adjusted association between physical performance measures and all-cause mortality was estimated by implementing Cox proportional hazards models adjusted for age, cognition, comorbidity, depressive symptoms, BMI, and pre-fracture LPADL limitations. Physical performance measures were modeled as considering linearity regarding exposure variables and mortality over time. Linearity

assumption was tested with residual plots. In *hypothesis2.1B* effect moderation by sex concerning the association between physical performance and mortality was assessed using an interaction term (i.e., physical performance*sex) that was added to the Cox proportional hazards models implemented to address *Hypothesis 2.1A.* To assess differential associations over varying lengths of follow-up concerning the primary exposure variable and mortality outcome, an interaction term was added between physical performance measures and time (in years). The goodness-of-fit of the models was tested by using a likelihood ratio test compared to the null model. The associations tested in each model had 80% power and a 5% significance level. The analyses were performed using SAS, version 9.4 (SAS Institute, Inc., Cary, NC).[140]

Models for Hypothesis 2.1A

h (t; physical performance, sex x) = $\lambda_0(t)$ exp {$beta_1$Physical Performance + $beta_2$ sex + $beta_i$ x_i}

Models for Hypothesis 2.1B

h (t; physical performance, sex x) = $\lambda_0(t)$ exp {$beta_1$Physical Performance + $beta_2$ sex + $beta_3$ Physical Performance*Sex + $beta_i$ x_i}

h (t; physical performance, sex x) = $\lambda_0(t)$ exp {$beta_1$ Physical Performance + $beta_2$ sex + $beta_3$ Physical Performance *time + $beta_i$ x_i}

Where x denotes additional covariates. Time is operationalized as continuous years.

3.3.3 Analysis for Aim 2.2

CART analysis was performed to identify a set of predictors that can best discriminate 10-year mortality after a hip fracture. CART analysis was performed using the rpart package in R software (version 4.0.3), and cross-validation was used to "prune" less important splits to prevent overfitting and produce a more parsimonious tree. The data were randomly partitioned into train and test data sets (70/30) without replacement. Cross-validation in the training set was performed by using leave-one-out cross validation technique. The CART model used time-to-event data where the time values were pre-scaled to fit an exponential model. Since the outcome variable was pre-scaled, a subgroup analysis was performed in the original time scale using the "where" option in "Survfit" function to create Kaplan-Meier curves. To improve the CART model, changes in the nodes based on shrinkage, which gives different Bayes estimates of hazard, was examined.[144] Later, the pruned model was evaluated in the test data set. Two Cox proportional hazard models were run, one each in the train data first and then in the test data to compare the all-cause mortality discrimination by the categories identified by the final pruned CART tree.

3.3.4 Power Calculation

3.3.4.1 SPPB

Two sample log-rank test was used. Two categories with SPPB ≥ 3 and SPPB <3 was created based on median for the sample. Given each group had at least 87 participants with median survival in those with SPPB ≥ 3 of 75 months and in those with SPPB <3 of 39 months and using a two-sided alpha level of 0.05, a power of 93% is estimated. A software nQuery was used for power calculation. [141,142]

3.3.4.2 Gait Speed

Two sample log-rank test was used. Two categories with gait speed ≥ 0.3 and gait speed < 0.3 was created based on median for the sample. Given each group had at least 86 participants with median survival in those with gait speed ≥ 0.3 of 78 months and in those with gait speed < 0.3 of 44 months and using a two-sided alpha level of 0.05, a power of 84.6% is estimated. A software nQuery was used for power calculation. [141,142]

3.3.4.3 Grip strength

Two separate power calculations were done for men and women and two sample log-rank test was used for both. For men, two categories with grip strength ≥ 28 and grip strength < 28 was created. Given each group had at least 102 participants with median survival in those with grip strength ≥ 28 of 64.8 months and in those with grip strength < 28 of 36 months and using a two-sided alpha level of 0.05, a power of 92.6% is estimated. A software nQuery was used for power calculation. [141,142]

For women, two categories with grip strength ≥ 19 and grip strength < 19 was created. Given each group had 102 participants with median survival in those with grip strength ≥ 19 of 64.8 months and in those with grip strength < 28 of 36 months and using a two-sided alpha level of 0.05, a power of 90.7% is estimated. A software nQuery was used for power calculation. [141,142]

3.4 Aim 3 Design and Methods

Aim 3 eligibility criteria included having blood sample data 2 months post-fracture and serum measurement of TNFα-R1. TNFα-R1 is the optimal proxy for TNFα

because TNFα-R1 has a long-term bioavailability in the stored serum. In addition, participants must have 2-month depressive symptom data. The Aim 3 complete-case analysis sample for the analysis is 202 (male=89, female=104).

3.4.1 Measures

3.4.1.1 Outcome

All-cause mortality was the study outcome. Death data were obtained from 2006-2018 for a maximum of 10.2 years and verified through the National Death Index.

3.4.1.2 Tumor Necrosis Factor Alpha Receptor 1 (TNFα-R1, Exposure)

Blood specimens were collected between 7 a.m. and 10:00 a.m. and transported to the university campus no later than 1:00 p.m. for processing. Samples were processed within 6 hours of collection and serum was stored at -80 degrees Centigrade until assayed. TNFα-R1 was measured in sera using the Quantikine Human sTNF enzyme-linked immunosorbent assay (ELISA) and V-Plex MSD (Meso Scale Diagnostics). Continuous TNFα-R1 values were then categorized into tertiles: 1st tertile (≤ 2587 pg/ml), 2nd tertile (2588 – 3512 pg/ml), and 3rd tertile (≥3513 pg/ml).

3.4.1.3 Depressive symptoms (Mediator)

CES-D were measured at 2 months. Questions ask about symptomology occurring in the last week, and responses are scored on a Likert scale that yields a summary score ranging from 0-60, with higher scores indicating more severe depressive symptoms.[145]

3.4.1.4 Covariates

Potential confounders were selected a priori based on prior research showing them to be predictive of mortality.[38,113,132–135] The conceptual framework in **figure 3.3** shows the association of the exposures, outcome, and covariates diagrammatically.

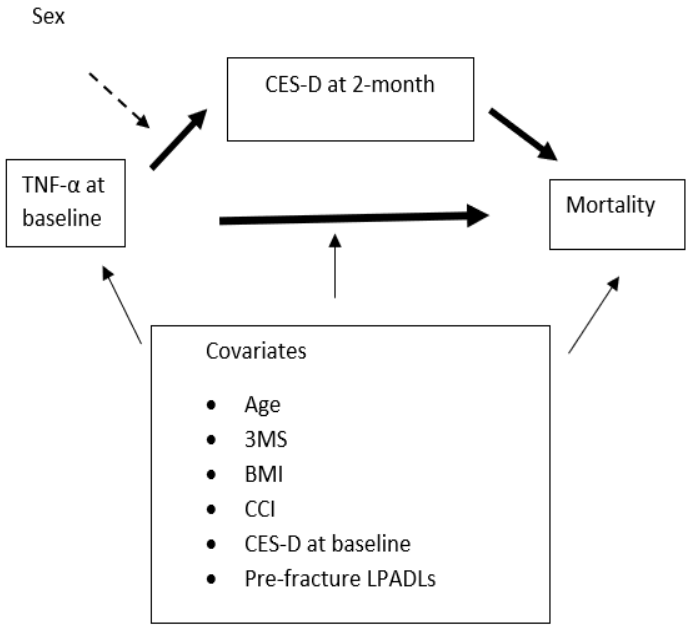


Figure 3. 3: Conceptual framework for Aim 3

3.4.2 Analysis

Variable distributions were described by sex to assess the characteristics of the complete-case samples. Percentages and frequencies were estimated for the categorical variables and means, and standard deviations were calculated for continuous variables. To assess the mediating effect of depressive symptoms in the association of TNFα-R1 with all-cause mortality, an Aalen additive hazard model, a semiparametric model for survival outcomes was fit in the analytic cohort comprising both men and women.[146] Mortality was regressed on depressive symptoms, TNFα-R1 and covariates using the Aalen model to estimate the direct effect (DE) of TNFα-R1 on mortality. To compute the

total effect (TE) and indirect effect (IE) of TNFα-R1 on mortality, depressive symptoms were linearly regressed on TNFα-R1 and covariates and post processed per a published approach. [146] The DE, IE, and TE are interpreted as absolute difference in mortality rate comparing two TNFα-R1 tertiles. This estimate (multiplied by 1,000) is interpreted as a difference in the number of deaths per 1,000 persons per year. The percent of mediation was estimated as IE/TE×100. Detailed R codes for analysis using the timereg package is provided in prior study. [146] The Aalen model was run separately on men and women to determine sex-specific DE, IE, and TE. A sensitivity analysis was done by repeating the approach with TNFα-R1 as a continuous variable. For sensitivity analysis, TNFα-R1 was log transformed and standardized to get a normal distribution. The analyses were performed using R software (version 4.0.3).

3.4.3 Power

Monte Carlo Power Analysis for Indirect Effects was used for power calculation.[147] We used a one mediator model. We set the number of replications at 5000. According to Schoemann et al, [147] 5000 replications are enough to generate a stable power estimate. Confidence interval width for all indirect effect calculated within each replication is set at 95%. Based on Figure 3.4, a and c` shows the association of TNFα-R1 with depressive symptoms and mortality, respectively. Similarly, b shows the association of depressive symptoms with mortality. Population parameter for the coefficients a, b, and c` are set at 0.22, 0.3, and 0.4, respectively, based on past findings.[17,96,148] A sample size of 95 is required to examine indirect effect (ab path in **figure 3.4**) with a 0.81 power.

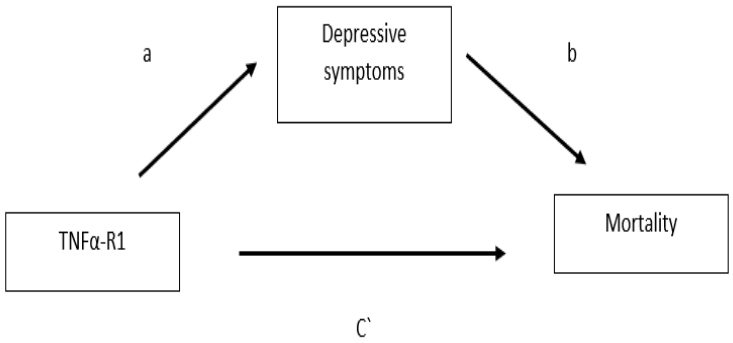


Figure 3. 4: Shows the association of TNFα-R1 with depressive symptoms and mortality

CHAPTER 4 - LONG-TERM SEX DIFFERENCES IN ALL-CAUSE AND INFECTION-SPECIFIC MORTALITY POST HIP FRACTURE (AIM 1)

4.1 Abstract

Background Mortality rates among men are double that of women in the first two years after hip fracture and may be related to more infections. Research has only examined differences in short-term mortality after hip fracture. Thus, the objective was to determine if long-term all-cause mortality and infection-specific mortality are higher in men compared to women.

Methods Data come from a prospective cohort study (Baltimore Hip Studies 7th [BHS-7]) with up to 10.2 years of follow-up (2006-2018). The participants were selected from eight acute-care hospitals in the 25-hospital BHS network. Sample of women were frequency-matched (1:1) to men on timing of admission for hip fracture that yielded an analytic sample size of 300 participants (155 women, 145 men). Associations between sex and mortality were analyzed using Cox proportional hazard models and cause-specific Cox models adjusted for age, cognition, body mass index, pre-fracture lower extremity activities of daily living limitation, depressive symptoms, and comorbidity.

Results Participants had a mean age of 80 years, 48% (n=145) were men and the median mortality follow-up was 4.9 (Interquartile Range=2.3-8.7) years. Over the follow-up period after hospital admission for hip fracture, 237 (79.0%) of participants died of all causes (132 among men vs. 105 among women) and 38 (12.7%) died of infection-specific causes (25 among men vs. 13 among women). Men had significantly higher all-

cause mortality risk [Hazard Ratio(HR)=2.31(95% confidence interval(CI) 2.02-2.59)] and infection-specific mortality [HR=4.43(95% CI 2.07-9.51)] compared to women.

Conclusions Men had a two-fold higher risk of all-cause mortality and four-fold higher risk of infection-specific mortality compared to women over a follow-up period of up to 10.2 years. Findings imply that interventions to prevent and treat infections, tailored by sex, may be needed to narrow significant differences in long-term mortality rates between men and women after hip fracture.

Keywords: Infection-specific, Mortality, Hip-fracture, Sex Difference

4.2 Introduction

Hip fracture is a disabling medical event that represents the most significant consequence of osteoporosis and often result in death among older adults. The United States (U.S.) age-adjusted mortality rate for hip fracture in 2017 was 3.4 per 100,000 people.[34] Fifty-percent of hip fracture patients die within the first 5 years post fracture.[5,149] Since three out of four hip fractures occur in women, women comprise the majority of participants in extant research, and the results may not be generalizable to men.[40] Nonetheless, hip fracture rates among men are projected to increase by 51% from 2010 to 2030, while the number of hip fractures among women is expected to decrease by 3.5%.[2] Men with hip fracture tend to be younger than women at the time of fracture, yet they are frailer and have more comorbid conditions than women, and die at a higher rate in the first two years after fracture compared to their female counterparts.[6]

Previous studies have consistently demonstrated that sex is a significant risk factor for all-cause mortality in 60-day, 3-month, 6-month, and 1-year follow-up after hip fracture.[41] Even after adjustment for age, dementia, and other comorbidities that might impact mortality post-hip fracture, men are twice as likely to die up to two years post-hip fracture compared to women.[6,35,42] There are unclear findings among the few studies that have assessed sex differences in all-cause mortality beyond two years post-hip fracture. Men had a higher risk of all-cause mortality in a 3-year and 5-year follow-up study but it was not always statistically significant.[18,19] Scant data are available regarding the changing relationship of sex with all-cause mortality over longer periods of follow-up after hip fracture.

