BOONE, ANNA W., Ph.D. An Exploration of the Relationship between Frailty in the Older Adult and Recurrence of Clostridium difficile. (2018)
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The purpose of this retrospective cohort research study was to explore the relationship between frailty and recurrent *Clostridium difficile* (CDI) in adults 55 years and older hospitalized between December 31, 2013 through December 31, 2015, with data extracted from 2012 to 2016 to identify initial and recurrent admission for CDI. A researcher-derived frailty index, based on the Accumulation of Deficits framework by Mitnitski, Mogilner, and Rockwood (2001), was created after careful review of the components contributing to frailty and following the guidance by Searle, Mitnitski, Gahbauer, Gill, and Rockwood (2008). As per Searle et al. (2008), the FI-CDI was constructed by following the method of selecting variables that are associated with health, increase with age, do not present early in the aging process, cover a wide representation of organ systems and not just one system, and items for the index remain unchanged when performing serial measurements in the sample. Variables for the FI-CDI included laboratory abnormalities, chronic diseases, functional status, and psychosocial indicators. The deficits were coded as "1" for present and "0" for absent, calculating the FI-CDI by dividing the number of deficits in an individual by the total number of deficits measured (36 in this study) as per the standard procedure for calculating the frailty index (Searle et al., 2008). Based on the derived FI-CDI, frailty was defined as ≥ 0.25.

The initial sample for the inclusion criteria consisted of 871 patients with CDI. Only 450 patients had complete data on admission to calculate the FI-CDI for the 36 deficits. The overall sample (n=871) had a recurrence rate of 23.9% (n=208) for the study

period. The average age for the overall sample was 73.6 years (*SD*=10.7), with 9.1% of the sample expiring during first hospitalization over the study period. Caucasian females comprised over half of the sample. Almost two-thirds (*n*=576, 66.1%) resided in a private residence prior to initial admission, followed by skilled nursing facility (*n*=125, 14.4%). About one-third of the patients were discharged to either home/self-care (*n*=279, 32.0%) or a skilled nursing facility (*n*=261, 30.0%) after initial admission. CDI recurrence was more prevalent for those discharged to a skilled nursing facility (37.5% vs. 27.6% with no recurrence) and with home health care services (24.5% vs. 15.2% no recurrence) ($p<0.001$). The average frailty score for the FI-CDI sample (*n*=450) was 0.37 (*SD*=0.10) on admission. The age group of 55 to 64 was significantly associated with recurrent CDI admission for both bivariate and logistic regression analyses. The chronic diseases found to be significantly more prevalent in recurrent CDI included hypertension (88.0% vs. 78.4%; $p=0.003$), heart failure (36.1% vs. 25.6%; $p=0.005$), and chronic kidney disease (34.1% vs 24.9%: $p=0.011$). Frailty prevalence, as measured by the FI-CDI (*n*=450) was 89.1% on admission as indicated by a FI-CDI score of ≥ 0.25. The FI-CDI scores on admission were significantly related to CDI recurrence, adjusting for sociodemographics. Proton pump inhibitor (PPI) use prior to initial admission was significantly associated with frailty in bivariate analysis, but PPI use was not associated with recurrent CDI.

Evidence from this study bridges a knowledge gap that exists regarding frailty and recurrent CDI. Limited research has been explored with frailty and recurrent CDI, and this study provides a foundation for prospective studies. The FI-CDI could be used with existing medical record data at time of hospitalization, assessing frailty and allowing

opportunities for intervention. The hospitalized frail older adult is vulnerable, with CDI as a stressor that can result in prolonged recovery time and possible recurrence. Recognition of frailty in this population through already existing medical record data can guide interventions to address the underpinnings contributing to frailty and decrease readmissions, recurrence, morbidity, and mortality.

AN EXPLORATION OF THE RELATIONSHIP BETWEEN FRAILTY IN THE OLDER ADULT AND RECURRENCE OF CLOSTRIDIUM DIFFICILE

by

Anna W. Boone

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Approved by

Laurie Kennedy-Malone
Committee Chair

This dissertation is dedicated to Joy Thomas Whitlock, who chose grace over judgment, courage over fear, and life over defeat. She leaves a legacy of faithfulness and hope, reminding me to be brave, even in the darkest of valleys. And to her best friend, who happens to be my mom, Charlotte Wentz. These pages are a result of the many sleepless nights when all you could do was pray, even as I was a young girl. He surely did the work that only He can do. Lamentations 3:22-23.

APPROVAL PAGE

This dissertation written by ANNA W. BOONE has been approved by the following committee of the Faculty of The Graduate School at The University of North Carolina at Greensboro.

Committee Chair _____
Laurie Kennedy-Malone

Committee Members _____
Deborah Lekan

_____
Robert M. Rourk

_____
Debra Wallace

_____
Date of Acceptance by Committee

_____
Date of Final Oral Examination

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CHAPTER I

INTRODUCTION

The concept of frailty is complex, characterized by age-associated decreases in reserve throughout many systems, resulting in an increased vulnerable state and subsequent poor outcomes (Maxwell & Wang, 2017). Multiple methods of measurement exist, with most falling into a physical phenotype or multi-dimensional approach (Walston & Bandeen-Roche, 2015). Frailty and functional deficits in the older adult are not new concerns, as articles dating to the 1960s called for recognition of the frail state in the older adult (Binks, 1968). Today, frailty is recognized as a geriatric syndrome and known to be an independent risk factor for detrimental outcomes and even mortality (Clegg, Young, Iliffe, Rikkert, & Rockwood, 2013). As the population continues to live longer, the complexity of healthcare deepens. The recognition of frailty is paramount to provide appropriate care.

Background

The National Institute on Aging, National Institutes of Health, and World Health Organization (2011) estimated 524 million of the global population were 65 years and older. This estimation is expected to increase to 1.5 billion by the year 2050. Eight percent of ages 65 and older are in the group 85 years and older. By 2050, centenarians are expected to increase 10-fold compared to 2010. In North America, 15.1% of the population is 65 and older, which is expected to increase to 22.5% by the year 2050

(Federal Interagency Forum on Aging Related Statistics, 2017). The United States continues to age at a steady rate, yet this has increased significantly as the generation born in 1946-1964 turns 65 through the years 2011 to 2029 (Federal Interagency Forum on Aging Related Statistics, 2017).

Frailty prevalence increases with age, yet it is independent from age chronologically (Clegg, Young, Iliffe, Rikkert, & Rockwood, 2013). The concept of frailty is important to grasp, as frailty may not be recognized in older adults as an area to intervene and maximize care and interventions, leading to improved outcomes. The factors contributing to frailty, including pathological processes, malnutrition, and psychological components (Dent, Kowal, & Hoogendijk, 2016), should be recognized in order to provide excellent care of the older adult. Frailty concepts and frailty prevalence are further described, providing a background on the need for frailty recognition.

Frailty Concepts

Frailty is known as a "cornerstone of geriatric medicine" (Walston, Buta, & Xue, 2018, p 25), with decreased defenses from recognized geriatric syndromes and poor resulting outcomes for individuals. Although chronological years result in normal processes of aging, not all older adults are frail. Frailty is a process that is dynamic, with physiologic abnormal underpinnings that propel the pathway of frailty (Maxwell & Wang, 2017). Due to the dynamic characteristic of frailty, early intervention may help to improve frailty status (Lekan et al., 2017; Maxwell & Wang, 2017).

Multiple pathophysiological processes contribute to frailty (Dent, Kowal, & Hoogendkijk, 2016; Maxwell & Wang, 2017), and multi-dimensional components such

as psychosocial factors, sociodemographics, and polypharmacy are recognized as contributors. Frailty is not synonymous with co-morbidities, aging, or disability (Dent et al., 2016). The decline of physiological systems accumulate deficits in an individual, with frailty increasing as reserves decrease (Dent et al., 2016). Although the pathophysiology of homeostasis is affected with advancing age, an individual is felt to have approximately 30% of reserves whereby one is still able to function, and frailty occurs when this threshold is exceeded (Lang, Michel, & Zekry, 2009).

A recent meta-analysis of 31 studies reviewed frailty concepts and the prediction of negative health outcomes in the older adult community, finding 29 different frailty instruments utilized that fell into the categories of physical measurement, multi-domain, and deficit accumulation (Vermeiren, et al., 2016). The association between mortality and frailty were reviewed from 24 prospective studies, with 25 different measurement tools. Findings were overall consistent with mortality likelihood increased with frailty presence (Vermeiren et al., 2016). Eleven studies reviewed hospitalization, with 16 different frailty instruments, confirming frailty increasing the risk of hospitalization (Vermeiren et al., 2016).

Frailty was shown to increase the risk of institutionalization for both frail and pre-frail individuals. Only physical measurement and accumulation deficit methods were used in measuring frailty during emergency room visits, with frailty increasing the risk of emergency room presentation. Basic and instrumental activities of daily living were included in 11 and 7 studies, respectively (Vermeiren et al., 2016). Frailty was shown to increase the risk of disabilities in basic and instrumental activities of daily living.

Increased risk of physical limitation and dependency were associated with frailty, and frailty significantly increased risk of falls and fractures after review of 11 articles (six studying falls and five studying fractures) (Vermeiren et al., 2016). Cognitive decline was measured with presence of frailty increasing potential cognitive decline. Body composition was only measured in one study, with significant findings for changes in frailty but not pre-frailty (Vermeiren et al., 2016), prompting the need for further research. Finally, lower overall life satisfaction was found to be associated with frailty but not a pre-frail status (Vermeiren et al., 2016).

Assessment of frailty remains a challenge, as appropriate utilization of clinical and research measurements are debated (Dent et al., 2016). A review of frailty measurements over the years 2009 to 2015 were performed by Dent and colleagues (2016). This review included research and review articles for samples that included ages 65 and older, objective measurement of frailty in observation, cross-sectional, or randomized control trials with the outcome of prognosis or classification of frailty (Dent et al., 2016). The authors reviewed 422 studies identified in the literature, with 29 varying frailty measurements for patient populations of cardiovascular, renal, geriatric, oncology, surgical, and orthopedic (Dent et al., 2016). The phenotype measurement and frailty index were most common, with measurement serving as prognostic (Dent et al., 2016). The review found many modifications of frailty measurements from original versions, with recommendations for identifying appropriate frailty measurements depending upon the clinical setting and population. The review emphasized the

importance of frailty measurements to accurately identify frailty, predict outcome and response to treatment, and have a foundation of biologic theory (Dent et al., 2016).

Finally, hospitalization of a frail older adult can result in longer lengths of inpatient stays and need for higher acuity of care, and a systematic review with meta-analysis by Muscedere et al. (2017) purposed to explore frailty consequences for older adults who are critically ill. The overall prevalence of frailty in the studies reviewed was 30%, with measurements of frailty in the study by clinical frailty scale, a frailty index, and physical phenotype (Muscedere et al., 2017). Frail patients were at an increased risk for inpatient mortality versus non-frail patients, and discharge to home after admission was less likely for frail patients (Muscedere et al., 2017). Interestingly, the meta-analysis did not find a significant difference between frail and non-frail patients for length of intensive care stay, receiving mechanical ventilation, or vasoactive drugs (Muscedere et al., 2017). Muscedere and colleagues (2017) raised the concern for choosing appropriate frailty assessments in clinical setting, similar to the discussion by Dent et al. (2016).

Common frameworks to support frailty include the phenotype by Fried et al. (2001) and the deficit accumulation by Mitnitski, Mogilner, & Rockwood (2001). Additional frameworks include the bio-psychosocial framework (Engel, 1981), applied to frailty by Lekan and colleagues (2017) and more recently the Systems Addressing Frail Elder (SAFE) Care model (Ansyran et al., 2018). The bio-psychosocial framework is comprised of three domains to include the biological, psychological, and social aspects of a person, emphasizing the interaction between these domains and bringing a holistic view to the person and their health care need. The SAFE Care model was piloted

as an inpatient intervention 2012-2013 with processes to include screening risk for skin integrity, problems eating, incontinence, confusion, evidence of falls, and sleep disturbance (SPICES) (Ansyran et al., 2018). SPICES screening was then followed by interdisciplinary assessments. These assessments included the assistance of nursing staff, social work, pharmacy, and a physician assessment of the medical record. The SAFE Care model used a multi-disciplinary approach to proactively assess frailty and provide intervention. The framework for purposes of this study will be discussed in further detail in Chapter I.

Frailty Prevalence

The prevalence of frailty in the United States differs depending on measurement used, with estimates ranging between 4% to 59% for older adults in the community and between 19-76% for nursing home residents (Vermeiren et al., 2016). The National Health and Aging Trends Study assessed 7,439 community-dwelling and residential care individuals (excluding nursing homes), utilizing the Fried phenotype measurement of frailty. Frailty was noted in 15% of the older adults, and 45% were pre-frail (Bandeen-Roche et al., 2015). Frailty prevalence increased to 38% for ages 90 and older. Additionally, the prevalence of frailty in the hospitalized older adult has been reported from 27% to 87.1% (Andela, Dijkstra, Slaets, & Sanderman, 2010; Chong et al., 2017; Dent et al., 2014; Eeles et al., 2012; Ekerstad et al., 2011; Joseph et al., 2015; Krishnan et al., 2014; Patel et al., 2014; Purser et al., 2006). Frailty prevalence is higher in women, racial and ethnic minorities, residential care facilities, and lower socioeconomic statuses (Bandeen-Roche et al., 2015). African American and Hispanics have shown 65-

85% more frailty prevalence than Caucasian, and the prevalence of frailty increases significantly with age (Bandeen-Roche et al., 2015). As the authors stated,

> Frailty is a strong predictor of disability and high multimorbidity, but a considerable portion of frail persons are free of these, consistent with conceptualizing frailty as an underlying physiological process and not merely an outcome or marker of disease and disability (Bandeen-Roche et al., 2015, p1432).

Frailty and Age, Co-Morbidity, and Disability

Despite the link between frailty and older age, chronologically advanced age does not immediately equate to frailty. Frailty is a dynamic entity, with possibilities of improving or worsening over time periods (Morley et al., 2013). Multiple factors surround the improvement or persisting and worsening of frailty in an individual. The combination of physiological diseases and already present age-related factors may be antecedents to frailty (Morley et al., 2013).

The literature has shown that frailty can be associated with disability, physical impairment, cognitive impairment, falls, hospitalization, increased length of stay, post-operative mortality and morbidity, discharge to a care facility, and death (Boyd et al., 2005; British Geriatrics Society, 2014; Cesari, Calvani, & Marzetti, 2017; Dent et al., 2016; Fried et al., 2001; Maxwell & Wang, 2017; Mitnitski, Mogilner, & Rockwood, 2001). The age of 65 and older has been extensively studied regarding frailty. The term disability is not interchangeable with frailty; however, the frailty syndrome may be a precursor to disability. Some researchers have used functional decline as a means to demonstrate frailty, with examples to include Lawton's Instrumental ADL, the Katz

score of activities of daily living, and the Score Hospitalier d'Evaluation du Risque de Perte d'Autonomie (Dent et al., 2013). However, this is not a true representation of frailty, as frailty may be a predictor of functional decline, as well as an outcome (Fried et al., 2004). In 2012, a Frailty Consensus Conference, comprised of six societies (International Association of Gerontology and Geriatrics; Society on Sarcopenia, Cachexia, and Wasting Diseases; International Academy of Nutrition and Aging; European Union Geriatric Medicine Society; American Medical Directors Association; American Federation for Aging Research) was held in Orlando, Florida, to define frailty, with the aim of describing an operational definition for frailty, discuss appropriate screening and treatment for frailty, and identifying populations who should be screened (Morley et al., 2013). Historically, multiple definitions of frailty caused lack of agreement, with explanations ranging from very broad to narrow in scale (Morley et al., 2013). The group developed the definition of physical frailty as

> a medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death (Morley et al., 2013, p 4).

The broader definition of frailty, encompassing co-morbidities, disability, cognition, and psychosocial factors was proposed as a construct by Rockwood and colleagues (2005) as a

> state of increased vulnerability due to impairments in many systems that may give rise to diminished ability to respond to even mild stresses, incorporates multimorbidity and central nervous system impairments that can be recognized in relation to cognitive and affective disorders (2013, p 4).

The Frailty Consensus Group meeting in 2012 confirmed that frailty in the older adult population increases the risk of morbidity and mortality (Abellan van Kan et al., 2008; Morley et al., 2013). The group recommended screening for frailty in all individuals older than 70 years and/or any individual with 5% weight loss or greater in the setting of chronic diseases (Morley et al., 2013). The presence of frailty is a better indicator than age for predicting hospitalization and possible early mortality (Mitnitski et al., 2001). When frail older adults experience an acute illness, the risk of death is increased when compared to healthier peer counterparts (Evans, Sayers, Mitniski, & Rockwood, 2014).

The International Academy on Nutrition and Aging (I.A.N.A) and the International Association of Gerontology and Geriatrics (I.A.G.G.) met in 2013 to discuss cognitive frailty with the aim of designing preventive, personalized intervention strategies that were multi-dimensional to target physical, cognitive, nutritional, and psychological components for the older adult (Kelaiditi et al., 2013) The frailty concept had been predominantly focused on physical characteristics, but recognition of the pathophysiology of the aging process prompted further definition and clarification for the cognitive component. Cognitive frailty was recognized as different from dementia, as the Alzheimer's dementia and other dementias were part of exclusion for Cognitive Frailty. Indeed, cognitive Frailty was proposed to be defined by cognitive impairment paired with physical frailty (Kelaiditi, 2013). Research has shown that frailty is linked with decreased cognitive performance in those with or without dementia (Kelaiditi, 2013). For this reason, cognitive impairment is now recognized as one of the factors

contributing to frailty. The I.A.N.A/I.A.G.G (2013) outlined four groups for characterization of Cognitive Frailty. These were defined as 1) robust older adults without physical frailty or cognitive deficits, 2) physically frail with normal cognition and may include those with subjective memory concerns, 3) older adults without physical frailty but portraying cognitive impairment, and 4) both physical frailty and cognitive impairment manifested in the older adult. Interventions for cognitive frailty may include one or both approaches of preventive care and rehabilitation (Kelaiditis, 2013).

The British Geriatrics Society (2014) developed best practice guidelines, defining frailty as a multi-dimensional decrease in body system reserves related to the aging process. The British Geriatrics Society advised against routine population screening but rather assessing individuals with each encounter and recognizing frailty characteristics, which would prompt the comprehensive geriatric assessment (CGA). The CGA would then prompt interventions for care, support, and referral to appropriate specialists (2014).

Despite multiple tools for capturing frailty, consensus for a standardized frailty measurement has yet to be accepted for acutely-ill, hospitalized older individuals (Dent, Chapman, Howell, Piantadosi, & Visvanathan, 2013). Existing frailty screening tools are numerous, but the reliability and clinical feasibility of these tools requires further research (Warnier et al., 2016). Frailty screening tools are helpful to identify those with higher risk for poor outcomes; yet, translating the results from screening to clinical practice interventions remains a challenge and agreement upon which instrument to use

varies. Lack of a standardized frailty definition and measurement affects recognition of frailty, resulting in inconsistent measurement of frailty and difficulty in establishing a dedicated tool (Warnier et al., 2016). However, literature has noted different measurement tools are appropriate for specific settings, depending on need such as general screening versus assessment of risk for outcomes in subspecialties (Walston, Buta, & Xue, 2018).