Respiratory infections, such as pneumonia and influenza, and other infections, like septicemia during the recovery period after hip fracture are strongly associated with mortality among both men and women.[35,43] Thirty-day risk of all-cause mortality is almost three times more likely in patients who experience an infection post-hip fracture after surgery compared to those who did not sustain an infection.[44] Past studies have shown that within two-years of hip fracture, men are more likely to experience a respiratory infection (e.g., pneumonia) and die compared to women.[6,20,21] However, it remains unclear if the higher incidence of infectious deaths post-hip fracture in men compared to women persists long-term. Therefore, the objective of this study was to determine whether male sex is associated with higher risks of all-cause mortality and infection-specific mortality after hip fracture over a 10.2-year follow-up period. With *hypothesis 1A*, we hypothesize that cumulative incidence of all-cause mortality is consistently greater for men compared to women over 10.2 years of follow-up post-hip fracture. With *hypothesis 1B*, we hypothesize that cumulative incidence of infection-specific mortality is consistently greater for men compared to women across 10.2 years of follow-up post-hip fracture.

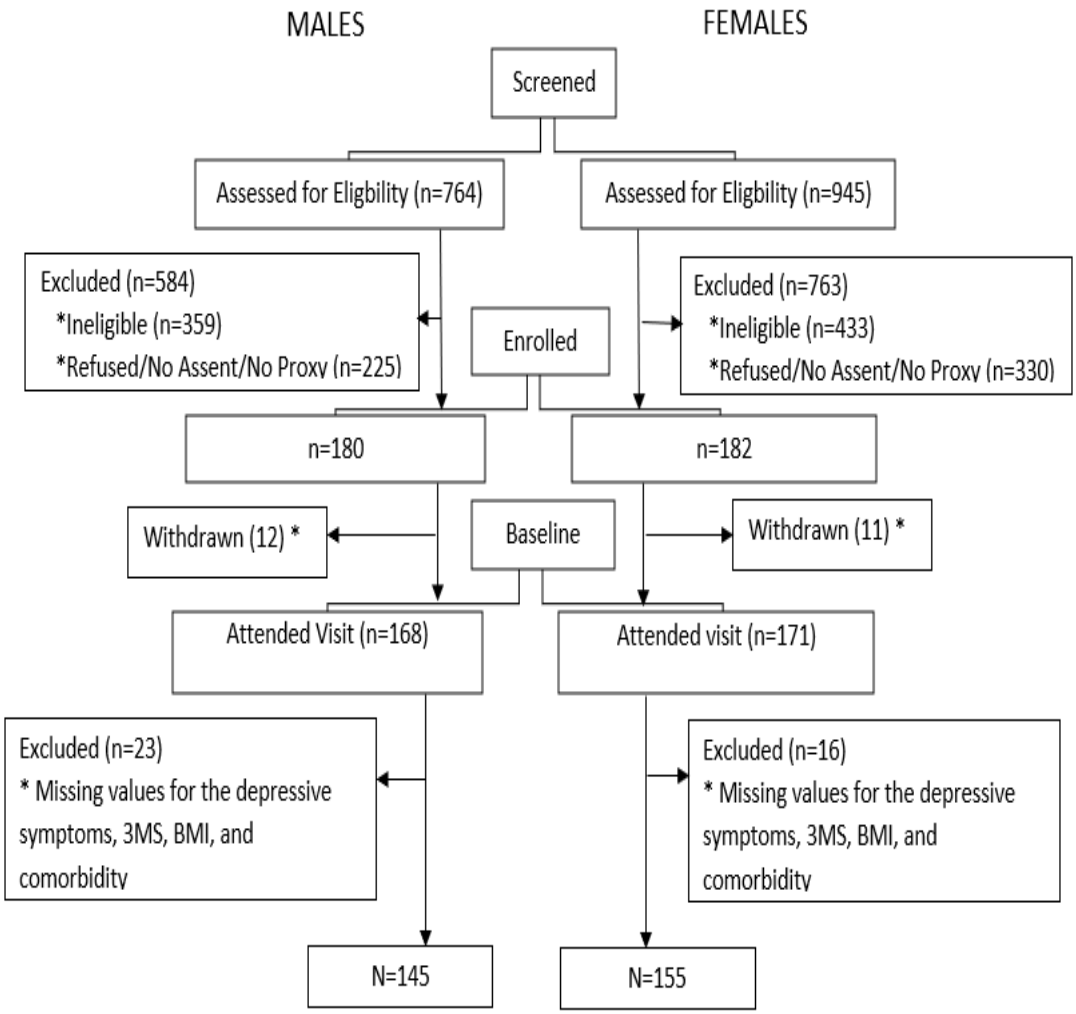
4.3 Methods

4.3.1 Study Design

This study was conducted using existing data from the Baltimore Hip Studies 7th (BHS-7) cohort. Participants (≥ 65 years old and community-dwelling) were enrolled from one of eight acute care hospitals in the 25-hospital BHS network and were admitted with a hip fracture diagnosis (ICD-9 codes 820.00-820.9). The enrollment period was from May 2006 through June 2011, and all participants were consented (or whose proxy

provided consent) within 15 days of admission. BHS-7 was designed to assess sex differences in the sequelae of hip fracture, and female patients were frequency-matched (1:1) to males on the timing of admission within each hospital to ensure equal numbers of men and women. Further details regarding the study design and methodology are available elsewhere.[40] The BHS-7 cohort enrolled 339 participants (168 men and 171 women) and was restricted to an analytic cohort of 300 participants (145 men, 155 women) with complete data on salient variables measured at baseline (**Figure 4.1)**.

Figure 4. 1. Flow diagram of study screening, enrollment, and complete case analysis sample, stratified by sex.



4.3.2 Mortality Outcomes

All-cause mortality and infection-specific mortality were the study outcomes, and death data were obtained from 2006-2018 for a maximum possible follow-up period of 10.2 years. All deaths and corresponding causes were verified through the National Death Index. Deaths were defined as infection-related if one or more contributing conditions or the underlying cause of death had any of the following ICD-10-CM codes: A04.7, A04.71-2, A41.9, A41.90, A49.0, A49.9, J15.20, J15.211-2, J15.29, J18.0-2, J18.8-9, J44.0, or N39.0.[131]

4.3.3 Measures

The primary predictor variable of interest was biological sex defined as male or female. Potential confounders were selected a priori based on prior research suggesting their association with mortality and difference between men and women who experienced a hip fracture. [38,113,132–135] The Modified Mini-Mental State Examination (3MS) was used to assess cognitive function.[150] The score ranged from 0-100. Comorbid conditions were evaluated using the Charlson Comorbidity Index (CCI), a weighted index of comorbidities that takes into consideration the number and seriousness of chronic conditions.[151] Higher CCI scores indicate greater comorbidity and are associated with greater mortality.[151] In the current study, CCI score ranged from 0-8 in which only moderate or severe (not mild) liver disease was recorded. The 20-item Center for Epidemiological Studies Depression scale (CES-D) measured depressive symptoms. Questions ask about symptomology occurring in the last week, and responses are scored on a Likert scale that yields a summary score ranging from 0-60.[145] Lower-Extremity Physical Activities of Daily Living (LPADL) function was assessed in the week prior to

fracture using a modified form of the Functional Status Index, which measures the ability to perform an activity and level of difficulty.[152] Response categories included no help, used equipment, used human assistance, used equipment and human assistance, did not perform due to health reasons, and did not perform due to non-health reasons. [152] Participants who responded needing equipment/human help to perform these activities and those who didn't perform because of health reasons were categorized as disabled.[4,7] LPADL score range from 0 to 12 with higher score indicating more disability. Body Mass Index (BMI) was measured as kilograms per meters squared (kg/m^2).

4.3.4 Statistical Analysis

Separately by sex, percentages and frequencies were estimated for categorical variables, and mean and standard deviations were calculated for continuous variables. Unadjusted associations between sex and all-cause mortality were evaluated using Kaplan-Meier survival curves and log-rank tests.[136] Unadjusted association between sex and infection-specific mortality was evaluated using cumulative incidence for competing risk method and Gray's test.[137] The adjusted association between sex and all-cause mortality was estimated using a Cox proportional hazards model. The adjusted association of sex and infection-specific mortality was assessed using a multivariable cause-specific Cox model to account for competing causes of death. [138] Both models were adjusted for age, cognition, comorbidity, depressive symptoms, BMI, and pre-fracture LPADL limitations. Secondary analyses assessed whether the relationship between sex and mortality changes over time during hip fracture recovery by including interaction term between sex and time (i.e. sex*time). Model goodness-of-fit was assessed using Akaike information criterion (AIC).[139] Lastly, sensitivity analyses were conducted to

assess differences in participant characteristics between those with and without missing data. Statistical significance was defined as $p < 0.05$ or 95% confidence intervals excluding the null, and all analyses were performed using SAS, Version 9.4 (SAS Institute, Inc., Cary, NC).[140]

4.4 Results

4.4.1 Sample Characteristics and Mortality Rates

The final analytic sample included 145 (48.3%) men and 155 (51.6%) women (**Table 4.1**). After a maximum 10.2 years of follow-up (median=4.9 years; IQR, 2.3-8.7), 90.9% (132/145) of men died, and 67.7% (105/155) of women had died. There were 38 infection-related deaths with 25 (17.2%) of men and 13 (8.3%) of women dying due to infection. Men had significantly higher cumulative incidence of both all-cause death (p-value < 0.001) (**Figure 4.2A)** and infection-specific death (p-value= 0.018) (**Figure 4.2B).**

Table 4. 1: Baseline characteristics of enrolled participants and death by the end of ten years for men and women

Measures	Total (n=300)	Male (n=145)	Female (n=155)	Missing Frequency No. (%)
Death (by the end of 10 y), No. (%)				
Infection related death	38 (12.6)	25 (17.2)	13 (8.3)	
Non-infection related death	199 (66.3)	107 (73.7)	92 (59.3)	
Alive	63 (21.0)	13 (8.9)	50 (32.2)	
Survival time from the date of admission, median (IQR), y	4.9 (6.4)	3.6 (5.1)	6.3 (6.6)	
Age, mean (SD), y	80.7 (7.7)	80.3 (7.7)	81.1 (7.7.)	

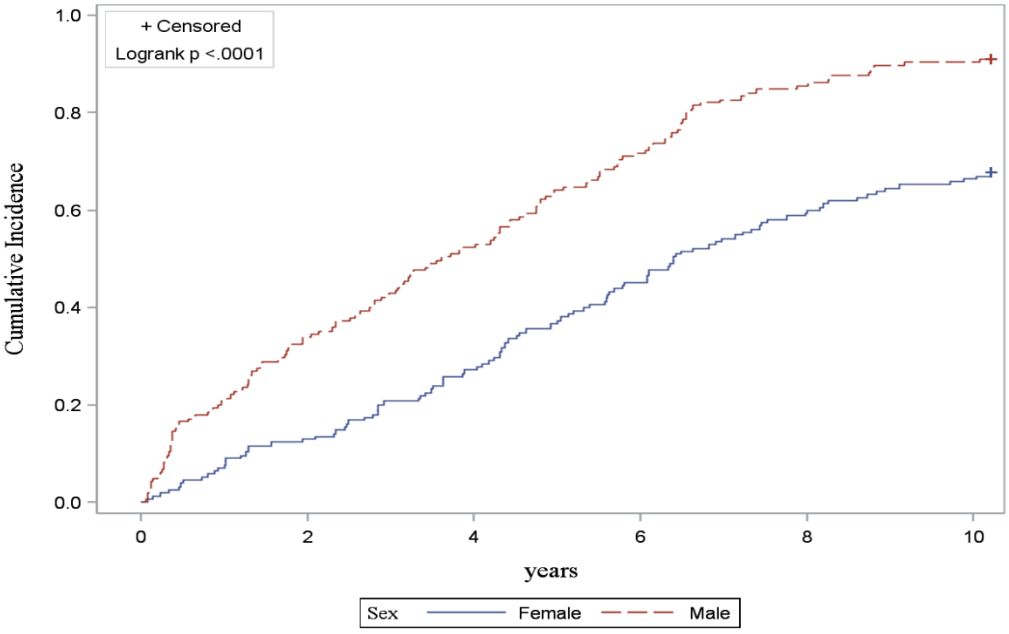


Figure 4.2 (A)

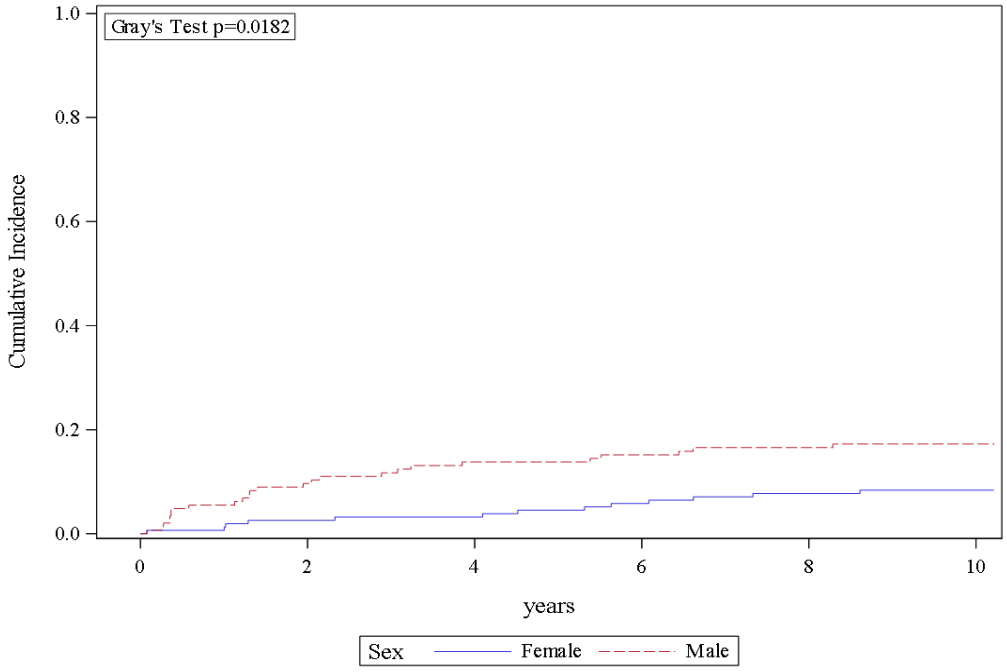


Figure 4.2 (B)

Figure 4. 2: Figures showing the association of all-cause mortality and infection-specific mortality by sex over 10 years. Figure 2(A): Probability of all-cause mortality (failure probability = Survival-1) post hip fracture by sex. Figure 2(B): Cumulative incidence of infection-specific mortality post hip fracture by sex.