Several simple methods for routine screening of frailty would include questionnaires, assessment of gait speed and physical assessment such as the Timed up and Go test (TUGT), self-reporting of health, provider assessment, polypharmacy whereby five or more medications are taken, and the Groningen Frailty Indicator questionnaire (British Geriatrics Society, 2014). In urgent situations, the aforementioned tools would not be appropriate for frailty assessment. Instead, timing is essential, requiring prompt assessment of current functioning status and evidence of confusion. The outpatient surgical arena holds opportunity to screen for frailty, utilizing an approach such as the Edmonton Frail Scale (British Geriatrics Society, 2014; Dent et al., 2016). The phenotype approach, accumulation of deficits approach, and FRAIL scale have been used in both the clinic and population setting (Dent et al., 2016).

Frailty Measures

Although many frailty measures are available, a standardized method of measurement has not been accepted (Partridge, Harari, & Dhesi, 2012). The two main categories that broadly encompass the measurements of frailty include the phenotype and the deficit accumulation approach (Dent et al., 2013). The Frailty Phenotype

incorporates physical measurements, and the Deficit Accumulation approach includes a multidimensional approach (Dent et al., 2013; Mitnitski, Mogilner, & Rockwood, 2001). The necessary frailty measurements for specific patient populations continues to remain unclear (Partridge et al., 2012).

Frailty phenotype framework. The frailty phenotype utilizes five indicators to measure frailty (Fried et al., 2001): recent weight loss, self-reported weakness and fatigue, slow gait speed, and decreased physical activity, where the presence of three of the five indicators indicate frail, and two of the five indicate pre-frail. This approach views frailty as a syndrome, based on age-related changes as measured by the five variables assessing weight loss, weakness, fatigue, slowed gait, and decreased physical activity. The frailty cycle is proposed in this phenotype, with many entry points in the cycle that may precipitate and progress frailty (Fried et al., 2001).

Accumulation of deficits. The accumulation of deficits framework measures the quantity of deficits in an individual instead of the actual health conditions individually (Theou, Walston, & Rockwood, 2015). The number of the deficits in an individual is more important than the nature, as the body accumulates these deficits resulting in system impairment to overcome and repair damage that is either an external or internal process (Theou et al., 2015). The accumulation of deficits is a multidimensional risk state, and the health deficits are not weighted. Operationalization of this approach is through a frailty index (Mitnitski, Mogilner, & Rockwood, 2001). Frailty is viewed as a state instead of a syndrome, which Fried and colleagues portray with the phenotype approach (2001). When frailty is viewed as a state, the individual is characterized in a

whole manner (Rockwood & Mitnitski, 2007). To describe the accumulation of deficits approach as a syndrome would not be appropriate, as a syndrome is a comprised of "a collection of specific symptoms and signs" (Rockwood & Mitnitski, 2007, p 725).

Frailty measurement examples. Many common operational definitions exist in measuring frailty, with examples to include the Edmonton Frail Scale (Rolfson, Majumdar, Tsuyuki, Tahir, & Rockwood, 2006) the Tilburg Frailty Indicator (Gobbens, van Assen, Luijkx, Wijnen-Sponselee, & Schols, 2010), the Groningen Frailty Indicator (Schuurmans, Steverink, Lindenberg, Frieswijk, & Slaets, 2004), the FRAIL scale (Abellan et al., 2008), and Clinical Frailty Scale (CFS) (Rockwood et al., 2005). Description of these common measurements are located in Table 1.

Table 1. Frailty Measurements

Frailty Instrument	Description	Reference
Frailty Phenotype	Five indicators including recent weight loss, self-reported weakness and fatigue, slow gait speed, decreased physical activity.	Fried et al., 2001
Accumulation of Deficits	Operationalized by a frailty index comprising variables that are counted as deficits, dividing deficits by total number of variables measured to calculate frailty score.	Mitnitski, Mogilner, & Rockwood, 2001.
Edmonton Frail Scale	comprising 11 questions that include cognition, functional independence and performance, health status, social support, medications, nutrition, mood, and continence	Rolfson et al., 2006 ,
Tilburg Frailty Indicator	25 questions that cover physical, psychological, and social domains	Gobbens et al., 2010
Groningen Frailty Indicator	15 questions that measure physical (mobility, vision, hearing), nutrition, co-morbidity, and psychosocial components	Schuurmans et al., 2004
FRAIL Scale	scale forms the acronym "fatigue, resistance, ambulation, illness, and loss of weight", comprised of five questions	Abellan et al., 2008
Clinical Frailty Scale	9 point scale ranging from 1 (very fit) to 9 (terminally ill). Uses brief descriptions attached to silhouette pictures	Rockwood et al., 2005

The use of existing electronic medical record data to assess frailty is an approach that has been explored by researchers. Such research has produced a frailty risk score comprised of 16 variables that include geriatric syndromes, symptoms, and biomarkers pulled from existing data that included the combination of physiologic and biopsychosocial data (Lekan, Wallace, McCoy, Hu, Silva, & Whitson, 2017). Clegg and colleagues (2016) developed an electronic frailty index for the outpatient setting using medical codes in the United Kingdom that identify 36 deficits from multiple organ systems. The electronic medical record offers the opportunity to use existing data in real time to calculate a frailty score.

Frailty Research in Specialties

The impact of co-morbid conditions and frailty is emerging as an area for additional research. Multiple specialties have studied frailty. Heart disease, including atrial fibrillation, heart failure, and myocardial infarction (MI), have been studied in relation to frailty and adverse outcomes (Dominiquez-Rodriquez et al., 2016; Jha et al., 2016; Nguyen, Cummings, & Hilmer, 2016; Vidan et al., 2016). Older frail adults with atrial fibrillation had longer lengths of inpatient stays and increased mortality (Nguyen et al., 2016). Frailty in hospitalized heart failure patients was associated with increased 1-year-mortality rate in comparison to non-frail counterparts after adjusting for age, gender, co-morbidities, and severity of heart failure (Vidan et al., 2016). Frailty in older adults who had an MI was associated with inpatient and 1-month- mortality after adjustment for age, sex, previous history of MI, ejection fraction, diabetes, cardiovascular risk, and other health conditions (Ekerstad et al., 2011)

Pulmonology has focused on patients with chronic obstructive pulmonary disease (COPD) and increased risk of death with increasing frailty (Galizia et al., 2011). The presence of frailty in COPD patients awaiting transplant increased the risk of mortality prior to lung transplantation (Singer et al., 2015). Nephrology specialists noted that frail hemodialysis patients had a greater risk of death compared to non-frail counterparts when accounting for age, sex, comorbidities, and disabilities (McAdams-DeMarco et al., 2013). In the field of endocrinology, diabetes mellitus and frailty have been studied, with increased mortality in frail women and men by 31% and 60% (Cacciatore et al., 2013). The field of rheumatology has reported that osteoarthritis patients have increased risk of long-term mortality in the presence of frailty (Cacciatore et al., 2014). The field of gastroenterology has studied frailty with chronic liver diseases, noting an increased transplant waiting list mortality associated with increased frailty scores (Lai et al., 2014). The Model for End-Stage Liver Disease (MELD) score was measured in this population, and frailty continued to predict mortality even after adjustment for the MELD score (Lai et al., 2014).

Surgical and trauma specialists have also studied frailty in relation to their population. Trauma patients with index scores ≥ 0.25, which classifies frailty from a deficits approach, have higher incidence of hospital-related complications related to cardiac and pulmonary events, infection, deep venous thrombosis, and mortality in comparison to patients with index scores < 0.25 (Joseph et al., 2014). Although many specialties have undertaken frailty research, *Clostridium difficile* infection (CDI) and frailty have rarely been studied together, which is discussed further in Chapter II.

As frailty may predict hospitalization and mortality, an acute hospitalization of a frail older adult may result in an increased mortality rate compared to a healthy counterpart who is not frail. Hospitalization for disease processes and acute illnesses can be challenging, as the most common method of care is focusing on the admitting complaint with aims of discharge once improved. However, in the older frail adult, multiple deficits may be present, and recovery during and after hospitalization can be prolonged (Hatheway, Mitnitski, & Rockwood, 2017). For this reason, older frail adults admitted with CDI are a vulnerable population for increased morbidity, mortality, and prolonged hospitalization.

Clostridium difficile and the Older Adult

Multiple disease processes may affect the older adult and lead to hospitalization, and the bacterial illness *Clostridium difficile* infection (CDI) in this vulnerable population has the potential to lead to prolonged hospitalization, adverse outcomes, and possibly death. Age-related changes in this population, combined with a pathophysiological adverse process, could potentially affect the person's frailty status (Morley et al., 2013). For this reason, the relationship between frailty in the older adult and CDI needs further exploration.

One of the first published studies regarding CDI was in 1974, where Tedesco, Barton, and Alpers recognized the use of antibiotics as precipitating the disease. This prospective study of 200 patients had received clindamycin, with 21% having diarrhea and 10% with pseudomembranous colitis. Colonoscopy can confirm the presence of CDI by documentation of pseudomembranes, but the absence of pseudomembranes does not

confirm the absence of CDI. Tedesco and colleagues (1974) felt that early colonoscopy was necessary for diagnosis and advocated discontinuing the antibiotic.

As the use of antibiotics has become more routine, the prevalence of CDI has increased. Individuals 65 and older are at an increased risk for CDI compared to the younger population, and this age group is more prone to increased severity of CDI (Keller & Surawicz, 2014; Louie et al., 2013; Surawicz et al., 2013). Etiology for increased CDI prevalence in the older adult is felt to be secondary to multiple factors to include but not limited to co-morbidities (diabetes mellitus, cardiopulmonary disease, renal disease, neurological diseases and neoplasm), increased exposure to hospitalization and institutional care for other reasons, decreased immune response, and alterations in intestinal microbiota (Louie et al., 2013). Treatment success may falter with increasing age, while the risk of recurrence increases with age (Louie et al., 2013). CDI recurrence and mortality have been shown more prevalent with healthcare acquired CDI versus community acquired CDI (Lessa et al., 2015).

CDI is the leading cause for all gastroenteritis-associated deaths (Hall, Curns, McDonald, Parashar, Lopman, 2012; Moudgal & Sobel, 2012). CDI is spread via the fecal-oral route, and the bacteria produces spores that may reside on flat surfaces and objects such as door handles, toilets, and equipment. Spores have the capability to live up to several months, regardless of environmental severity (Keller & Surawicz, 2014). Bacteremia may occur in CDI, with mortality estimated at 20% (Johnson et al., 2012). Severe CDI in an older population are associated with a prior history of CDI, limited

ability to perform daily living tasks, advanced age, depression, heart failure, and immunocompromised state (Rao et al., 2013).

Recurrent CDI. A recent large study of Medicare beneficiaries (*n*= 8,465) noted an 8.5% readmission rate for those who survived initial admission for CDI approximately one month after first discharge (Collins, Ayturk, Anderson, & Santry, 2015). This study used Medicare claims from the years 2009-2011 to identify patients 65 years and older who had been hospitalized for CDI or developed CDI during an admission for other health reasons. ICD-9 code (008.45) was used to define CDI, and admissions to long-term care facility or skilled nursing facility was not included. Collins and colleagues reviewed antibiotic exposure after initial admission, length of stay, intensive care monitoring, mortality while hospitalized, and need for colectomy (2015).

This study found that 29% were admitted within 2 weeks, and 56% were readmitted within 30 days (Collins et al., 2015). Co-morbidities in this sample of 65 years and older increased the risk of readmission for CDI, and antibiotic use was the greater predictor for readmission in those who had not been hospitalized between an initial and recurrent admission (Collins et al., 2015). Hospitalization unrelated to CDI between initial diagnosis and recurrent CDI admission was a strong predictor for readmission (Collins et al., 2015) Although Collins et al. noted a readmission rate of almost 10%, estimates for recurrence of CDI indicate up to 40% chance of recurrence after an initial treatment (Garey, Sethi, Yadav, & DuPont, 2008; Kelly & LaMont, 2008). CDI recurrence with readmission is similar to heart failure at 20% within 30 days (O. Connor, 2017), COPD ranging from 5.6% to 20% (Harries et al., 2017), and

pneumonia estimated 1 in 5 patients within 30 days (De Alba & Amin, 2014). The need for intensive care monitoring increases during readmission. Interestingly, increasing age in this study did not correlate with risk of readmission, although age greater than 65 has been recognized as a risk factor for recurrence. Co-morbidity burden in the sample did predict increased risk of recurrence (Collins et al., 2015).

Risk factors. However, other literature supports risk increasing with advancing age. Antibiotics after CDI treatment, PPI therapy, and specific virulent strains of CDI continue to be risk factors for recurrence (Chakra, Pepin, Sirard, & Valiquette, 2014; Trifan et al., 2017). Risk factors for complicated CDI disease course includes older age, leukocytosis, renal failure, co-morbidities, and hypoalbuminemia (Chakra et al., 2014). Decreased ability of the older adult to respond with an appropriate immune response is felt to contribute to adverse effects in CDI (Louie et al., 2013). Recurrent CDI occurs usually one to three weeks after initial completion of antibiotics, characterized by diarrhea and positive stool test for CDI (Chopra & Krishna, 2014). Fifty percent of recurrent CDI episodes are likely from a different bacterial strain than the original infection (Chopra & Krishna, 2014). Recurrence and morbidity from CDI is associated more with healthcare-acquired infections than community-acquired infections (Lessa et al., 2015).

Significance

The increased risk of CDI and recurrence in older adults, coupled with the growing interest in frailty and preventing its adverse outcomes, requires further investigation. Understanding the relationship between CDI in the older adult and frailty

may provide guidance towards a holistic approach to providing care for the hospitalized older adult with CDI. The risk of recurrence in older adults is greater than the general population, but age alone does not account for the higher risk of recurrence in the elderly (Collins, et al., 2015). Further, recurrent CDI is not always explained by coexisting conditions (Schmid et al., 2014).

Wenisch and colleagues (2012) reviewed hospitalized patients with CDI and those without who were admitted between January 2009 and December 2009; the authors found that patients with CDI were more likely to die than patients hospitalized without CDI, independent of sex, age, or severity of co-morbidities. The literature differs regarding mortality from CDI and age, for instance, Bloomfield et al. (2012) performed a systematic review of literature to evaluate potential risk markers for CDI mortality during hospitalization. This review found that age (65 and older) was a marker for risk of mortality with CDI, along with increased creatinine, low serum albumin level, and increased white blood cell count, concluding these characteristics could be useful as part of a risk factor assessment at time of diagnosis (Bloomfield et al., 2012). Chintanaboina et al. (2017) conducted a retrospective study of patients with CDI, noting in multivariate logistic regression analyses, peptic ulcer disease, advanced age, Charlson comorbidity index, and intensive care admission were associated with a 30-day mortality.

Statement of the Problem

Although current research findings contribute to the knowledge base regarding CDI, to date there is a paucity of research in older adults exploring the relationship

between recurrent CDI and frailty. Gut microbiota of the older adult differs in composition compared to younger counterparts (Claesson et al., 2011; Mariat et al., 2009). The relation between microbiota and frailty has been explored in the literature, with increased frailty associated with less diverse microbiota (Jackson et al., 2016; Milani et al., 2016; Tongeren et al., 2005). Altered gut microbiota has been shown in older adults with CDI (Milani et al., 2016), which raises the question of a relationship between frailty and CDI in the hospitalized older adult. A knowledge gap remains, as chronological age alone continues to be unpredictable as a factor for the recurrence of CDI (Collins et al., 2015). Although many risk factors are known surrounding CDI, antibiotics are the only constant, independent risk factor. The relationship between frailty in the older adult and CDI deserves investigation, as recurrent CDI, severe CDI, and CDI-associated morbidity and mortality could be potentiated by the presence of frailty.

Purpose and Research Questions

The purpose of this study was to explore relationships between frailty and CDI as addressed by the following research questions:

1. What sociodemographic variables are related to recurrent CDI admission?
2. What sociodemographic variables are related to frailty during an initial admission for CDI?
3. What is the prevalence of the frailty index variables among members of the sample?

4. What proportion of the sample has a frailty index score of 0.25 and above indicating frailty?
5. What is the relationship between the frailty index score during the initial admission for CDI and documented recurrence of CDI within a year?
6. What is the relationship between proton pump inhibitor (PPI) use prior to admission, frailty, and recurrent hospitalization for CDI?

Conceptual Framework

This study used the Accumulation of Deficits framework as a guide, developed by Mitnitski, Mogilner, and Rockwood (2001). Operationalization of frailty was performed by using a researcher-derived frailty index. In this frailty measurement, numerous health deficits were combined and comprised into an index. The number of deficits present in an individual were summed, with the outcome calculated as the number of deficits present divided by the total number of deficits in the index (Mitnitski et al., 2001; Theou, Walston, & Rockwood, 2015). This provided a score from 0 to 1, with higher scores indicating severity of frailty. A continuum exists between fit and frail individuals, with the frailty index placing individuals on this continuum. The accumulation of health problems predisposes to vulnerability (Mitniski, Song, and Rockwood, 2013). The Reliability Theory of Aging and Longevity by Gavrilov and Gavrilova (2001) was inspiration for the accumulation of deficits model (Mitnitski, 2001).

The Reliability Theory of Aging and Longevity

Reliability Theory of Aging and Longevity (Gavrilov & Gavrilova, 2001) states that living organisms are designed with only a finite number of redundant capabilities to maintain life. Through the aging process, deficits accumulate and result in decreased physiological reserve and the potential for increasing mortality (Gavrilov & Gavrilova, 2001). This theory proposes the process of aging as a "system redundancy" (p. 539). Mitnitski, Song, and Rockwood (2013) derived the deficit accumulation model from the Reliability Theory of Aging and Longevity, whereby the interactions between environmental stress (causing distress in multiple areas of the organism) and recovery result in the degree of deficit accumulation.

Mitnitski, Song, and Rockwood (2013) used a mathematical stochastic dynamics approach to support the accumulation of deficits. Although individuals may have multiple differing health issues, the common theme remains that the total number of health problems actually increases with age but also increases quicker in individuals with poor health (Kulminski et al., 2007; Yashin et al., 2007). This mathematical concept describes the length of a queue in relation to the stream of arrivals to a system, the systems schedule priorities, service, and waiting times (Mitnitski et al., 2013).

Little's Law further explains this mathematical concept, stating, "the average number of items in a queuing system (L) equals the average arrival rate (人) multiplied by the average waiting time of an item in the system, (W)" (Mitnitski et al., 2013, p. 711). For the accumulation of deficits, Little's Law is then revised to state that the average number of deficits in a given time in an individual (N), will equal environmental

stress rate (⅄), multiplied by the average recovery time (R) (Mitnitski et al., 2013). This mathematical relationship represents that recovery in an individual is a proportional equation associated with the average deficits in an individual at a given time. As the rate of an individual's recovery becomes slower, resulting in longer recovery times, the deficits accumulate with age (Mitnitski et al., 2013). The slowing of recovery increases with age, which is not completely explained in this model.