4.4.2 Sex-Differences in Post-Fracture Mortality

After adjustment for covariates, men had 2.31 times higher all-cause mortality hazard rates (95% confidence interval [CI]= 2.02-2.59) and 4.43 times higher infection-specific mortality hazard rates (95% CI=2.07-9.51) than women (**Table 4.2**). The interaction term between sex and time (years) was not significant for all-cause (p-value=0.84) and infection-specific (p-value=0.31) mortality, providing little evidence that the association between sex and mortality changed over time.

Table 4. 2: Unadjusted and adjusted association of sex with all-cause mortality and infection-specific mortality

	Model 1 [a]		**Model 2 [b]**		**Model 3 [b]**	
		***P* value**		***P* value**		***P* value**
All-cause mortality						
Male (HR, 95% CI)	1.06 (1.04-1.07)	<.001	2.31 (2.02-2.59)	<.001	2.21 (2.71-1.71)	<.001
Male*time (ratio of HR, 95% CI)					1.01 (0.91-1.10)	0.84
Infection-specific mortality						
Male (HR, 95% CI)	2.20 (1.13-4.27)	0.02	4.43 (2.07-9.51)	<.001	7.09 (2.07-24.21)	<.001
Male*time (ratio of HR, 95% CI)					1.15 (0.87-1.53)	0.31

[a] Unadjusted
[b] Adjusted for age, Modified Mini-Mental Status (3MS), Charlson Comorbidity Index (CCI), Center for Epidemiological Studies Depression scale (CES-D), Body Mass Index (BMI), and Lower Extremity Physical Activities of Daily Living (LPADL)

4.5 Discussion

Consistent with prior research, results from this study demonstrated that 79% of participants died by 10.2 years post hip fracture, where 91% of men and 67% of women

died during this period.[39] Moreover, almost one-fifth of deaths were infection related among men but only a tenth of these deaths were infection related in women. The cumulative incidence of all-cause deaths and infection-related deaths were significantly higher in men compared to women over ten years of follow-up with negligible evidence of a change in the association over time after hip fracture. Collectively, these results indicate that older men have greater long post-fracture mortality rates compared to women that (in part) may be explained by a greater likelihood of infection-related causes.

Men were twice as likely to die of all-cause compared to women even after controlling for known risk factors for mortality in hip fracture patients such as age, pre-fracture activities of daily living limitations, comorbidity and cognition.[38,113,132–135] Consistent with prior findings, men were at a survival disadvantage, despite being younger than women and having higher pre-fracture functional ability.[6] More baseline comorbidity among men compared to women may explain greater all-cause mortality in men because comorbid conditions prior to fracture have been consistently demonstrated to predict post-fracture mortality.[8,135,153] Lower cognitive function at hospital admission among men than women could also explain their higher all-cause mortality rate since it has been shown that impaired cognition is associated with all-cause mortality at 6-months after hip fracture.[133] However, both comorbidity and cognitive function were adjusted for in the models, so they are not likely to explain men's increased mortality. While more comorbidity and poor cognition is associated with greater mortality, there may be specific co-occurring conditions like infections that increase risk of death and develop frequently among men than women after hip fracture.

Men had a four times higher rate of infection-related death compared to women. A higher rate of infection-specific mortality in men compared to women may be explained by sex-based differences in the immune system.[154] Immunosenescence occurs with normal aging; however, research has shown there is a male-specific decline of B cells than women after 65 years of age.[154] B cells are a component of adaptive immunity and protect against infection by producing antibodies that are explicitly targeted to individual pathogens. Thus, a male-specific decline of B cells could make them more vulnerable to adverse outcomes associated with infectious disease. Alternatively, women may have greater protection against acute infection as studies imply the majority of the genes responsible for immune cell division after activation of cytokines are on the X-chromosome.[155,156] Additionally, other prognostic factors that are associated with infectious diseases may be related to sex difference in long-term mortality rates after hip fracture.

4.5.1 Strengths and Limitations

First, there were missing data on baseline variables, which impacted inclusion into the analytic sample and hence may reduce generalizability to a general population of patients with hip fracture. However, descriptive data showed that participants with missing data did not significantly differ from those with complete data, which mitigates concerns about generalizability (**Table 4.3**). Second, the BHS-7 sample was predominantly white and participants were all from Baltimore-area hospitals so the findings may not be generalizable to other populations. Additionally, this study could not determine whether the higher risk of long-term mortality in men compared to women with hip fracture could explicitly be attributed to hip fracture, or if it is because, on

average, men have a shorter lifespan than women as there were no matched comparators without hip fracture. Although there was no comparison group, national data from a representative population of older adults indicates that men only have 1.7 times higher risk of death than women over 13 years.[157] By contrast, older men in this study had over 2 times higher rate of 10 year mortality compared to women. This is the first study to evaluate sex differences in mortality beyond 2 years of follow-up after hip fracture. Similarly, no prior research has assessed the risk of male sex as a predictor of infection-specific mortality post hip fracture. Moreover, the BHS-7 cohort study was specifically powered to examine sex difference in the sequelae of hip fracture, which has been a limitation of past studies among these patients.

Table 4. 3: Differences in complete data and missing data based on outcome (duration from date of admission and death) and exposure (sex, age, comorbidity, and BMI)

Measures	Missing data (n=39)	Non missing data (n=300)	P value
Death (by the end of 10 y), No. (%)			
Yes	29 (74.3)	237 (79.0)	0.96 [c]
No	10 (25.6)	63 (21.0)	
Sex, No. (%)			
Male	145 (48.3)	23 (58.9)	0.21 [d]
Female	155 (51.6)	16 (41.0)	
Duration from date of admission, median (IQR), y	4.8 (4.0)	5.3 (3.4)	0.48 [e]
Age, mean (SD), y	82.0 (8.9)	80.7 (7.7)	0.34 [e]
CCI, mean (SD) [a]	1.9 (1.7)	2.0 (1.7)	0.68 [e]
BMI, (kg/ m^2), mean (SD) [b]	25.5 (4.5)	25.2 (5.1)	0.67 [e]

[a] Charlson Comorbidity Index ranges from 0 (no comorbidity) to 8.
[b] Body Mass Index, 21-25 kg/m^2 is normal range per World Health Organization.
[c] Log-rank test
[d] Chi-square test
[e] T-test

4.6 Conclusion

Male sex was associated with a higher risk of all-cause mortality and infection-specific mortality throughout ten years of follow-up after hospital admission for hip fracture. More specifically, men had a four-fold higher rate of infection-specific mortality compared to women, and a two-fold higher rate of all-cause mortality. Findings imply that interventions during hip fracture recovery to prevent and treat infections, tailored by sex, may be needed to narrow significant differences in long-term mortality rates between men and women. In a general population of adults (≥60 years), infections like hepatitis B and methicillin-resistant Staphylococcus Aureus are more common in men, while rotavirus and urinary tract infection are more common in women.[158] Future studies should explore sex difference regarding pathogens causing infection among older adults post hip fracture so that tailored screening and treatment regimens can be developed. Since typical signs of infection, like fever, may be blunted in older adults, clinicians should be vigilant of other signs like unexplained change in physical abilities or cognitive status compared to baseline.[159]

CHAPTER 5 - SEX-SPECIFIC ASSOCIATION OF PHYSICAL PERFORMANCE WITH ALL-CAUSE MORTALITY AND PREDICTORS OF ALL-CAUSE MORTALITY (AIM 2)

5.1 SEX-SPECIFIC ASSOCIATION OF PHYSICAL FUNCTION WITH ALL-CAUSE MORTALITY (Aim 2.1)

5.1.1 Abstract

Background Physical performance measures (grip strength, Short Physical Performance Battery (SPPB), and 3-meter gait speed) are strong predictors of short-term and long-term mortality among community-dwelling older adults, but it is unclear if these measures predict post-hip fracture mortality and if there are any differences by sex.

Methods Data came from the Baltimore Hip Studies-7th (BHS-7). The associations of physical performance measures at 2 months pos- hip fracture and mortality were determined using Cox proportional hazards models. Interaction of sex and time with physical performance measures were successively added in the Cox models to determine if associations between physical performance and mortality differed by sex and changed over time, respectively.

Result Mean age was 81 years, and 48%(n=102) were men. A one-unit increment in each physical performance measure was associated with lower rate of mortality: SPPB 9% lower (HR=0.91,95%CI=0.83-0.98); gait speed (0.1 meter/second) 2% lower (HR=0.98,CI=0.97-0.99); and grip strength (kg) 5% lower (HR=0.95,CI=0.93-0.98). The interactions of the physical performance measures with sex and time were not significant ($p>.05$). The sex-specific association of grip strength with mortality was significant only in men (HR= 0.95, 95% CI= 0.91-0.98) but not women (HR= 0.96, 95% CI= 0.90-1.01).

Conclusion Physical performance was associated with mortality over 10.2 years. The association was not different based on sex except for grip strength; higher grip strength was associated with a lower mortality risk only in men. Future interventions, tailored by sex, with a target to improve upper body strength, may be more beneficial for survival in men.

5.1.2 Introduction

More than 300,000 older adults are hospitalized for hip fracture each year in the United States (U.S.).[1] As the older adult population is a growing proportion of the U.S. population, the incidence of hip fracture is projected to increase to 750,000 per year by 2050.[2] Mortality rate post-hip fracture is also high with almost 60% of hip fracture patients dying within five years post-hip fracture surgery.[5] Extant research shows that men die at a twice higher rate than women for the first two years post hip fracture.[6] Higher post-operative mortality in men is attributed to chronic comorbidities prior to hip fracture and higher likelihood of postoperative complications such as delirium, pneumonia, and acute renal failure in men.[5] The current literature lacks evidence for clinical characteristics in post-acute phase that can explain sex differences in short-term and long-term (up to 10 years) mortality. Identifying clinical characteristics that may account for sex differences in morality after hip fracture have the potential to identify individuals who may be pre-disposed for poor survival.

Physical performance measures like Short Physical Performance Battery (SPPB), gait speed, and grip strength are a standard criterion to predict future health outcomes and may explain sex difference in post hip fracture short- and long-term mortality.[45] Although the association between physical performance measures and mortality in hip fracture patients has not been examined in the extant literature, physical performance measures are strongly associated with mortality in the general older adult population.[10–15] The moderating effect of sex on the association of physical performance measures and mortality in non-hip fracture population has been mixed with stronger association of grip strength with mortality in women compared to men and statistically insignificant sex

differences in the association of gait speed and mortality. [14,22,23] Given the change in functional status following a hip fracture and the level of dependency observed out to one year post fracture, hip fracture provides a unique model for studying the impact of sudden functional disability and mortality. Additionally, sex differences seen in community-dwelling older adults suggest a possible moderation effect of sex with physical performance and mortality in hip fracture population.[14,22,23]

Therefore, the objective of this study was to determine if sex moderated the association between physical performance (measured by SPPB, gait speed, and grip strength) at 2 months post-hip fracture and all-cause mortality over 10 years. We propose that poor physical performance at 2 months post hip fracture will predict poor short-term and long-term (up to 10 years) all-cause mortality (*hypothesis 2.1A*). We hypothesize that the strength of the association of SPPB and gait speed with all-cause mortality will be significantly stronger for men compared to women for both short- and long-term, but the strength of the association of grip strength with all-cause mortality will be significantly stronger for women compared to men for both short- and long-term (*hypothesis 2.1B*).

5.1.3 Methods

5.1.3.1 Study design

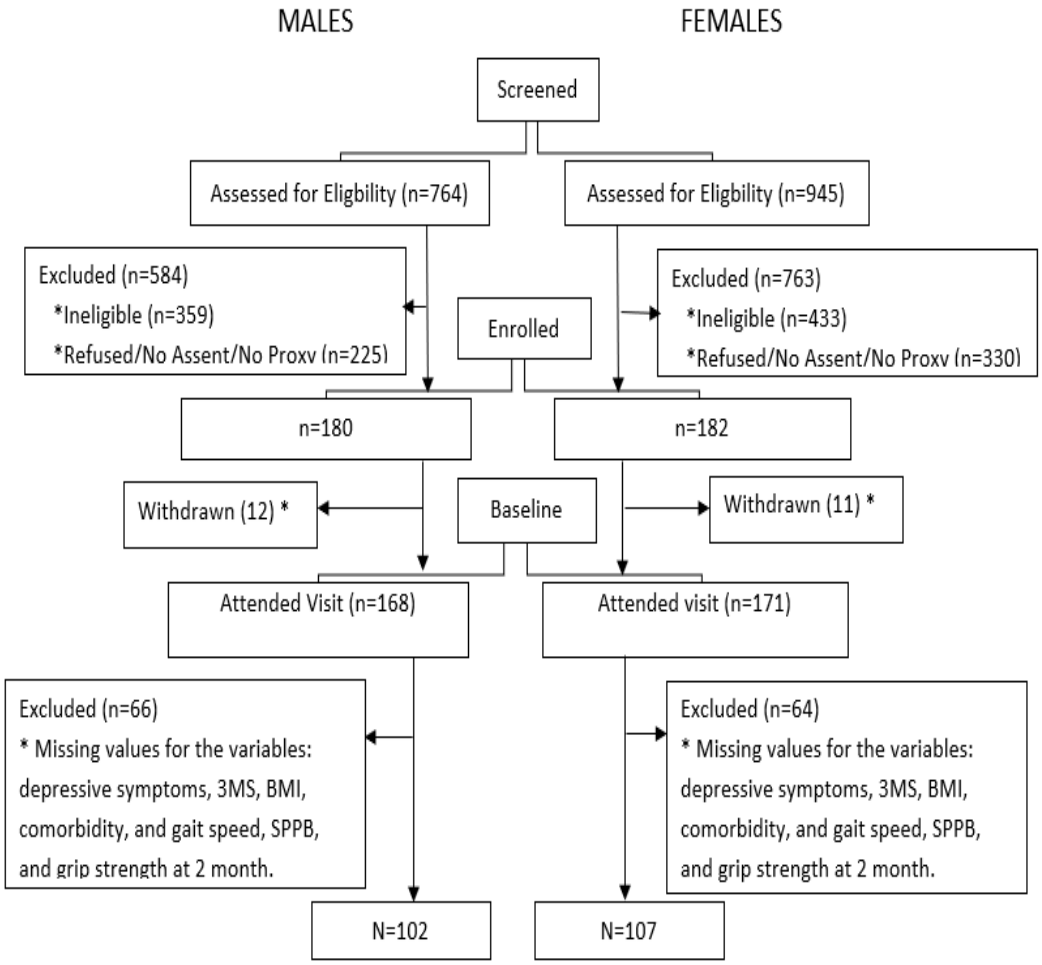
The study was conducted using existing data from the Baltimore Hip Studies 7th (BHS-7) cohort. Participants (≥ 65 years old and community-dwelling) were enrolled from one of eight acute care hospitals in the 25-hospital BHS network and were admitted with a hip fracture diagnosis (ICD-9 codes 820.00-820.9). The enrollment period was from May 2006 through June 2011, and all participants were consented (or whose proxy

provided consent) within 15 days of admission. BHS-7 was designed to assess sex differences in the sequelae of hip fracture, and female patients were frequency-matched (1:1) to males on the timing of admission within each hospital to ensure equal numbers of men and women. Further details of the study design can be found in a prior publication.[40] The present analysis utilizes physical performance measures collected at the 2-month follow-up visit. The BHS-7 cohort (n=339, 168 men and 171 women) was restricted to 209 participants (102 men and 107 women) who survived until 2 months post-fracture, had physical performance data at 2 months follow-up, and had complete data for all baseline covariates included in the adjusted models (**Figure 5.1)**.

5.1.3.2 Outcome and Exposure

Outcome was death and the data were obtained from 2006-2018 for a maximum of 10.2 years. All deaths were verified through the National Death Index. Exposure variables included the Short Physical Performance Battery (SPPB), 3-meter gait speed, and grip strength obtained at 2 months after a hip fracture admission. The SPPB measures balance, gait, strength, and endurance.[46] Standing balance was measured through timed side-by-side, semi-tandem, and tandem stands. Gait speed was assessed by a 3-meter gait speed test, where participants were instructed to walk at their usual speed from a starting line to a finish line. Finally, participants were assessed for their ability to rise from a chair 5 times as fast as possible. The participants were timed from first sitting to final standing position. Each task was scored from zero to four, and a summary score was calculated (0-12, with 12 the highest functioning) by combining all three component scores. Grip strength was measured in kilograms using a JAMAR Hydraulic Hand Dynamometer.[143]

Figure 5. 1. Flow diagram of study screening, enrollment, and complete case analysis sample, stratified by sex.



5.1.3.3 Covariate Measures

Potential confounders were selected a priori based on literature review and included age, comorbidity, cognition, depressive symptoms, body mass index (BMI), and pre-fracture lower-extremity Physical Activities of Daily Living (LPADL) limitations collected at baseline. These variables were selected as covariates because prior research has shown them to be predictive of mortality in older adults with hip fracture.[38,113,132–135] Comorbid conditions were evaluated using the Charlson Comorbidity Index (CCI), a

weighted index of comorbidities that takes into consideration the number and seriousness of chronic conditions.[151] Higher CCI scores indicate greater comorbidity and are associated with greater mortality.[151] In the current study, CCI score ranged from 0-8.The Modified Mini-Mental State Examination (3MS) was used to assess cognitive function.[150] The score ranged from 0-100. The 20-item Center for Epidemiological Studies Depression scale (CES-D) measured depressive symptoms. Questions ask about symptomology occurring in the last week, and responses are scored on a Likert scale that yields a summary score ranging from 0-60.[145] LPADL was assessed in the week prior to fracture using a modified form of the Functional Status Index, revised specifically to address functional issues related to hip fracture patients.[152] Response categories included no help, used equipment, used human assistance, used equipment and human assistance, did not perform due to health reasons, and did not perform due to non-health reasons. [152] Participants who responded needing equipment/human help to perform these activities and those who didn't perform because of health reasons were categorized as disabled.[4,7] LPADL score range from 0 to 12 with higher score indicating more disability. BMI was measured as kilograms per meters squared (kg/m^2).

5.1.3.4 Statistical Methods

Variable distributions were described by sex to assess the characteristics of the complete-case analysis samples. Percentages were estimated for the categorical variables; means and standard deviations were calculated for continuous variables. Bivariate associations between categorical variables and all-cause mortality were evaluated using Kaplan-Meier survival curves and log-rank tests.[136] Unadjusted Cox proportional hazard

models were used to estimate associations between continuous variables and all-cause mortality.

In *hypothesis 2.1A,* the adjusted association between physical performance measures and all-cause mortality was estimated by implementing Cox proportional hazards models adjusted for age, cognition, comorbidity, depressive symptoms, BMI, and pre-fracture LPADL limitations. Physical performance measures were modeled as considering linearity regarding exposure variables and log hazards over time. Linearity assumption was tested with residual plots. In *hypothesis2.1B* effect moderation by sex concerning the association between physical performance and mortality was assessed using an interaction term (i.e., physical performance*sex) that was added to the Cox proportional hazards models implemented to address *Hypothesis 2.1A.* To assess differential associations over varying lengths of follow-up concerning the primary exposure variable and mortality outcome, an interaction term was added between physical performance measures and time (in continuous years). Model goodness-of-fit was assessed using Akaike information criterion (AIC).[139] The associations tested in each model had 80% power and a 5% significance level. The analyses were performed using SAS, version 9.4 (SAS Institute, Inc., Cary, NC).[140]

5.1.4 Results

5.1.4.1 Participant Characteristics

By the end of 10.2 years post-hip fracture, 70 (65%) out of 107 women had died and 91 (89%) out of 102 men had died (**Table 5.1)**. The average SPPB score at 2 months after hip fracture for men was 3.5 [standard deviation (SD)=2.6] and for women was 2.9

(SD=2.6). The average gait speed for both men and women were 0.3 m/s (SD=0.2). The average grip strength for men was 29.8 kg (SD=8.2) and for women was 18.7 kg (SD=5.8).

Table 5. 1 Baseline characteristics of the participants by sex

Variables	Frequency (%)			Missing Frequency (%)
	Total (n=209)	Male (n=102)	Female (n=107)	
Death (by the end of 10 y), No. (%)				
Dead	237 (79.0)	91 (89.2)	70 (65.4)	
Alive	63 (21.0)	11 (10.7)	37 (34.5)	
Duration from the date of admission, median (IQR), y	5.3 (3.4)	4.1 (3.1)	6.4 (3.3)	
Age, mean (SD), y	80.7 (7.7)	80.2 (7.7)	80.7 (7.4)	
3MS, mean (SD) [a]	85.7 (13.4)	84.7 (12.5)	88.3 (13.2)	7 (2.3)
CCI, mean (SD) [b]	2.0 (1.7)	2.4 (1.9)	1.5 (1.5)	1 (0.3)
CES-D, mean (SD) [c]	17.6 (10.9)	16.8 (9.4)	17.1 (11.1)	36 (12)
BMI (kg/ m^2), mean (SD) [d]	25.2 (5.1)	25.7 (4.2)	25.4 (6.0)	16 (5.3)
LPADL, mean (SD) [e]	2.4 (2.4)	2.3 (2.3)	2.4 (2.5)	13 (4.3)
SPPB, mean (SD) [f]		3.5 (2.6)	2.9 (2.6)	35 (14.4)
Gait speed (m/s), mean (SD) [g]		0.3 (0.2)	0.3 (0.2)	37 (15.2)
Grip strength (Kg), mean (SD) [h]		29.8 (8.2)	18.7 (5.8)	33 (13.6)

[a] Modified Mini-Mental Status ranges from 0 to 100. Higher score indicates better cognition.
[b] Charlson Comorbidity Index ranges from 0 (no comorbidity) to 8.
[c] Center for Epidemiological Studies Depression scale ranges from 0 to 60. Higher score indicates greater depressive symptoms.
[d] Body Mass Index, 21-25 kg/m^2 is normal range per World Health Organization.
[e] Lower Extremity Physical Activities of Daily Living ranges from 0-12 with higher score indicating more disability
[f] Short Physical Performance Battery ranges from 0-12 with higher score indicating better physical performance.

5.1.4.2 Association of Physical Performance and All-Cause Mortality

In unadjusted models, each unit increment in SPPB was associated with a 15% [Hazard Ratio (HR)=0.85, 95% Confidence Interval (CI) = 0.78-0.91] lower hazard of all-cause mortality post-hip fracture (**Table 5.2)**. One meter per second faster gait speed was associated with a 3% (HR=0.97, 95% CI=0.96-0.98) lower hazard of all-cause mortality. Grip strength was not significantly associated with all-cause mortality (*p*=0.24). Men were twice (HR=2.19, 95% CI=1.93-2.44) as likely to die as compared to women. In adjusted cox proportional hazard models, each unit increment in SPPB was associated with a 9% (HR= 0.91, 95% CI=0.83-0.98) lower hazard of all-cause mortality post-hip fracture (**Table 5.3)**. One meter per second faster gait speed was associated with a 2% (HR= 0.98, 95% CI= 0.97-0.99) lower hazard of all-cause mortality. One kg higher grip strength was associated with a 5% (HR= 0.95, 95% CI= 0.93-0.98) lower hazard of all-cause mortality.

Table 5. 2 Univariable association of SPPB, gait speed, grip strength, age, cognition, comorbidity, depression symptoms, BMI, LPADL, and sex with all-cause mortality

Variable	HR (95% CI)	P value
SPPB [a] (per 1 point)	0.85 (0.78-0.91)	<.01
Gait speed (per 0.1 m/s)	0.97 (0.96-0.98)	<.01
Grip strength (per kg)	0.99 (0.97-1.00)	0.24
Age (per year)	1.06 (1.04-1.07)	<.01
Mini-Mental Status Examination	0.97 (0.96-0.97)	<.01
Charson Comorbidity Index	1.24 (1.16-1.31)	<.01
Center for Epidemiological Studies-Depression Score	1.01 (0.99-1.02)	<.01
Body Mass Index (kg/m^2)	0.98 (0.95-1.00)	0.12
Lower Extremity Physical Activities of Daily Living	1.08 (1.03-1.12)	<.01
Male	2.19 (1.93-2.44)	<.01

[a] Short Physical Performance Battery ranges from 0-12 with higher score indicating better physical performance.

Table 5. 3 Association of SPPB, gait speed, and grip strength at 2 months post hip fracture with all -cause mortality by sex

	HR (95% CI)			Interaction with sex [a] (*P* value)
	Overall	Male	Female	
SPPB (per 1 point) [b,c]	0.91 (0.83-0.98)	0.92 (0.83-1.01)	0.92 (0.79-1.05)	0.86
Gait speed (0.1 m/s) [c]	0.98 (0.97-0.99)	0.91 (0.80-1.01)	0.89 (0.77-1.02)	0.84
Grip strength (per kg) [c]	0.95 (0.93-0.98)	0.95 (0.91-0.98)	0.96 (0.90-1.01)	0.68

[a] SPPB*sex; gait speed*sex; grip strength*sex
[b] Short Physical Performance Battery ranges from 0-12 with higher score indicating better physical performance.
[c] Adjusted for age, sex, 3MS (Modified Mini-Mental Status), CCI (Charlson Comorbidity Index), CES-D (Center for Epidemiological Studies Depression), BMI (Body Mass Index), LPADL (Lower Extremity Physical Activities of Daily Living)

5.1.4.3 Moderating Effect of Sex on the Association of Physical Performance and All-cause mortality

The interaction terms between sex and all three physical performance measures with all-cause mortality were not significant: SPPB (p=0.86), gait speed (p= 0.84), and grip strength (p= 0.68) (**Table 5.3)**. Although the interaction of sex with physical performance measures was not significant, the sex-specific association of grip strength with mortality was significant only in men (HR= 0.95, 95% CI= 0.91-0.98) but not women (HR= 0.96, 95% CI= 0.90-1.01).

5.1.4.4 Interaction of Time with Physical Performance Measures

The association of the interaction of all three physical performance measures and time with all-cause mortality was not significant: SPPB (p=0.43), gait speed (p=0.57), and grip strength (p=0.32) **(Table 5.4).** When stratified by sex, the interaction of time with SPPB, gait speed, and grip strength remained non-significant. These findings suggest that the association of SPPB, gait speed, and grip strength with all-cause

mortality does not vary with increasing duration from the date of admission post-hip fracture for both men and women.