Increased maintenance and metabolic demands are placed on the individual during the normal aging process (Mitnitski et al., 2013). Deficit accumulation is viewed as a state of an individual, focusing on number of deficits impaired in an individual instead of the nature of the health problems (Theou, Walston, & Rockwood, 2015, p. 67). The deficits accrued affect the individual's system to heal. Aging involves accumulation of deficits, but the number of these deficits present will affect the recovery time in an individual (Mitnitski & Rockwood, 2015).

The recovery time of each individual is different and varies in individuals the same age (Mitnitski & Rockwood, 2015). Recovery is dependent on genetic factors, health, access to health care, living environment, and underlying cellular characteristics of the aging process (Howlett & Rockwood, 2013; Theo et al., 2013; Yashin et al., 2013). The frailty index of an individual will increase an average of 10-fold between the ages of 20 and 90. Little's Law reinforces that the recovery time is the changing factor over the lifespan (Theou et al., 2015). This concept explains the reasoning behind the increased score of the frailty index. This index consistently is associated with poor health outcomes, women are noted to have more accumulation of deficits than men of

similar age, and a maximum frailty index score is around 0.7 (Theou et al., 2015). The frailty index score and mortality rate are considered a "dose-response" function (Theou et al., 2015, p. 68). A frailty index may be researcher-derived, following specific guidelines (Searle et al., 2008). The development of the frailty index for purposes of this study is discussed in Chapter 3.

Frailty indices are used with the assumption that the more deficits an individual has is more important than understanding exactly what is wrong with the individual (Theou & Rockwood, 2015). The pathway to frailty is unique to each individual. The value of the frailty index is not affected by the precise variables that are included; when enough variables are included in the index, even randomly selected, similar results are found (Rockwood, Mitnitski, Song, Steen, & Skoog, 2006). Although random variables may be selected, a strict method to composing the index must be followed. Any health-related variables that cover a broad range of bodily systems, are linked with adverse outcomes, and are known to increase with age but not universal may be included (Mitnitski & Rockwood, 2015).

The frailty index has consistent reproducibility regarding association with adverse outcomes, without a linear increase, threshold of limits in deficits, and increased scores in women versus men despite the combination of variables in various studies (Mitnitski & Rockwood, 2015). This consistency is due to the interdependent play amongst the health deficits, relating to the premise of system redundancy; many deficits may hold information regarding other deficits, supporting the accumulation of deficits. Although the frailty index has been controversial (Mitnitski & Rockwood, 2015), it must

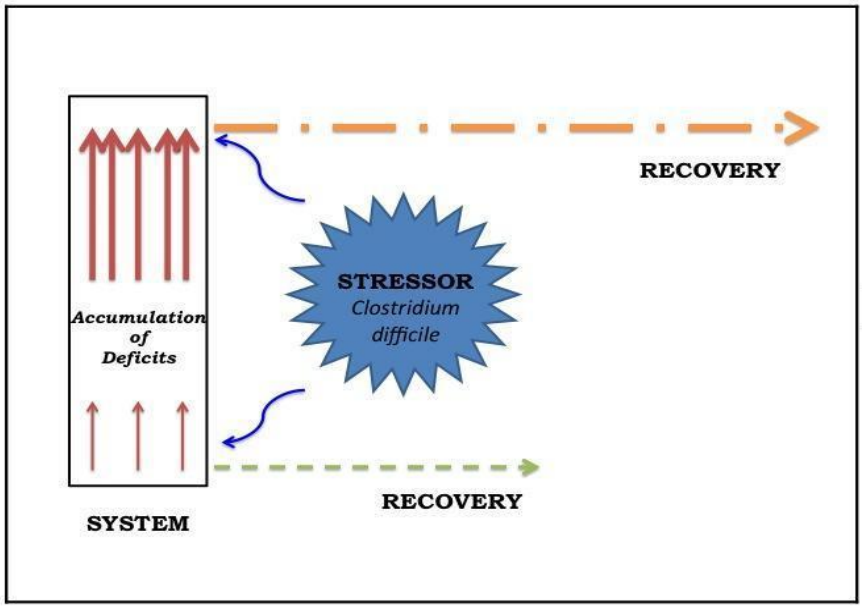
be understood that the emphasis is not on each individual deficit but rather the synergistic effects of deficits on the individual, giving rise to frailty. The biological systems-perspective of viewing a human, comprising many mutually interacting subsystems that contribute to health, encompasses the understanding of the accumulation of deficits approach.

Components of Framework

The Accumulation of Deficits framework was used to guide this study, with CDI as an acquired infection from the environment, hereby depicted as an external stressor that causes physiologic changes in the individual. The interdependent deficits included in the frailty index are affected by the presence of CDI. The interdependent deficits as symptoms, signs, diseases, disabilities, and laboratory abnormalities comprise the accumulation of deficits, as illustrated in the model.

The proposed model for frailty, derived from the accumulation of deficits framework, is depicted in Figure 1. As the number of deficits affect the potential recovery time in an individual, it was hypothesized that higher frailty scores would result in impaired and longer recovery time and potentially increase the risk of recurrent CDI and hospital readmission.

Figure 1. The Accumulation of Deficits Model for CDI



In this model, the external, physiologic stressor of CDI is a threat. This may affect recovery time, in turn leading to a recurrence of CDI in a system already compromised by multiple deficits. A system with the burden of deficits, translated into a frailty score, may not be able to adequately recover if the deficits are too great; this results in poor recovery and possible recurrence of CDI or other adverse events. These deficits were derived from the literature as entities that are related to frailty and discussed in Chapter 2.

Definitions

Frailty. For this study, frailty was conceptually defined as a multidimensional state, secondary to the accumulation of deficits that are externally or internally generated, hindering the individual from recovery and increasing risk for adverse outcomes (Mitnitski et al., 2001; Theou, Walston, & Rockwood, 2015). Frailty was

operationalized using a researcher-derived frailty index based on variables available in the electronic health record (EHR). The Frailty Index for *Clostridium difficile* infection (FI-CDI) was developed by following the procedure outlined by Searle and colleagues (2008). The deficits must be signs, symptoms, disabilities, and diseases; the deficits must be associated with health status, general increase with age, do not saturate quickly (such as routine age-related processes), cover a range of body systems, and the derived frailty index must be identical for measurement in the sample if it is serially applied (Searle et al., 2008). Further development of the frailty index is discussed in Chapter 3. The FI-CDI score was derived by adding the number of deficits present in an individual divided by the total number of deficits possible. Therefore, the FI-CDI result is a decimal number, used to identify the severity of frailty. Research demonstrates that a threshold has been consistently shown, whereby the maximum number of deficits that any one individual will have approximates two-thirds of the total number of deficits, with an empirical limitation of a Deficit Index score of 0.7 (Rockwood & Mitniski, 2007; Theou et al., 2015). The use of a continuous Frailty Index score instead of a cut point score for frailty has been recommended (Theou & Rockwood, 2015).

***Clostridium difficile* infection.** CDI was determined from the EHR by the ICD-9 and/or ICD-10 codes of 008.45 and A04.7, in the electronic health record. The presence of these codes indicates a diagnosis by a healthcare provider during hospitalization, which could be prompted by the collection of stool studies to diagnose the presence or absence of CDI or through clinical judgment by the provider if stool testing is

inconclusive and suspicion is high for CDI. CDI is recognized as the external stressor on the system in this conceptual framework.

Frailty index variables and demographic variables. The sociodemographic variables and frailty index variables extracted from the EHR are listed and operationally defined in Table 2 and 3, respectively. Sociodemographic variables include age, sex, race, ethnicity, marital status, residence prior to admission, living arrangements prior to admission, discharge plan at first admission, length of hospital stay, days from first discharge to recurrent admission, and expired during admission.

Table 2. Sociodemographic Variables

Variable	Definition/Choices Available in EHR
Age	Measured chronologically in years and recorded as a whole number on initial admission
Sex	Male or female
Race	American Indian, Asian, Black/African American, White, Other, Unavailable
Ethnicity	Hispanic, Non-Hispanic, unavailable
Marital Status	Divorced, Legally Separated, Married, Single, Unknown, Widowed
Living Arrangements	Spouse/Significant other, Alone, Children, Other
Residence prior to admission	Assisted Living, Group Home, Nursing Home, Private Residence, Skilled Nursing Facility, Other
Discharge plan at first admission	Home/Self Care, Transferred Short Term Hospital, Skilled Nursing Facility, Intermediate Care Facility, Home Health Care, Left against medical advice, Expired, Federal Hospital, Hospice/Home, Hospice/Medical facility, Rehab facility, Long Term Care, Another institution, Inpatient rehab/Acute care Hospital
Length of hospital stay	Date of admission to date of discharge defined as number of days
Days from discharge to recurrent admission	Length of time measured in days
Expired	Death during admission, yes or no

Summary

The relationship between frailty in the hospitalized older adult and CDI (initial or recurrence) has not been directly explored in the literature. CDI affects young and old alike, but the older population has been shown to experience more adverse effects, increased risk of recurrence, morbidity, and mortality (Wenisch et al., 2012). Frailty may be an important factor that influences CDI recurrence and treatment failure. The

identification of frailty may be a vital component to preventing recurrent disease and numerous adverse outcomes. This retrospective cohort research study focuses on the association between frailty and recurrent CDI with hospital admission, utilizing a 36 item frailty index. The accumulation of deficits framework guided the study design and identification of the variables in the EHR for the frailty index, and the data obtained shall be used to bridge a known gap between frailty in the older adult and risk of recurrence and readmission for CDI. The measurement of frailty in the acute care setting is challenging, as no clinical tool has been identified as optimal for risk prediction and care planning. There remains inconsistency in choice of frailty tools, when to measure frailty, and which patients should be identified; frailty assessment should be a priority in providing care for adults during the normal aging process (Lekan et al., 2017). The researcher-derived frailty index utilizes existing collected data in the EHR, offering practical advantages over other frameworks that require new data collection or lengthy new data collection.

CHAPTER II

LITERATURE REVIEW

Frail individuals are at risk for prolonged hospitalizations, morbidity, and mortality; age-related changes in this population, combined with a pathophysiological adverse process could potentially affect the person's frailty status. Recognition of frailty in the hospitalized older adult for CDI is vital to deliver care in both the inpatient and outpatient management. In this chapter, the concept of frailty will be further discussed. Clinical studies that have addressed frailty in the hospitalized older adult using a specific frailty index are presented here. Finally, current research surrounding the relationship between CDI and frailty will be discussed.

Pathophysiology of Frailty

Frailty is dynamic and requires a myriad of failures across the physiologic workings in an individual (Clegg et al., 2013). With frail individuals, multiple different failures in the system give rise to the state of frailty. Aging, in itself, is a natural process of a breakdown in the physiological processes and reserves of the body; however, in frailty, the process is quickened and failing systems occur (Ferrucci et al., 2002). The imbalance in homeostasis of the human body and stressful occurrences in health result in poorer health.

Numerous studies outline markers correlating with frailty. From a standpoint of dysfunction, certain markers of inflammation, hormonal changes, blood clotting pathway

activation, and metabolic derangements exist with frailty (Cappola, Xue, & Fried, 2009; Reiner et al, 2009; Walston et al., 2006). Sarcopenia and its associated consequences of decreased strength, speed of gait, and overall physical function are well known frailty indicators (Zasvlavsky, Thompson, & Demeris, 2012). Neurological indicators of frailty include impaired sensory function, cognitive impairment, and even psychological entities such as depression (Zasvlasky et al., 2012).

The human body is comprised of many organ systems; however, the overlapping qualities of many of these systems allow for physiological stamina, which propels the overall body in functioning despite aging and disease (Lipsitz, 2002). Skeletal muscle, immune system, endocrine system, neurological system, respiratory system, cardiovascular, renal, and hematological system have been studied in frailty (Clegg et al., 2013). The brain, skeletal muscle, endocrine system, and immune system will be reviewed in further detail, as they have been most studied in frailty development (Clegg et al., 2013).

Brain

The brain undergoes natural aging processes, with the neurons that necessitate higher metabolic demands possibly more affected in function (Bishop, Lu, & Yankner, 2010). An example of this type of neuron would be those in the hippocampus, which are responsible for metabolic needs. Cognitive failing would be linked to the hippocampus, which is an important ingredient in the physiological stress response (Miller & Callaghan, 2005). The link between frailty, dementia, and cognitive impairment has shown increasing frailty linked with a quicker cognitive decline rate (Clegg et al., 2013).

This cognitive impairment and affective disorders lead to a vulnerable state in the individual. (Rockwood et al., 2005). The presence of frailty leads to a higher risk of cognitive deficits long-term (Boyle, Buchman, Wilson, Leurgans, & Bennett, 2010). Cognitive frailty is recognized as a subcategory of frailty, whereby the individual demonstrates both physical frailty and impaired cognition that is unrelated to Alzheimer dementia or other clinically diagnosed dementias (Kelaiditi et al., 2013; Maxwell & Wang, 2017).

Endocrine

The endocrine system and brain are interconnected via the hypothalamo-pituatary axis, responsible for homeostasis properties (Bishop et al., 2010). Growth hormone, sex hormones, and cortisol have been posited as linked with frailty (Clegg et al., 2013). Persistently elevated cortisol in the older adult has been thought to result in an increase in catabolism, resulting in muscle mass loss, loss of appetite, loss of weight, and decreased energy, all of which are linked to frailty. Diabetes is a risk factor for the development of frailty. Elevated blood glucose levels in individuals without a diagnosis of diabetes increase risk for frailty (Zaslavsky, Walker, Crane, Gray, & Larson, 2016). Glucose levels have been highly predictive of mortality in the hospitalized older adult (Fontana et al., 2013).

Immune

With aging, stem cells wane, T-lymphocytes production change, and the antibody response is altered and less effective (Clegg et al., 2013). During stress-free periods, the older adult will continue to function well but may not be able to have an appropriate

immune response during an acute inflammatory event (Sahin & Depinho, 2010). A state of inflammation is linked with loss of appetite, breakdown of fatty tissue and skeletal muscle, muscle fatigue, and loss of weight, contributing to poor overall nutrition and linked with the frailty picture (Clegg et al., 2013). Markers recognized as associated with frailty include interleukin-6 (IL-6), C-reactive protein (CRP), tumor necrosis factor-α (TNFα), and CXC chemokine ligand-10 (CXCL-10). However, these are not routinely measured on hospital admission, making inclusion in frailty measurement difficult.

Skeletal Muscle

Skeletal muscle mass loss and decreased ability in strength is a known characteristic of frailty (Manini & Clark, 2012). Decreased mobility is recognized in frail states. (Bandeen-Roche et al., 2006). The degree of frailty has been related to mobility recovery in acute hospital admission, with recovery time of mild mobility impairment individuals quicker than those who were less frail (Hatheway, Mitnitski, & Rockwood, 2017). Although actual weight loss is identified with the syndrome of frailty, the morbidly obese patient has been reported frail as well (Waters et al., 2013). Sarcopenia, which is a triad of lost skeletal muscle mass, strength, and power, is a recognized marker of frailty (Clegg et al., 2013). A term "sarcopenic obesity", is recognized as the presence of increased body fat in conjunction with decreased skeletal muscle (Cooper et al., 2012, p. 1843). Sarcopenic obesity is linked with mobility impairment in the older adult. Homeostasis upset by neurological, endocrine, and immunological components in the frailty syndrome may affect the decline to sarcopenia (Clegg et al., 2013). Physical frailty is also recognized as a subcategory of frailty (Maxwell & Wang, 2017).

Chronic Diseases

Individuals with heart failure, cancer, kidney disease, and diabetes are more prone to frailty and subsequent adverse effects (Afilalo, 2011; Ng, Feng, Nyunt, Larbi & Yap, 2014; Ruiz, Reske, Cefalu & Estrada, 2013; Shilpak et al., 2004; Sinclair et al., 2012). Frailty risk is also increased in individuals who have both diabetes and dementia (Ulley & Abdelhafiz, 2017).

Other chronic diseases found in frail persons include asthma, COPD, stroke, depression, hearing and visual impairment, anemia, and renal disease (Galizia et al., 2011; Ng et al., 2014). A historical diagnosis of cancer has led to a higher state of frailty with advancing age, and a higher risk in those with a recent diagnosis (Pérez-Zepeda, Cárdenas-Cárdenas, R, Navarrete-Reyes, & Gutiérrez- Robledo, 2016). Arthritis increases severity of frailty, leading to higher mortality rates (Cacciatore et al., 2014). Non-alcoholic fatty liver disease (NAFLD) is prevalent in the older adult population, with severity of liver fibrosis associated with advancement of age and higher risk of mortality (Frith, Day, Henderson, Burt, & Newton, 2009). NAFLD severity has been associated with low albumin and higher alkaline phosphatase levels (Frith et al., 2009). Sarcopenia and NAFLD share similar pathophysiological pathways, with insulin resistance mediating accumulation of fat in the liver and muscle mass (Bertolotti et al., 2014).

Polypharmacy is strongly associated with likely development of frailty (Morley et al., 2013). Older adults taking five or more medications have an increased likelihood for risk of falls and delirium (Inouye, 1998). The literature has recognized that the presence

of six or more drugs are indicative of polypharmacy, which in turn may result in adverse outcomes (Rolland & Morley, 2016). The risk for 30-day hospital readmission is increased in older adults who have multiple medication adjustments (Shapiro et al., 2017). The frailty syndrome coincides with changes in pharmacokinetics, thereby altering bioavailability of drugs (McMillian & Hubbard, 2012).

Depression has been linked with frailty, and the presence of depression increases risk of mortality (Almeida et al., 2015; Makizako et al., 2015). Urinary incontinence has been shown to contribute to frailty and felt to be a marker of frailty (Berardelli et al., 2013). Finally, with older adults at risk for falls and adverse outcomes, the association of frailty and falls has been studied. Higher frailty scores have been associated with higher risk for falls, along with frailty as a predictor for risk of falls in the future (Li et al., 2014; Liu et al, 2016; Sanchez-Garcia et al., 2017). Lifestyle behaviors to include alcohol use and smoking in midlife has been associated with progression to frailty over time (Kojima, Iliffe, Jivraj, Liljas, & Walters, 2017; Ulley & Abdelhafiz, 2017). Kojima and colleagues noted that current smokers were also were found to be significantly frailer in comparison to those who did not smoke (2017).

Functional Status

The inability to perform activities of daily living (ADLs) is associated with frailty, with the literature supporting the association of frailty with deficits in one or more difficulty in performing ADLs (Sanchez-Garcia, 2017). The multi-faceted aspect of frailty that affects normal day to day activities include decreased cognition, weakness and exhaustion, loss of weight, all of which are reflected in measurement by the Braden scale

(Ogg, 2016). The Braden scale is a commonly used measurement to assess risk of pressure ulcers, including the following six domains: sensory perception/communication, moisture, activity, mobility, nutrition, friction and shear (Braden & Bergstrom, 1994).