Table 5. 4 Interaction effect with time (SPPB*time, gait speed*time, grip strength*time) in complete case and stratified by sex (Time is operationalized as continuous years)

	Ratio of HR (95% CI)	*P* value
SPPB*time		
combined sample	1.01 (0.98-1.03)	0.43
men	1.01 (0.98-1.04)	0.36
women	1.00 (0.95-1.05)	0.96
	Gait speed	
Gait speed*time		
combined sample	1.00 (0.99-1.00)	0.57
men	0.99 (0.63-1.35)	0.98
women	1.18 (0.73-1.62)	0.46
	Grip strength	
Grip strength*time		
combined sample	1.00 (1.01-0.99)	0.32
men	1.00 (0.99-1.01)	0.39
women	1.00 (0.98-1.02)	0.62

Note: the models are adjusted for Adjusted for age, sex, 3MS (Modified Mini-Mental Status), CCI (Charlson Comorbidity Index), CES-D (Center for Epidemiological Studies Depression), BMI (Body Mass Index), LPADL (Lower Extremity Physical Activities of Daily Living)

5.1.5 Discussion

Consistent with past studies in general population of older adults, higher SPPB scores and grip strength and faster gait speed were associated with better survival in hip fracture patients even after controlling for important predictors of mortality like age and comorbidity. The association between physical performance measures and mortality also persisted both in short-term and long-term durations of follow-up time.[11,13] However, sex did not moderate the association between physical performance measures and all-cause mortality and nor did the observed relationships change over time among men and women. That being said, the association of grip strength with mortality was significant

only in men but not women. The results indicate that all three physical performance measures at 2 months post-hip fracture have potential to identify individuals at a greater risk of mortality in both short- and long-term follow up irrespective of sex, while grip strength may be a better indicator of mortality in men compared to women not SPPB and gait speed.

We did not find strong evidence that the association of SPPB and gait speed with mortality after a hip fracture differed by sex. Even though there are no past studies to compare the findings, the results are consistent with a prior study that examined the association of SPPB and other health outcomes associated with mortality in older adults like recurrent fall in non-hip fracture population and did not find a moderating effect by sex.[160] Similarly in another study of sex difference in gait speed, women on average scored 0.05 m/s lower compared to men, which is a clinically relevant difference; however, the slower gait speed in women did not translate to poor health outcomes in both hip fracture and non-hip fracture population.[161,162] In contrast, grip strength requires upper extremity function and may capture more variance in mortality outcome in hip fracture patients compared to SPPB and gait speed, which are a direct measure of lower extremity function.

Past studies in non-hip fracture populations have yielded findings with some showing a stronger association of grip strength and mortality in women and the other in men.[14,78,163] In this study, the moderating effect of sex (examined by grip strength*sex) on the association of grip strength with all-cause mortality was not significant. However, in a stratified analysis, each kg increment of grip strength was associated with better survival only in men but not women, indicating that muscle weakness seen after a hip

fracture may be disadvantageous for men compared to women. Although the magnitude of association was similar in both sexes, one plausible explanation can be the higher prevalence of sarcopenia after a hip fracture in men compared to women.[164] One-third of hip fracture patients suffer from sarcopenia and the rate of mortality is 15% higher in hip fracture patients diagnosed with sarcopenia.[165] The findings indicate that grip strength may be a better indicator of mortality in men than women. It is unclear if muscle strengthening interventions promote survival; however, studies examining the sex-specific impact of muscle strengthening interventions on survival after a hip fracture is warranted.

All three physical performance measures examined in this study predicted short- and long-term mortality as shown by the statistically significant association of each performance measure with mortality and insignificant interaction effect (physical performance*time). One explanation is that these performance-based measures have good reliability and stability and as such the association of these variables with an outcome remains relatively stable over long time periods.[166,167] Although time interactions were not examined in past studies, this finding is in line with previous research that showed that physical performance measured at baseline can predict mortality in both short- and long-term follow-up in a non-hip fracture population of older adults.[11] The results indicate that physical performance measures are a good indicator of both short- and long-term mortality and can explain variability in mortality risk that is not captured by other factors like age, sex, comorbidity, and other variables included in the adjusted models.

5.1.5.1 Limitations and Strengths

There were several limitations and strengths. First, there were missing data on baseline variables, which impacted inclusion into the analytic sample and may reduce generalizability to a general population of patients with hip fracture. Second, there were some missing data in physical performance measures. Given participants need a certain level of ability to perform these activities, those not able to perform these measures might be those at a greater risk of poor survival. However, descriptive data showed that participants with missing data did not significantly differ from those with complete data, which mitigates concerns about generalizability. Additionally, the BHS-7 sample was predominantly white and participants were all from Baltimore-area hospitals so findings may not be generalizable to other populations. Our research is the first to determine if physical performance measures are a predictor of short-term and long-term mortality post hip fracture. This study was powered to assess sex difference, which has been a limitation of past studies, in hip fracture patients. To prevent bias because of intermediate variables, all the selected confounders are measured prior to the exposure.[168]

5.1.6 Conclusion

SPPB, gait speed, and grip strength were associated with all-cause mortality throughout 10.2 years of follow up after hospital admission for hip fracture. The association was not different based on sex except for grip strength; higher grip strength was associated with a lower mortality risk only in men. Findings imply that SPPB and gait speed do not contribute to sex differences in mortality rates after hip fracture and interventions tailored by sex to improve SPPB score and gait speed post hip fracture may not be beneficial. Interventions like progressive resistance exercise intervention

combined with nutritional supplement, tailored by sex, with a target to improve upper body strength, on the other hand, may be more beneficial for survival in men. [169]

5.2 EXPLORATORY AIM: PREDICTION OF HIP FRACTURE MORTALITY OVER 10.2 YEARS (Aim 2.2)

5.2.1 Abstract

Introduction Physical performance measures (grip strength, Short Physical Performance Battery (SPPB), and 3-meter gait speed) are strong predictors of long-term mortality among community-dwelling older adults, but it is unclear if physical performance measures are better at predicting long-term mortality in hip fracture patients compared to previously known predictors of mortality in hip fracture patients.

Methods Data came from the Baltimore Hip Studies-7th (BHS-7). Groups that discriminate mortality risk were determined using a Classification and Regression Tree (CART) analysis. The CART model included age, sex, 3MS (Modified mini-mental state), comorbidity (Charlson's comorbidity index), pre-fracture Lower Extremity Activities of Daily Living (LPADL) limitations, CESD (Center for epidemiological studies depression scale) and physical performance measures.

Results Poor cognition at baseline (3MS< 98), male sex and age (≥ 74 years) were identified as predictors of 10.2-year mortality. The four risk groups identified by the CART model were: 1) 3MS ≥ 98, 2) men with 3MS < 98, 3) women younger than 74 years with 3MS < 98, and 4) women older than 74 with 3MS < 98. The highest incident death was observed in men with 3MS < 98 (10.2-year mortality=96%) followed by women older than 74 years with 3MS < 98 (10.2-year mortality=76%). The lowest incident death was observed in older adults with 3MS ≥ 98 (10.2-year mortality=14%).

Conclusion After accounting for cognition, age, and sex, adding physical performance measures did not improve prediction of long-term hip fracture mortality. Future studies should explore if cognition can explain sex difference in long-term mortality.

5.2.2 Introduction

Assessing physical performance measures in clinical settings takes more resources and time compared to information like age and comorbidity, which can be easily obtained by asking simple questions or from medical records. Determining if physical performance measures can predict long-term mortality better than previously known predictors could help clinicians make an informed decision about the need to examine physical performance measures during hip fracture recovery. A past study done in older adults with acute myelogenous leukemia found that adding SPPB into their model with geriatric assessment measures improved the discrimination of mortality.[24] Similarly, gait speed and SPPB were predictive of mortality among general population older adults even after controlling for important predictors of mortality like age and comorbidity.[25] However, it is unclear if physical performance measures are better at predicting long-term mortality in hip fracture patients compared to previously known predictors. Thus, this research aimed to determine if measuring physical performance measures (SPPB, gait speed, and grip strength) alone or in combination with sex, cognition (Mini-mental Status Examination), depressive symptoms (Center for Epidemiological Studies- Depression scale), age, body mass index (BMI), and pre-fracture Lower Extremity Physical Activities of Daily Living (LPADL) limitation improves discrimination of post hip fracture mortality (*Exploratory Aim 2.2*).

5.2.3 Methods

5.2.3.1 Study design

The study was conducted using existing data from the Baltimore Hip Studies 7th (BHS-7) cohort. Participants (≥ 65 years old and community-dwelling) were enrolled from one of eight acute care hospitals in the 25-hospital BHS network and were admitted with a hip fracture diagnosis (ICD-9 codes 820.00-820.9). The enrollment period was from May 2006 through June 2011, and all participants were consented (or whose proxy provided consent) within 15 days of admission. BHS-7 was designed to assess sex differences in the sequelae of hip fracture, and female patients were frequency-matched (1:1) to males on the timing of admission within each hospital to ensure equal numbers of men and women. Further details of the study design can be found in a prior publication.[40] The physical performance measures were collected at the 2-month follow-up visit. The BHS-7cohort (n=339, 168 men and 171 women) was restricted to 209 participants (102 men and 107 women) who survived until 2 months post-fracture, had physical performance data at 2 months follow-up, and had complete data for all variables included in the model.

5.2.3.2 Measures

The variables included were mortality, SPPB, gait speed, grip strength, Age, comorbidity, cognition, depressive symptoms, body mass index (BMI), and pre-fracture lower-extremity Physical Activities of Daily Living (LPADL) limitations. Death data were obtained from 2006-2018 for a maximum of 10.2 years. All deaths were verified through the National Death Index. Physical performance measures include Short Physical Performance Battery (SPPB), 3-meter gait speed, and grip strength obtained at 2 months after a hip fracture admission. The SPPB measures balance, gait, strength, and

endurance.[46] Standing balance was measured through timed side-by-side, semi-tandem, and tandem stands. Gait speed was assessed by a 3-meter gait speed test, where participants were instructed to walk at their usual speed from a starting line to a finish line. Finally, participants were assessed for their ability to rise from a chair 5 times as fast as possible. The participants were timed from first sitting to final standing position. Each task was scored from zero to four, and a summary score was calculated (0-12, with 12 the highest functioning) by combining all three component scores. Grip strength was measured in kilograms using a JAMAR Hydraulic Hand Dynamometer.[143] Comorbid conditions were evaluated using the Charlson Comorbidity Index (CCI), a weighted index of comorbidities that takes into consideration the number and seriousness of chronic conditions.[151] Higher CCI scores indicate greater comorbidity and are associated with greater mortality.[151] In the current study, CCI score ranged from 0-8.The Modified Mini-Mental State Examination (3MS) was used to assess cognitive function.[150] The score ranged from 0-100. The 20-item Center for Epidemiological Studies Depression scale (CES-D) measured depressive symptoms. Questions ask about symptomology occurring in the last week, and responses are scored on a Likert scale that yields a summary score ranging from 0-60.[145] LPADL was assessed in the week prior to fracture using a modified form of the Functional Status Index, revised specifically to address functional issues related to hip fracture patients.[152] Response categories included no help, used equipment, used human assistance, used equipment and human assistance, did not perform due to health reasons, and did not perform due to non-health reasons. [152] Participants who responded needing equipment/human help to perform these activities and those who didn't perform because of health reasons were categorized as disabled.[4,7] LPADL score

range from 0 to 12 with higher score indicating more disability. BMI was measured as kilograms per meters squared (kg/m^2).

5.2.3.3 Statistical Methods

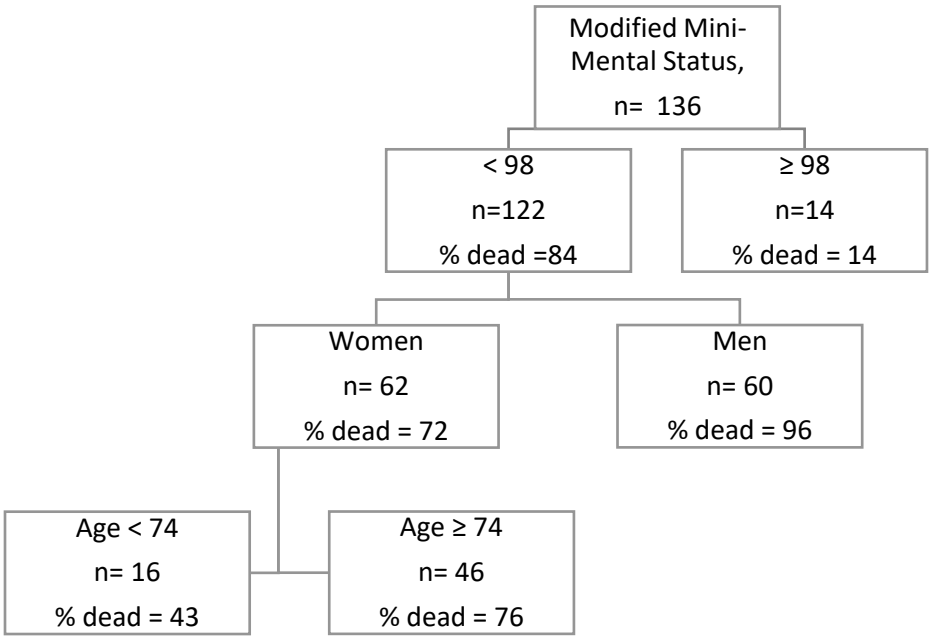
CART analysis was performed to identify a set of predictors that can best discriminate 10.2-year mortality after a hip fracture. CART analysis was performed using the rpart package in R software (version 4.0.3), and cross-validation was used to "prune" less important splits to prevent overfitting and produce a more parsimonious tree. The data were randomly partitioned into train and test data sets (70/30) without replacement. Cross-validation in the training set was performed by using leave-one-out cross validation technique. The CART model used time-to-event data where the time values were pre-scaled to fit an exponential model. Since the outcome variable was pre-scaled, a subgroup analysis was performed in the original time scale using the "where" option in "Survfit" function to create Kaplan-Meier curves. To improve the CART model, changes in the nodes based on shrinkage, which gives different Bayes estimates of hazard, was examined.[144] Later, the pruned model was evaluated in the test data set. Two Cox proportional hazard models were run, one each in the train data first and then in the test data to compare the all-cause mortality discrimination by the categories identified by the final pruned CART tree.

5.2.4 Results

As shown in **Figure 5.2**, CART analysis performed on the complete-case sample, split the data into four subgroups with differing mortality rates. Poor cognition at baseline (3MS< 98), male sex and age (≥ 74 years) were identified as predictors of 10.2-year

mortality post hip fracture after pruning. The four risk groups identified by the CART model were: 1) 3MS greater than 98, 2) men with 3MS less than 98, 3) women younger than 74 years with 3MS less than 98, and 4) women older than 74 with 3MS less than 98. The highest incident death was observed in men with 3MS less than 98 (10.2-year mortality= 96%) followed by women older than 74 years with 3MS less than 98 (10.2-year mortality= 76%). The lowest incident death was observed in older adults with 3MS greater than or equal to 98 (10.2-year mortality= 14%).

Figure 5. 2: Classification and Regression Tree for discriminating ten-year mortality in older adult's post hip-fracture in training dataset.



The Cox proportional hazard model run with the training data showed that the hazard of death for men with 3MS < 98 was 19.2 times (95% CI= 4.6-79.3) the hazard

for the reference category (older adults with 3MS greater than or equal to 98) (**Table 5.5**). The hazard of death for women ≥ 74 years of age with 3MS < 98 was 10 times (HR=10.2, 95% CI 2.5-42.3) the hazard for the reference category. Women < 74 years of age with 3MS < 98 were not different than the reference category. The Cox proportional hazard model run with the test data showed smaller estimates of hazard ratios, but similar results as seen in the training data set. The hazard of death for men with a cognition < 98 was 4 times (95% CI=1.8-9.4) the hazard for the reference category. The hazard of death for women with cognition < 98 and ≥ 74 years of age as well as ≤ 74 years of age were not significantly different compared to the reference category.

Table 5. 5 Cox proportional hazard model showing the association of CART categories on 10-year mortality in train data and test data

	Train data (n=136)	Test data (n=59)
	HR (95% CI)	HR (95% CI)
3MS [a] greater than 98	1	1
3MS less than 98 and men	19.2 (4.6 - 79.3)	4.1 (1.8 - 9.4)
3MS less than 98, women, and age less than 74 years	2.1 (0.3 - 12.3)	2.2 (0.3 - 17.6)
3MS less than 98, women, and age greater than or equal to 74	10.2 (2.5 - 42.3)	2.2 (0.9 - 5.3)

[a] Modified Mini-Mental Status ranges from 0 to 100. Higher score indicates better cognition.

5.2.5 Discussion

Poor cognition at baseline (3MS< 98), male sex and age ≥ 74 years were identified as predictors of 10.2-year mortality post hip fracture. Men with a 3MS<98 was identified as the group most vulnerable to dying over 10.2 years follow up. None of the physical performance measures were selected as the predictor of mortality. The findings

indicate that if a clinician has information about the age, sex, and baseline cognitive function, then measuring physical performance score may not add any value to predicting post hip fracture mortality.

Cognitive function (3MS ≥ 98) was identified as the most important predictor of survival at 10.2 years in hip fracture patients. A cognition score of 98 is relatively high because the optimal cut off to identify cognitive impairment in older adults is a 3MS < 78.[170] However, we also know from the past studies that individuals with good cognition are more likely to have a better recovery outcome due to several reasons including greater adherence to post hip fracture rehabilitation and lower likelihood of subsequent falls and secondary fractures.[171,172] It is likely that individuals who scored 98 and above in 3MS within 15-22 days post hip fracture are the healthiest category of patients and have the best prognosis for long-term survival. However, it needs to be taken into consideration that the group with a 3MS ≥ 98 was relatively small and further study with a larger sample size is warranted.

None of the physical performance measures were selected as predictors of all-cause 10.2-year mortality. One reason is that only first three splits in the CART model was considered to keep the cross-validation error at the minimum. It is possible that if we considered more than first three splits, at least one of the physical performance measures would have been selected. Another reason for physical performance measure not being selected may be contributed by how CART operates. CART creates the categories at each split to minimize the misclassification cost.[173] Hip fracture patients score relatively low in SPPB and gait speed at 2 months creating a risk of floor effect, as such other variables like cognition, with more variability, may create more homogeneous groups with regards

to long-term mortality in CART models. It is also likely that once cognition, age, and sex are accounted for, the "cost" of including physical performance does not justify the improvement.

5.2.5.1 Limitations and Strengths

There were some limitations and strengths. There are some missing data in physical performance measures. Given participants need a certain level of ability to perform these activities, those not able to perform these measures might be those at a greater risk of poor survival. Thirty-nine participants with missing covariate data were also removed for complete case analysis. However, descriptive data showed that participants with missing data did not significantly differ from those with complete data, which mitigates concerns about generalizability. Our sample was predominantly white recruited from Baltimore area hospitals, as a result these findings may not be generalizable to other population. As for strength, the categories selected by CART for discrimination of mortality in the training dataset was tested for accuracy on the unused test dataset. Checks were in place to make sure that transformation of time scale did not affect the selected CART categories.

5.2.6 Conclusion

After accounting for cognition, age, and sex, adding physical performance measures did not improve prediction of long-term hip fracture mortality. A group of hip fracture patients with 3MS $\geq$ 98 had the highest probability of long-term survival, however, the sample size was small (n=14). Future studies with a larger sample size are

needed to confirm that an extremely high 3MS score can predict long-term survival irrespective of other important predictors of mortality like age, sex, and comorbidity.

CHAPTER 6 - SEX AS A MODERATOR OF THE TNFα-DEPRESSIVE SYMPTOMS-MORTALITY ASSOCIATION AFTER HIP FRACTURE (AIM 3)

6.1 Abstract

Introduction Evidence suggests that increased tumor necrosis factor-α (TNFα) leads to depressive symptoms and higher levels of both are associated with mortality. Moreover, the association of TNFα and depressive symptoms with mortality is stronger in men than women. It is unknown if depressive symptoms contribute to the association between TNFα and mortality and whether any mediating effects differ by sex.

Methods Data come from Baltimore Hip Studies7th (BHS-7) (n=193). Soluble tumor necrosis factor alpha receptor (TNFα-R1) was measured at baseline (within 22 days of hospitalization for fracture) and depressive symptoms were measured 2 months later. To assess the mediating effect of depressive symptoms regarding the association of TNFα-R1 with mortality, Aalen additive hazard models were used and run separately on men and women to examine the moderating effect of sex.

Results In men, compared to the 1st tertile of TNFα-R1, the total effect of TNFα-R1 increased the total number of deaths by 118 (95% CI=9.1 – 225.2) and 161 (95% CI=36.5 – 286.4) per year per 1000 hip fracture patients at risk in the 2nd and the 3rd tertile of TNFα-R1, respectively. Among women, compared to the 1st tertile of TNFα-R1, the total effect of TNFα-R1 increased the total number of deaths by 3 (95% CI=-58.4 – 66.2) and 16 (95% CI=-58.0 – 89.0) per year per 1000 hip fracture patients at risk in the 2nd and the 3rd tertile of TNFα-R1, respectively. Depressive symptoms did not significantly mediate the association of TNFα-R1 and mortality in men or women (p>.05).

Conclusion Evidence is consistent with TNFα-R1 impacting mortality in men, but not women, after a hip fracture and via pathways other than depressive symptoms. Future research should identify other clinically meaningful inflammatory biomarkers that can predict mortality after hip fracture among men and women.

6.2 Introduction

More than 260,000 older adults are hospitalized for hip fracture each year in the United States (U.S.).[1] As the older adult population is a growing proportion of the U.S. population, the incidence of hip fracture is projected to increase to 750,000 per year by 2050.[2] Mortality post hip fracture is high and almost 60% of hip fracture patients die within five years after surgical intervention for hip fracture.[5] Extant research has shown that men die at a twice higher rate than women for the first two years post hip fracture.[6] There is little evidence explaining why there is sex difference in mortality after a hip fracture.[8,40] Clinical characteristics like tumor necrosis factor alpha (TNFα) and depressive symptoms are more strongly associated with mortality among men compared to women in older adults without hip fracture.[16,17] As such, these biological factors may impact mortality outcomes in hip fracture differently between men and women.

TNFα are small proteins that are primarily secreted by helper T cells and macrophages, both components of our immune system.[26] Although post fracture acute elevation in TNFα levels are important to protect against immediate infections, systemic inflammation has also been linked to outcomes such as multiple organ failure and lung injury.[92] Biological evidence also suggests that higher and sustained TNFα exposure leads to depressive symptoms by reducing bioavailability of serotonin, a key hormone that stabilizes mood.[124,125] Approximately 10% of hip fracture patients experience persistent depressive symptoms for at least a year after a hip fracture.[108] Evidence also shows that older adults with depressive symptoms are less interested in activities like exercise, social engagement, and medication adherence, which can contribute to poor

survival.[114,115] More importantly, it is unknown whether depressive symptoms explain (in part) the association between TNFα and mortality after hip fracture.

The association of TNFα and depressive symptoms with mortality among the general population of older adults is stronger in men than women.[28,29] A potential explanation for higher mortality among men is a greater susceptibility to cardiovascular disease due to lower threshold for chronic inflammatory exposure compared to women.[104] Higher mortality in men may also be explained by behavioral tendencies as women with depressive symptoms seek out mental health care services.[119] Although the association of inflammation with mortality is stronger in men, women are more likely to experience depressive symptoms with elevated serum inflammation.[28,32,33] Thus, there may be a stronger mediating effect of depressive symptoms regarding the relationship between TNFα and mortality among women. However, it is unclear if the TNFα→Depressive Symptom→Mortality pathway is sex specific in general older adult population or those with hip fracture.

To address current research gaps, this study assessed the mediating role of depressive symptoms in the association of TNFα-R1 and mortality. TNFα-R1 is the optimal proxy for TNFα because TNFα-R1 has a long-term bioavailability in the stored serum. We tested the hypotheses that higher TNFα-R1 is associated with a greater risk of mortality (*hypothesis 3.1A*) and those depressive symptoms partially explain the association of TNFα-R1 and mortality (*hypothesis 3.1B*). We further determined if the mediating effect of depressive symptoms in the association of TNFα-R1 and mortality is sex specific. We also tested the hypotheses that the association between TNFα-R1 and all-cause mortality is stronger for men compared to women *(hypothesis 3.2A*) and a larger

portion of the association between TNFα-R1 and mortality is explained by depressive symptoms in women compared to men (*hypothesis 3.2B*).

6.3 Methods

6.3.1 Study Design

This study was conducted using existing data from the Baltimore Hip Studies 7th (BHS-7) cohort. Participants (≥ 65 years old and community-dwelling) were enrolled from one of eight acute care hospitals in the 25-hospital BHS network and were admitted with a hip fracture diagnosis (ICD-9 codes 820.00-820.9). Participants were enrolled from May 2006 through June 2011, and all participants were consented (or whose proxy provided consent) within 15 days of admission. BHS-7 was designed to assess sex differences in the sequelae of hip fracture, and female patients were frequency-matched (1:1) to males on the timing of admission within each hospital to ensure equal numbers of men and women. Further details regarding the study design and methodology are available elsewhere.[40] The BHS-7 cohort enrolled 339 participants (168 men and 171 women) and was restricted to 193 participants (89 men and 104 women) with serum measurement of soluble tumor necrosis factor alpha receptor I (TNFα-R1) at baseline (within 22 days post admission) and depressive symptom data at 2-month follow-up and complete covariate data.

6.3.2 Outcomes, Exposure, and Mediator

All-cause mortality was the study outcome. Death data were obtained from 2006-2018 for a maximum of 10.2 years and verified through the National Death Index. TNFα-R1 is the exposure. Blood specimens were collected between 7 a.m. and 10:00 a.m. and transported to the university campus no later than 1:00 p.m. for processing. Samples were

processed within 6 hours of collection and serum was stored at -80 degrees Centigrade until assayed. TNFα-R1 was measured in sera using the Quantikine Human sTNF enzyme-linked immunosorbent assay (ELISA) and V-Plex MSD (Meso Scale Diagnostics). Continuous TNFα-R1 values were then categorized into tertiles: 1st tertile (≤ 2587 pg/ml), 2nd tertile (2588 – 3512 pg/ml), and 3rd tertile (≥3513 pg/ml). Depressive symptoms is the mediator. The 20-item Center for Epidemiological Studies Depression scale (CES-D) measured depressive symptoms. Questions ask about symptomology occurring in the last week, and responses are scored on a Likert scale that yields a summary score ranging from 0-60, with higher scores indicating more depressive symptoms.[145]

6.3.3 Covariate Measures

Potential confounders were selected a priori based on prior research showing them to be predictive of mortality and being different between men and women at the time of fracture.[38,113,132–135] The Modified Mini-Mental State Examination (3MS) was used to assess cognitive function. The score ranged from 0-100.[150] Comorbidity were evaluated using the Charlson Comorbidity Index (CCI), a weighted index of comorbidities that takes into consideration the number and seriousness of chronic conditions.[151] Higher CCI scores indicate greater comorbidity and are associated with greater mortality.[151] In the current study, CCI scores ranged from 0-8 and only moderate or severe (not mild) liver disease was recorded. Lower-extremity Physical Activities of Daily Living (LPADL) function was assessed in the week prior to fracture using a modified form of the Functional Status Index, which measures the ability to perform an activity and level of difficulty.[152] Response categories included no help, used equipment,

used human assistance, used equipment and human assistance, did not perform due to health reasons, and did not perform due to non-health reasons. [152] Participants who responded needing equipment and/or human help to perform these activities and those who didn't perform because of health reasons were categorized as disabled.[4,7] LPADL score range from 0 to 12 with higher score indicating more disability. Body Mass Index (BMI) was measured as kilograms per meters squared (kg/m^2).