Clinical Laboratory Markers of Frailty

Laboratory studies are easily accessible in the hospitalized patient, and many researchers have studied markers in relation to frailty. Serum sodium imbalances place the older adult at risk for hospitalization, mental status changes, and falls, thereby contributing to frailty (Morley, 2015). Inflammatory markers such as increased white blood cells and increased CRP have been associated with frailty in the older adult (Kanapuru & Ershler, 2009; Lekan et al., 2017; Mitnitski et al., 2015; Ng et al., 2014). Thrombocytopenia, low hemoglobin, and low albumin have been identified as biomarkers that contribute to the development of frailty (Fontana et al., 2013; Mitnitski et al., 2015). Low or low normal hemoglobin has been shown to be an independent risk factor for frailty (Chaves et al., 2005). Leukocytosis and hypoalbuminemia are biomarkers that are not only contributors to the development of frailty but strongly associated with mortality in the hospitalized older adult (Fontana et al., 2013). A decreased serum level of ALT in an older adult could be indicative of frailty and stem from decreased liver size and decreased blood flow (Liu, Que, Xu, & Peng, 2014). Vitamin D is vital for many purposes, including maintaining appropriate calcium and phosphorous concentration in the body, contributing to bone strength, and influential in immunological processes (Adams & Hewison, 2010). Vitamin D deficiency may be

found in pre-frailty and frail individuals (Fernandez-Garrido, Ruiz-Ros, Buigues, Navarro-Martinez, & Cauli, 2014).

Psychosocial Variables

The lack of psychosocial support for the older adult has been linked with the potential for frailty and poor outcomes (Hoogendijk et al., 2014a). Solitary living status, depression, and socioeconomic status have been linked with frailty (Ng et al., 2014). Increased social support has shown to be associated with decreased frailty (Woo, Giggins, Sham, & Ho, 2005). Social support is important in the older adult population as it can improve outcomes (Hoogendijk et al., 2014a). Although the psychosocial component is linked to frailty, more research is needed to assess the outcomes in relation to the association between frailty, functional decline, and mortality. Hoogendijk and colleagues did not find a statistically significant association between psychosocial factors with functional decline and mortality, after adjusting for age, sex, educational level, and frailty (2014b). Psychosocial factors in the study by Hoogendijk and colleagues (2014b) were identified through mastery and self-efficacy, identification of instrumental and emotional support through personal networks such as friends and family. Further research over time is needed to investigate the psychosocial component to frailty outcomes in the older adult.

Depression has been linked with higher frailty scores (King, Fillenbaum, & Cohen, 2017). Low educational level may affect availability of psychosocial resources, and these individuals are more likely to have experienced environmental adverse effects (Hoogendijk et al., 2014b). Older adults with lower educational levels were more likely

to be frail than higher educational level counterparts, but frailty rate did not disproportionately increase over time in those with lower educational frailty levels. This finding shows that there was not an interaction effect between time and educational status (Hoogendijk et al., 2014b). The association between educational level and frailty was mediated by income, self-efficacy, cognitive status, chronic diseases, and obesity (Hoogendijk et al., 2014b). These findings support the multifactorial properties of frailty. A higher socioeconomic status was linked with greater perceived control of situations, in turn resulting in lesser degree of frailty (Mooney, Elliot, Douthit, Marquis, & Seplaki, 2016).

Self-neglect in the older adult has been associated with functional limitations, co-morbidities, living alone, and greater likelihood of frailty (Lee, Burnett, & Dyer, 2016; Papaioannaou, Raiha, & Kivela, 2012). Self-neglect has been shown as an independent risk factor for early demise of the older adult (Papaioannaou, Raiha, & Kivela, 2012). J. Lee and colleagues performed a secondary data analysis to explore frailty and self-neglect, with findings of pre-frail individuals more likely to exhibit self-neglect, and those who were self-neglecting were more overweight and obese than counterparts in the study (2016). This finding was hypothesized as the result of possible physical constraints and decreased activity promoting a more sedentary lifestyle, progressing more to frailty and self-neglect. Frailty status was felt to lead to worsening self-neglect, but further research is needed with frailty and self-neglect.

Frailty, physical decline, and difficulty with ADLs are risk factors for elder abuse, with abuse encompassing the realms of psychological, physical, sexual, financial, and

neglect (Johannesen & LoGiudice, 2013). Psychological abuse is further delineated by verbal and social abuse displayed in actions or threats. Cooper and colleagues estimated that approximately 6% of older community-dwelling adults will likely have experienced abuse (2008).

CDI and the Older Adult

CDI is a spore-forming, gram-positive, anaerobic bacteria that releases toxins in the intestinal system, specifically flourishing in the setting of an altered, post-antibiotic exposure intestinal tract. Asymptomatic colonization and carrier of the bacteria is possible (Behar et al., 2017). Due to persistent overuse of antibiotics, potent strains of the bacterium now exist, which may lead to complicating features (Postma, Kiers, & Pickkers, 2015). CDI has doubled in prevalence from the years 2000 to 2010, with an estimated 453,000 cases in 2011 (Lessa et al., 2015). In 2011, The Centers for Disease Control and Prevention (CDC) reported 29,000 deaths secondary to CDI (Centers for Disease Control and Prevention, 2015a). Long-term care patients have an incidence of this infection varying from 4% to 50% (Kee, 2012). The incidence of CDI is four times higher in individuals aged 65 and older versus counterparts, and 70-80% of CDI cases are comprised of age 65 and older (Lessa et al., 2015; Simor, 2010).

All ethnicities are affected, but Caucasians have been found to have higher incidences than other ethnicities (Lessa et al., 2015; Yang, Rider, Baehr, Ducoffe, & Hughe, 2016). A large retrospective study noted the CDI incidence in Caucasians was 57% more than African Americans (Argamany, Delgado, & Reveles, 2016). Yet, African Americans developed more severe disease courses and a higher rate of mortality than

Caucasians (Argamany et al., 2016). Freedberg and colleagues noted the African American race as an independent risk factor for recurrent CDI (2013). The reason for disparities in race and ethnicity is unclear. Argamany and colleagues hypothesized that incidences of CDI in younger ages of black individuals, health insurance obstacles, and access to care could contribute to less recognition of the disease (Argamany et al., 2016). Although this disease affects both male and female, females have a higher rate of CDI (Lessa et al., 2015).

Risk Factors

Risk factors for CDI are multiple. Advanced age, prior antibiotic use, and facility admissions are the most widely known and accepted risk factors; however, other factors also include proton pump inhibitor use, presence of feeding tube, inflammatory bowel disease, immunosuppressive states, hepatic and renal disease, and history of gastrointestinal surgeries (Keller & Surawicz, 2014; Leibovici-Weissman et al., 2017; Surawicz et al., 2013; Zilberberg, Shorr, Wang, Baser, & Yu, 2016). Individuals with chronic comorbidities have a higher risk of developing CDI than those without comorbidities (Zilberberg et al., 2016). Also, the risk for CDI increases with intensive care admission, a recent hospital admission within several months, respiratory support via ventilation, enteral feedings, histamine blockers, proton pump inhibitors (PPIs), malnutrition, and hypoalbuminemia (Kim et al., 2012; Morrison et al., 2011; Roughead et al., 2016; Tleyjeh et al., 2013). Prolonged stays in health care facilities increase risk of exposure to CDI, specifically if common toilets are shared. Co-existing malignancy and poor host immune response are also risks (Hessen, 2010; Kim, Lee, & Jeong, 2010;

Morrison, Hall, Said et al., 2011; Tleyjeh et al., 2013). The use of PPIs as a risk factor for recurrent CDI requires further investigation, as the literature reports mixed findings. Although observations have noted a significant association between PPI usage and CDI recurrence (Linksy, Gupya, Lawler, Fonda, & Hermos, 2010; McDonald, Milligan, Frenette, & Lee, 2015; Roughead et al., 2016; Trifan et al., 2017), Freedberg and colleagues (2013) did not find an association between PPI usage and recurrent CDI. Freedberg et al., (2013) did not adjust for antibiotic re-exposure, which must be considered. A large systematic review and meta-analysis of PPI therapy and CDI risk reviewed 56 studies, which showed a significant association between PPI use and CDI risk, compared with those not on a PPI (Trifan et al., 2017). Also of note, the risk for CDI while on a PPI was not statistically different for adults 65 and older, compared to those younger (Trifan et al., 2017). Causality was not confirmed, as the studies in the meta-analysis were all observational.

Some chemotherapeutic agents may increase risk for CDI, but the literature is mixed regarding findings (Cozar-Llisto, Ramos-Martinez, & Cobo, 2016). Body mass index (BMI) has recently been studied in association with severe CDI. A BMI greater than 35 kg/m^2 was an independent predictor for severe presentation of CDI in both a community and hospital-acquired infection (Mulki et al., 2016). Any exposure to antibiotics has the potential to increase CDI risk, but common offenders include fluoroquinolones, broad-spectrum penicillins to include amoxicillin/clavulanate, clindamycin, and second and third generation cephalosporins (Clark & Wiselka, 2008; Hensgens, Goorhuis, Dekkers, & Kujper, 2012; Hessen, 2010; Keller & Surawicz, 2014).

Further classification of offending agents by tier was noted by Clark and Wiselka (2008), with clindamycin, second and third generation cephalosporins, penicillins, and quinolones as high risk; macrolides, tetracyclines, and aminoglycosides medium risk; and metronidazole and vancomycin as rare risk for CDI.