6.3.4 Statistical Analysis

Variable distributions were described by sex to assess the characteristics of the complete-case samples. Percentages and frequencies were estimated for the categorical variables and means, and standard deviations were calculated for continuous variables. To assess the mediating effect of depressive symptoms in the association of TNFα-R1with all-cause mortality, an Aalen additive hazard model, a semiparametric model for survival outcomes was fit in the analytic cohort comprising both men and women.[146] Mortality was regressed on depressive symptoms, TNFα-R1 and covariates using Aalen model to estimate the direct effect (DE) of TNFα-R1 on mortality. To compute the total effect (TE) and indirect effect (IE) of TNFα-R1 on mortality, depressive symptoms were linearly regressed on TNFα-R1 and covariates and post processed per a published approach. [146] The DE, IE, and TE are interpreted as absolute difference in mortality rate comparing two TNFα-R1 tertiles. This estimate (multiplied by 1,000) is interpreted as a difference in the number of deaths per 1,000 person per year. The percent of mediation was estimated as IE/TE×100. Detailed R codes for analysis using the timereg package is provided in prior study. [146] The Aalen model was run separately on men and women to determine sex-specific DE, IE, and TE. A sensitivity analysis was done by repeating the

approach with TNFα-R1 as a continuous variable. For sensitivity analysis, TNFα-R1 was log transformed and standardized to obtain a normal distribution. The analyses were performed using R software (version 4.0.3).

6.4 Results

6.4.1 Sample characteristics

The complete-case analysis sample included 89 (46.1%) men and 104 (53.8%) women (**Table 6.1)**. After 10.2 years of follow up post-hip fracture, 88.7% (79/89) of men died and 66.3% (69/104) of men and women died, respectively. Women had significantly higher cognitive function at baseline compared to men (3MS=89.9 vs 86.4, $p < 0.05$). Additionally, men had significantly more comorbid conditions (CCI = 2.4 vs 1.5, $p < 0.05$) and higher TNFα-R1 concentrations at baseline (TNFα-R1= 3220.2 vs 2757.5 pg/ml, $p < 0.05$) compared to women.

Table 6. 1: Descriptive table separately for men and women (n=193)

	Men (n=89)	Women (n=104)	P-value
Death (by the end of 10.2 y), No. (%)			
Yes	79 (88.7%)	69 (66.3%)	<0.001 [f]
No	10 (11.2%)	35 (33.6%)	
Age, mean (SD), y	80.1 (7.6)	80.6 (7.4)	0.51 [g]
3MS, mean (SD) [a]	86.4 (11.5)	89.9 (9.4)	0.02 [g]
CCI, mean (SD) [b]	2.4 (1.8)	1.5 (1.6)	<.001 [g]
BMI (kg/ m^2), mean (SD) [c]	26.0 (4.5)	25.2 (5.8)	0.30 [g]
LPADL, mean (SD) [d]	2.2 (2.2)	2.4 (2.3)	0.42 [g]
TNFα-R1 (pg/ml), median (IQR)	3220.2 (2601.2-3895.4)	2757.5 (2170.7-3515.1)	<.001 [h]
CES-D, mean (SD) (baseline) [e]	16.6 (8.6)	16.8 (10.9)	0.93 [g]
CES-D, mean (SD) (2-months)	9.5 (8.7)	10.4 (8.1)	0.42 [g]

[a] Modified Mini-Mental Status ranges from 0 to 100. Higher score indicates better cognition.
[b] Charlson Comorbidity Index ranges from 0 (no comorbidity) to 8.
[c] Body Mass Index, 21-25 kg/m^2 is normal range per World Health Organization.
[d] Lower Extremity Physical Activities of Daily Living ranges from 0-12 with higher score indicating more disability
[e] Center for Epidemiological Studies Depression scale ranges from 0 to 60. Higher score indicates greater depressive symptoms.
[f] Log-rank test
[g] t-test
[h] Wilcoxon signed rank test
[i] Chi-square

6.4.2 Association of TNFα-R1 with Mortality in the Analytic Cohort Comprising Men and Women

Compared to the 1st tertile of TNFα-R1, the total effect of TNFα-R1 increased the total number of deaths by 43 (95% CI=-10.1 – 97.0) and 68 (95% CI=13.5 – 123.5) per year per 1000 hip fracture patients at risk in the 2nd and the 3rd tertile of TNFα-R1, respectively (**Table 6.2)**. Approximately 0.09% of the total effect in the 2nd tertile and 4.6% of the total effect in the 3rd tertile was mediated through depressive symptoms. However, the indirect effect was not statistically significant [3rd vs. 1st =3 (95% CI=-6.9 –

18.1) and 2nd vs. 1st = 0.04 (95% CI=-7.5 – 7.8) deaths per year per 1000 hip fracture patients at risk]. Compared to the 1st tertile of TNFα-R1, the direct effect of TNFα-R1 increased the total number of deaths by 43.1 (95% CI=-10.4 – 96.6) and 65.7 (95% CI=4.1 – 127.0) per year per 1000 hip fracture patients at risk in the 2nd and the 3rd tertile of TNFα-R1, respectively.

Table 6. 2: Aalen model showing Total Effect (TE), Direct Effects (DE) and Indirect Effects (IE) for estimated increased deaths per year per 1,000 persons in 2nd and 3rd tertiles of TNFα-R1 compared to 1st tertile

	TE (95% CI) × 10^{-3}	**DE (95% CI) × 10^{-3}**	**IE (95% CI) × 10^{-3}**
		Complete case	
TNFα-R1 at baseline			
1st tertile	0.00	0.00	0.00
2nd tertile	43.1 (-10.1 – 97.0)	43.1 (-10.4 – 96.6)	0.04 (-7.5 – 7.8)
3rd tertile	68.8 (13.5 – 123.5)	65.7 (4.1 - 127.0)	3.2 (-6.9 – 18.1)
		Men	
TNFα-R1 at baseline			
1st tertile	0.00	0.00	0.00
2nd tertile	118.8 (9.1 – 225.2)	119.0 (7.6 - 230.0)	-0.2 (-20.7 – 20.5)
3rd tertile	161.4 (36.5 - 286.4)	162.0 (41.3 - 283.0)	-1.3 (-32.4 - 28.4)
		Women	
TNFα-R1 at baseline			
1st tertile	0.00	0.00	0.00
2nd tertile	3.4 (-58.4 - 66.2)	3.9 (-58.2 – 66.1)	-0.2 (-12.9 – 12.0)
3rd tertile	16.6 (-58.0 – 89.0)	13.9 (-57.8 – 85.6)	2.9 (-9.5 – 19.5)

6.4.3 Association of TNFα-R1 and Mortality by Sex

In men, compared to the 1st tertile of TNFα-R1, the total effect of TNFα-R1 increased the total number of deaths by 118 (95% CI=9.1 – 225.2) and 161 (95% CI=36.5 – 286.4) per year per 1000 hip fracture patients at risk in the 2nd and the 3rd tertile of TNFα-R1, respectively (**Table 6.2)**. Approximately 0.2% of the total effect in the 2nd

tertile and 0.8% of the total effect in the 3rd tertile was mediated through depressive symptoms. However, the indirect effect was not significant [2nd vs. 1st = -0.2 (-20.7 – 20.5) and 3rd vs. 1st = -1.3 (-32.4 – 28.4) persons per year per 1000 hip fracture patients at risk]. Compared to the 1st tertile of TNFα-R1, the direct effect of TNFα-R1 increased the total number of deaths by 119 (95% CI=7.6 – 230.0) and 162 (95% CI=41.3 – 283.0) per year per 1000 hip fracture patients at risk in the 2nd and the 3rd tertile of TNFα-R1, respectively.

In women, compared to the 1st tertile of TNFα-R1, the total effect of TNFα-R1 increased the total number of deaths by 3 (95% CI=-58.4 – 66.2) and 16 (95% CI=-58.0 – 89.0) per year per 1000 hip fracture patients at risk in the 2nd and the 3rd tertile of TNFα-R1, respectively. Approximately 5.8% of the total effect in the 2nd tertile and 17.4% of the total effect in the 3rd tertile was mediated through depressive symptoms. However, the indirect effect was not statistically significant [2nd vs. 1st = -0.2 (-12.9 – 12.0) and 3rd vs. 1st = 2.9 (-9.5 – 19.5) deaths per year per 1000 hip fracture patients at risk]. Compared to the 1st tertile of TNFα-R1, the direct effect of TNFα-R1 increased the total number of deaths by 4 (95% CI=-58.2 – 66.1) and 14 (95% CI=-57.8 – 85.6) per year per 1000 hip fracture patients at risk in the 2nd and the 3rd tertile of TNFα-R1, respectively.

6.4.4 Sensitivity Analysis

The sensitivity analysis performed on continuous log-transformed TNFα-R1 found the association of TNFα-R1 and mortality in the same direction as tertiles with no significant mediation effect by depressive symptoms in the overall sample as well as by sex. For example, the total effect of one standard deviation increase in TNFα-R1 on

mortality was 1,387 (95% CI=340-2480) and 282 (95% CI=-464-1037) increased deaths per year per 1000 hip fracture patients in men and women, respectively (**Supplementary table S6.1**).

Supplement Table S6. 1: Total Effect (TE), Indirect Effect (IE), and Direct Effect (DE) in the association of TNFα-R1 and mortality; estimated increased deaths per year per 1,000 persons for each SD of log-transformed TNFα-R1

	DE (95% CI) × 10^{-3}	**IE (95% CI) × 10^{-3}**	**TE (95% CI) × 10^{-3}**
TNFα-R1[a] at baseline (in Complete case)	704 (92-1320)	15 (-88 - 136)	719 (118 – 1330)
TNFα-R1 at baseline (in Men)	1410 (340-2480)	-21 (-304-205)	1387 (304 -2470)
TNFα-R1 at baseline (in Women)	228 (-532-988)	50 (-93-252)	282 (-464-1037)

[a] pg/ml

6.5 Discussion

Consistent with past studies, TNFα-R1 was strongly associated with all-cause mortality in the analytic cohort comprising both men and women. [174,175] In the stratified analysis, TNFα-R1 was associated with mortality only among men. Depressive symptoms did not mediate the association between TNFα-R1 and mortality in the overall sample, nor in the samples stratified by sex. Collectively, findings suggest that systemic inflammation after hip fracture may contribute to excess mortality, particularly among older men, and that this relationship is mediated by intermediaries other than symptoms of depression.

Analogous to prior studies in general population older adults, TNFα was associated with mortality in men but not women.[28] Although the etiological mechanisms behind this effect heterogeneity is still not clear in the research literature, a potential reason for more deaths in men is that they have more underlying chronic conditions compared to women at the time of hip fracture. More specifically, extant comorbidity could make men more susceptible to the effect of elevated and sustained inflammatory activation, which are accompanied by muscle catabolism and impaired metabolism, and ultimately lead to poorer survival compared to women.[28,135] Another possible explanation for increased mortality among men is a greater susceptibility to cardiovascular disease than women, a consequence of a lower exposure threshold to inflammatory cytokines and their corresponding physiological effects.[104] Nonetheless, these results demonstrate that TNFα-R1, a marker of inflammatory activation after hip fracture, explains (in part) sex differences in all-cause mortality following the occurrence of an acute and disabling musculoskeletal injury. Therefore, systemic inflammation should be a consideration when designing hip fracture interventions for older men and women to decrease post-fracture mortality rates.

Previous research has shown strong associations between TNFα and depressive symptoms, and both inflammatory activation and major depression increase mortality rates among older adults.[28–31] However, the current study results imply no statistically significant mediation by depressive symptoms regarding the association between TNFα-R1 and all-cause mortality in the overall sample or when stratified by sex. The present research is the first study to evaluate this pathway in hip fracture as well as general population older adults, and it is unclear why no statistically significant indirect effects

mediated through depressive symptoms were observed. One possibility may be that the acute inflammatory response to injury, measured in this study within 22 days of admission, is not as a reliable predictor of depressive symptoms as persistent inflammation lasting for a longer duration. In contrast to these results, previous BHS research has also shown a strong association between TNFα-R1 measured at 2 months and depressive symptoms among hip fracture patients.[31] Another reason for the small indirect effects may be related to controlling for depressive symptoms at baseline in adjusted models. In this study, a clear temporal ordering considering the exposure (TNFα-R1 at baseline) and mediator (depressive symptoms at 2 months) was maintained. Accordingly, the correlation is larger in magnitude for TNFα-R1 and depressive symptoms measured concurrently at baseline compared to TNFα-R1 measured at baseline and depressive symptoms measured at 2 months. Therefore, adjusting for depressive symptoms at baseline may induce multicollinearity in the adjusted models and reduce the indirect effect mediated by depressive symptoms regarding the association of TNFα-R1 at baseline and all-cause mortality. [176] Similarly, smaller indirect effects may be attributed to adjustment for other covariates like age, cognition, and comorbidity that may act an alternative mediators for the association between TNFα-R1 and mortality. [176]

6.5.1 Limitations and strengths

There were several limitations and strengths of this study. First, although several confounders were controlled in our model, it is still possibility for confounding by unmeasured factors not included in your analysis. Second, the confidence intervals were wide for all the direct, indirect, and total effect estimates and indicate a high degree of uncertainty. This lack of measurement precision may be attributed to the relatively small

sample size, especially in the sex-stratified analysis. Furthermore, categorizing TNFα-R1 into tertiles could have further increased the variability associated with effect estimates.[177,178] Nonetheless, sensitivity analyses performed using continuous log-transformed TNFα-R1 values yielded similar associations of TNFα-R1 and mortality in the same direction as tertiles and no mediation by depressive symptoms and, support primary findings. There were missing data on several measured variables, and it is likely that those who refused or were not able to provide data maybe at a higher risk of worse outcome. The BHS-7 sample was predominantly white and participants were from Baltimore-area hospitalsso findings may not be generalizable to other populations. However, our research is the first to assess whether inflammatory biomarkers predict mortality beyond 2 years of hip fracture and whether this relationship is mediated by depressive symptoms. Lastly, the study design included a clear temporal sequencing of the exposure (baseline hospitalization), mediator (2 months), and outcome (time-to-event outcome from 2 months and beyond) variable and robust adjustment for an array of potential confounders.

6.6 Conclusion

Higher TNFα-R1 levels in the early post-acute period after hip fracture were associated with a greater number of deaths in men but not women over 10.2 years of follow-up. Thus, TNFα-R1 may be a valid and reliable biomarker to identify older men at a greater risk of mortality after a hip fracture. Future studies should further explore if other inflammatory biomarkers commonly used in clinical settings, such as C-reactive protein and erythrocyte sedimentation rate, also predict mortality in hip fracture patients

and whether there are sex-based differences in these associations as this can help to improve post-fracture acute medical care and potentially promote targeted intervention strategies. Depressive symptoms did not mediate the association between TNFα-RI and all-cause mortality in the overall sample or by sex. Accordingly, research should strive to identify the physiological consequences and relevant mediating mechanistic factors of elevated and prolonged inflammation among older men after hip fracture that lead to greater mortality.

CHAPTER 7: DISSERTATION DISCUSSION

7.1 Summary

Past findings show that despite being younger than women and having higher pre-fracture functional ability, the risk of mortality is twice higher in men for the first two years after a hip fracture.[6] Given the annual number of hip fractures is going to increase over next several years, such that more than one-third of hip fractures will occur in men by 2030, it is crucial to examine factors that could explain sex differences in post-hip fracture mortality.[2] Past studies have found Short Physical Performance Battery (SPPB),[10,11] gait speed,[12,13],grip strength[14,15], TNFα and depressive symptoms, [16,17] to be associated with mortality differently by sex in general older adult populations and these characteristics may explain mortality outcomes in hip fracture patients. This dissertation examined sex difference in mortality outcomes through two approaches (1) determining if there were sex difference in all-cause mortality and infection-specific mortality, and (2) whether protective factors (higher score in physical performance measures) and risk factors (TNFα and depressive symptoms) have a unique relationship with mortality by sex over a period of 10 years. In addition, a prediction model was built to identify the most important predictors of 10-year mortality.

Aim 1 of this dissertation showed that men were twice more likely to die of all-cause and four times more likely to die of infection-specific cause over 10 years post-hip fracture. Men were more likely to die even after controlling for known risk factors of mortality in hip-fracture patients like age, comorbidity, cognition, pre-fracture LPADLs, and depressive symptoms. [38,113,132–135] These finding highlights two points. First, it shows that sex alone explains a portion of post-hip fracture mortality that cannot be explained

by other factors associated with hip fracture mortality based on literature.[38,113,132–135] Second, infection-related mortality that occurs intermittently over the ten-years could explain (in part) higher overall post-hip fracture mortality in men compared to women. The higher infection-related intermittent death in men could be explained by several factors including increased age-associated decline in immune function in men compared to women [154] and higher pre-fracture comorbidity that makes men more susceptible to infections.[8,135,153]

While aim 1 showed that men were more likely to get infection over the period of 10 years and die of infections compared to women, aim 3 further showed that infection during the acute period, measured by serum TNFα-R1 level within 22 days of admission after a hip fracture, may contribute to more long-term deaths in men compared to women. One reason for the association of TNFα-R1 and long-term mortality is that in older adults 'inflamm-aging' (a progressive rise in proinflammatory status with aging) may worsen the challenge posed to the immune system by acute infection during the injury.[99] The acute infection on top of 'inflamm-aging' can overwhelm the aging immune system such that the hyperinflammatory status may extend for a longer period causing significant damage to several tissues and organ systems and lead to higher mortality.[99,100] More deaths, especially in men, could be explained by higher pre-fracture comorbidity and men being more susceptible to cardiovascular changes at a lower threshold of inflammatory biomarkers compared to women.[104]

Aim 3 further examined if depressive symptoms at 2-months after a hip fracture could explain the TNFα-R1 (baseline) and mortality link. Depressive symptoms did not mediate the association between TNFα-R1 and mortality in both men and women. One

reason for lack of mediation effect by depressive symptoms could be that the acute rise in TNFα-R1, as measured in this study, may not be as good a predictor of depressive symptoms as shown by the past studies.[31] It is also likely that controlling for depressive symptoms measured at baseline could have dampened the association of TNFα-R1 and depressive symptoms at 2 months. Similarly, a smaller indirect effect may be due to inclusion of other covariates like age, cognition, and comorbidity in the adjusted model as each control variable may act as an alternate explanation for the association of TNFα-R1 and mortality. [176]

Aim 2 found that physical performance had an association with mortality. Every unit of improved performance in SPPB, gait speed and grip strength (assessed at 2-months post-hip fracture) had a protective effect on both short- and long-term mortality. Moreover, these performance-based measures have good reliability and validity, which may be the reason that the association of these variables with an outcome remains relatively stable long-term.[166,167] Aim 2 also showed that the association of SPPB and gait speed with mortality was not different by sex, but better grip strength was significantly protective only in men. This indicates that overall muscle weakness seen after a hip fracture may be disadvantageous for men compared to women. One plausible explanation can be the higher prevalence of sarcopenia after a hip fracture in men compared to women.[164] One-third of the hip fracture patients suffer from sarcopenia and the rate of mortality is 15% higher in hip fracture patients diagnosed with sarcopenia.[165]

Although the adjusted Cox models in aim 2 showed that physical performance measures had a protective effect in post-hip fracture mortality, in the prediction model none of the physical performance measures were selected by the Classification and

Regression Tree (CART) Analysis. The findings from the prediction model and Cox model are not necessarily contradictory because there are several reasons why CART did not pick up any of the physical performance measures as a predictor of mortality. One reason is that only the first three splits in the CART model were considered to keep the cross-validation error at a minimum. It is possible that if we considered more than first three splits, at least one of the physical performance measures would have been selected. Another reason may be how CART creates the categories at each split to minimize the misclassification cost.[173] Hip fracture patients score relatively low on SPPB and gait speed at 2 months creating a floor effect, whereas other measures, like cognition and age, with more variability may create more homogeneous groups with respect to long-term mortality in CART models. Because of these reasons, the importance of physical performance measure in predicting mortality should not be discounted. Moreover, other prediction models with smaller selection bias compared to CART like Generalized, Unbiased Interaction Detection and Estimation (GUIDE) should be explored. [179]

The CART model also identified cognition as the most important predictor of mortality and being male played a role in mortality only when 3MS was less than 98. This finding highlights two main points. First, 3MS ≥ 98 out of total 100 points is a very high score,[170] and it is likely that individuals who scored 98 and above in 3MS within 15-22 days post hip fracture are an 'elite' category of patients and have the best prognosis for a long-term survival. Second, an appreciation of how sex is influencing post hip fracture mortality has important implications for clinical management as sex was selected as the second most important variable to predict mortality. For those not in the 'elite' category, being male predicted the largest number of incident deaths.

7.2 Implications and Future Studies

The findings from aim 1 and aim 3 indicate that interventions during hip fracture recovery to prevent and treat infections, tailored by sex, may be needed to narrow significant differences in long-term mortality rates between men and women. In a general population of adults (≥60 years), infections like hepatitis B and methicillin-resistant Staphylococcus Aureus are more common in men, while rotavirus and urinary tract infection are more common in women.[158] Future studies should explore sex differences regarding pathogens causing infection among older adults post hip fracture so that tailored screening and treatment regimens can be developed. Since typical signs of infection, like fever, may be blunted in older adults, clinicians should be vigilant of other signs like unexplained change in physical abilities or cognitive status compared to baseline.[159]

The results from aim 3 particularly demonstrated that TNFα-R1 explains (in part) sex differences in all-cause mortality following the occurrence of an acute and disabling musculoskeletal injury. Therefore, systemic inflammation should be a consideration when designing hip fracture interventions for older men and women to decrease post-fracture mortality rates. Future studies should further explore if other inflammatory biomarkers commonly used in clinical settings, such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), also predict mortality in hip fracture patients and whether there are sex-based differences in these associations as this can help to improve post-fracture acute medical care and potentially promote targeted intervention strategies. Given the sex differences in infection-related causes of mortality found in Aim 1, future studies should also examine the association of TNFα-R1 and infection-specific mortality.

The results from aim 2 indicated that all three physical performance measures assessed at 2 months after a hip fracture have potential to identify individuals at a greater risk of mortality in both short- and long-term follow up, irrespective of sex. As such, interventions to promote recovery could use SPPB, gait speed, or grip strength as an indicator of recovery to design interventions to promote long-term survival. In addition, the findings from aim 2 indicated that grip strength is a better indicator of mortality in men. It is unclear if muscle strengthening interventions promote survival; however, studies examining the sex-specific impact of muscle strengthening interventions on survival after a hip fracture is warranted. There is also evidence showing some of these physical performance measures may be associated with specific causes of death instead of all-cause mortality. [180] Future studies should explore if there are sex differences in the association of these physical performance measures with cause-specific mortality.

Finally, the results from the CART analyses performed in Aim 2 showed that sex interacts with cognition at predicting long-term post-hip fracture mortality and identified cognitive status as the most important predictor of 10-year mortality. Moreover, men with cognition less than 98 were at the greatest risk of poor survival based on CART. Future studies examining sex difference in the association of cognition and long-term post hip fracture mortality is warranted.

7.3 Contribution to Gerontology

A major discussion in gerontology is changing demographics and how it might impact the aging population. Given the number of hip fractures is projected to increase disproportionately in men in near future and men living longer, the findings from this

study have important implications in improving survival in older adults with hip fracture. In addition, physical performance measures used in aim 2 of this dissertation are biomarkers of aging process because these measures can capture the natural wear and tear in aging cells and organs that accumulate over several years and gradually manifest as functional limitations. Determining if these measures can be used in specific populations, in this case hip fracture, could certainly promote use of these indicators in clinical settings. The findings from this study could also provide evidence to support integration of performance measures in standard of care for hip fracture patients as well as other clinical populations.

7.4 Limitations and Strengths

7.4.1 Limitations

There are limitations to consider in this series of analyses. There was missing data for depressive symptoms and physical performance variables. It is likely that those who refused or were not able to provide data on their depressive symptoms may be the ones more likely to be at the risk of depression. Similarly, given participants need to have a certain level of ability to conduct the activities in physical performance measures, those not able to perform these measures might be those at a greater risk of poor survival. We did not find any significant difference with respect to sex, age, comorbidity, and baseline cognition between those with complete data and missing data. Our sample was predominantly white and all the patients were recruited from hospitals in one metropolitan area, so the results may not be generalizable to other population. Additionally, this study could not determine whether the higher risk of long-term mortality in men compared to women with hip fracture could explicitly be attributed to

hip fracture, or if it is because, on average, men have a shorter lifespan than women as there were no matched comparators without hip fracture. Although there was no comparison group, national data from a representative population of older adults indicates that men only have 1.7 times higher risk of death than women over 13 years follow up.[157] By contrast, older men in this study had over 2 times higher rate of 10-year mortality compared to women.

7.4.2 Strengths

This is the first study powered to assess sex differences in all-cause and infection-specific mortality over 10 years post-hip fracture utilizing the unique design that frequency-matched females to males and followed longitudinally. This has been a limitation of past studies in hip fracture patients and most studies did not assess mortality beyond 2 years after hip fracture. This is also the first research to determine if certain characteristics (physical performance measures and TNFα-R1) explain sex differences in mortality. Similarly, there have been no studies examining the role of depressive symptoms in the pathway between TNFα and all-cause mortality in hip-fracture patients. Robust statistical models were used to examine the proposed associations. When appropriate, sensitivity analyses were performed to determine if the associations between the dependent and independent variables are stable under different statistical assumptions. All the covariates were meticulously selected and were measured prior to the exposure[168] to prevent bias because of intermediate variables. Finally, the temporal sequence of the exposure (baseline TNFα-R1), mediator (2-month depressive symptoms), and outcome (time-to-event outcome from 2 months and beyond) variables was maintained in aim 3.

7.5 Conclusion

It is known that men have twice higher risk of death than women for the first two years after a hip fracture; however, little evidence is available to explain sex difference in post hip fracture mortality. The objective of Aim 1, Aim 2, and Aim 3 of this dissertation was to identify clinical and biological indicators that can explain higher mortality in men. Aim 1 of this dissertation added to the current evidence by showing that the twice higher risk of death in men persist long-term, at least up to 10.2 years after a hip fracture. Further evidence from aim 1 showed that the higher death in men (in part) may be explained by intermittent infection-related causes over 10.2 years as men had four times higher risk of infection-specific mortality.

As recovery in physical performance (SPPB, gait speed, and grip strength) after a hip fracture differs by sex and better recovery may be associated with better survival, aim 2 of this dissertation examined the moderating effect of sex in the association of physical performance measures at 2 months after a hip fracture and mortality. Aim 2 showed that physical performance measures are good indicators of both short- and long-term mortality; however, there was no evidence of these performance measures being a better indicator of mortality in one sex versus the other as shown by statistically insignificant interaction (physical performance*sex) effect. Additionally, in a secondary sex stratified analysis, only grip strength had a protective effect on mortality in men suggesting that grip strength may be a better indicator of mortality in men. In the CART analysis (Aim 2.2), cognition, sex, and age were identified as the predictors of long-term mortality and none of the physical performance measures were selected. However, the importance of physical performance measures in predicting long-term post-hip fracture mortality should

not be discounted as there can be reasons specific to the algorithm created by the prediction model that could impact the results.

Aim 3 result was consistent with prior findings as higher TNFα-R1 levels within 22 days of admission increased mortality in men but not women suggesting that TNFα-R1 is a better marker of mortality in men after a hip fracture. Depressive symptoms were not a mediating pathway between TNFα-R1 and mortality in both men and women.

In conclusion, current literature does not have evidence of sex-specific clinical and biological indicators that can identify individuals at a greater risk of mortality. As such, targeted interventions to promote recovery and survival is lacking. The results from this study could help identify older men and women at acute phase and post-acute phase of hip fracture recovery who could have survival benefit from timely interventions that are tailored by sex.

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