Fluoroquinolones are associated with a specific strain of CDI most often seen in the older population, increasing recurrence rate and challenging to achieve remission (Keller & Surawicz, 2014; Surawicz et al., 2013). Freedberg and colleagues examined the risk of CDI associated with sequential bed placement in patients (2016). Individuals who were placed in beds of those who had previously received antibiotics were at a statistically significant increased risk for development of CDI, after adjusting for comorbidity, CDI colonization of prior individual, type of room, and exposure to antibiotics in patient taking over the bed. CDI development could be a concern in patients who are occupying beds of those who previously received antibiotics, regardless of CDI exposure. This raises the concern for the shedding of spores from an asymptomatic patient thereby passed to a new individual who takes up residence in the room. Historically, asymptomatic carriage of *Clostridium difficile* has felt to be protective of the host developing CDI (Cozar-Llisto et al., 2016). Yet, colonization present prior to an intensive care admission was found to be an independent risk factor for development of CDI during hospitalization (Tschudin-Sutter et al., 2015).

Furthermore, Behar and colleagues (2017) noted asymptomatic carriers compared to those who are non-carriers were more likely to have been hospitalized in the preceding three months, have had a prior diagnosis of symptomatic presentation for CDI, and had

higher Barthel scores and MUST scores (used as measurements to identify frailty for the study). The rate of asymptomatic *Clostridium difficile* colonization for hospitalized adults was found to be close to 10%, similar to other findings (Alasmari, Seiler, Hink, Burnham, & Dubberke, 2014; Behar et al., 2017; Bruminhent et al., 2014; Ziakas et al., 2015).

Clinical Manifestations

Clinical manifestations of CDI exist on a broad spectrum, ranging from unaffected carriers to a fulminant process leading to death. The most common characteristic of CDI is foul-smelling, watery diarrhea (Sams & Kennedy-Malone, 2017). Mild and moderate presentation of CDI may include the presence of diarrhea only, but other clinical manifestations may include abdominal discomfort and pain, nausea, and mild fever. In older adults, pyrexia may be an indication for severe CDI (Kee, 2012). Severe presentation is characterized by serum albumin less than 3 g/dL and either leukocytosis greater than 15,000 cells/mm or tender abdomen on physical exam (Surawicz et al., 2013). Severe and complicated presentation is characterized by at least one of the following indicators: intensive care hospital admission, hypotension, ileus, mental status changes, fever greater than 101.3º F, leukocytosis greater than 35,000 mm^3 or leukopenia, serum lactate greater than 2.2 mmol/L, or organ failure (Surawicz et al., 2013).

Rectal bleeding is not common with CDI. Clinical signs that could lead to adverse outcomes include sudden diarrhea cessation, worsening renal function, and colonic dilatation on imaging studies. Upon physical exam, extreme tenderness to palpation should raise suspicion for possible megacolon or perforation. The older adult may present

in an atypical fashion, with acute confusion, mental status changes as an initial symptom (Kee, 2012). The older adult may be afebrile, with other non-specific symptoms to raise concern for infection to include loss of appetite, weight loss, weakness, falls, and decreased physical capacity (Kee, 2012).

The incubation period of CDI is unclear but several studies have noted a time period of less than 1 week (Cohen et al., 2010; McDonald et al., 2007). The risk for CDI development may range from weeks to months after discharge. CDI within 4 weeks after hospitalization is felt to be hospital-acquired, whereas CDI after 4-12 weeks of a recent hospitalization is possibly linked with the prior hospitalization (Cohen et al., 2010).

Treatment

Hospitalization for supportive care is indicated for individuals with hypotension, multi-organ involvement, leukocytosis, pyrexia, dehydration, abdominal distension, and possible obstruction (Sams & Kennedy-Malone, 2017). While inpatient, supportive care may include intravenous fluids, anti-emetics, pain control, and diet as tolerated depending on clinical presentation. Close monitoring of intake and output, stool frequency and characteristics, and serial laboratory monitoring are imperative to document clinical improvement or worsening of status (Sams & Kennedy-Malone, 2017). Contact isolation precautions should be instituted for those with suspected or confirmed CDI.

The mainstay of pharmacological treatment for CDI includes metronidazole and vancomycin, but patients with diabetes and/or sepsis may be at risk for metronidazole treatment failure (Jung et al., 2010). An additional FDA approved antibiotic, Fidaxomicin, has shown similar effectiveness as vancomycin (Cornely et al., 2012;

Crawford, Husgen, & Danziger, 2012; Louie et al., 2012). Microflora has shown to be protected with Fidaxomicin, which translates to lower recurrence rates of CDI (Louie et al., 2012).

Metronidazole and vancomycin are preferred via oral rate; however, complicating features require alternate routes (Chopra & Krishna, 2014). Vancomycin colonic enemas may be required in complicated disease, as the intravenous rate is not highly effective (Chopra & Krishna, 2014). Fecal microbiota transplantation (FMT) is a promising and efficacious treatment for persistent and recurrent CDI (Yoon & Brandt, 2010; Musgrave, Bookstaver, Sutton, & Miller, 2011; Surawicz et al., 2013). Oral capsules containing frozen fecal microbiota have been studied for recurrent CDI, with CDI resolution in 82% of patients after single treatment and improvement to 91% curative rate after two treatments in a recent study by Youngster and colleagues (2016).

Treatment of choice for mild presentation of CDI was historically metronidazole; however, the Infectious Disease Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) updated guidelines advise vancomycin 125 mg orally four times a day for 10 days as initial treatment for non-severe of severe episode (McDonald et al., 2018). Fidaxomicin may also be used for initial non-severe or severe episodes. If neither vancomycin or fidaxomicin is available, metronidazole may be used 500 mg orally three times a day for 10 days. Initial fulminant episode, characterized by hypotension, shock, ileus, or megacolon, should be treated with vancomycin 500 mg orally four times a day, metronidazole 500 mg intravenously every eight hours, and consideration of rectal vancomycin enemas if ileus or inability to tolerate oral medication

(McDonald et al., 2018; Surawicz et al., 2013). Recurrent infections are managed similar to first episode; repeated recurrences may require vancomycin in a pulse dosed fashion or tapering; fidaxomicin may also be considered if vancomycin was the initial treatment. Fecal microbiota transplants (FMT) are indicated after second and subsequent recurrences, showing promising results for longstanding resolution.

Thirty days following treatment of CDI is crucial, as the colonic flora has been disrupted, providing a window of time for potential recurrence and additional infection (Kelly, 2012). The treatment of CDI is with antibiotics, typically metronidazole or vancomycin, depending on severity of clinical presentation. Metronidazole and vancomycin both alter colonic flora, possibly contributing to the inability to resist recurrence or reinfection (Kelly, 2012). Diabetes and sepsis have been found to be independent factors for treatment failure (Jung et al., 2010)

Diagnosis

Diagnosis of CDI may be challenging due to multiple tests available. CDI is confirmed through stool sample, with multiple laboratory tests available to include *C. difficile* culture, toxigenic culture, *C. difficile* cytotoxin neutralization assay, enzyme immunoassays (EIAs) that detect toxins A and B or glutamate dehydrogenase (GDH), and nucleic acid amplification tests (NAAT) (Sethi et al., 2010; Surawicz et al., 2013). A two-step algorithm is recommended, whereby a GDH EIA or NAAT is used first, which both have a higher negative predictive value; the second step in the algorithm includes a high positive predictive value test, which would be the EIA toxin A/B, which identify free toxin (Cronbach et al., 2016). If the original NAAT or GDH EIA are

negative, CDI is highly unlikely. However, if the NAAT or GDH EIA are positive, a positive EIA toxin A/B would indicate likely CDI but a negative test would require clinical expertise. In this scenario, the individual could be a carrier. In complicated cases such as an ileus, rectal swabs may be used and tested via NAAT, TC, or GDH EIA (Cronbach et al., 2016). The decision to treat lies with the provider, as diagnostic testing requires the art of interpretation. Repeat testing for cure of CDI is not indicated.

Risk Factors for Mortality in CDI

Risk factors for 30-day mortality in the older adult include a high comorbidity burden as measured by Charlson comorbidity index, diabetes, hypoalbuminemia with albumin 2.5 g/dL or less, elevated creatinine, low hemoglobin, low diastolic blood pressure, sepsis upon initial presentation with CDI (Leibovici-Weissman et al., 2017). Chintanaboina and colleagues had similar findings with predictors of 30-day mortality including Charlson comorbidity index (2017). However, advanced age, PUD, heart failure, recurrent CDI, histamine-2 receptor blocker usage, and intensive care admission were significantly associated with a 30-day mortality in the population sample studied; yet, this sample included ages 18 and older, with a mean age of 62 years. There was no significant association between recurrent CDI and 30-day mortality noted (Chintanaboina et al., 2017).

Clostridium difficile and Frailty

The review of current literature provides limited information regarding the specific relationship between frailty and CDI. The focus of current CDI research includes fecal microbiota, functional deficits, age-related factors, and attempts to explain risk

factors for recurrence in the older adult. Understanding of the potential relationship between CDI and frailty is further explored by reviewing the literature involving prior frailty measurements with CDI, functional status and CDI, and co-morbidity relationships with recurrent CDI.

Frailty Measurements with CDI

The relationship between the intestinal microbiota and frailty is emerging as a topic of interest, but further research is needed. Intestinal flora plays a role in formation and excretion of important vitamins for the body, prevents harmful pathogens from colonizing in the GI system, aids in metabolism, and encourages immune and lymphatic systems (Biedermann & Rogler, 2015). The digestive pathway from the esophagus to the rectum holds different amounts of bacteria, starting with a lower amount in the esophagus and stomach, leading to a more concentrated bacterium in the terminal ileum and colon (Biedermann & Rogler, 2015).

Microbiota was not designed to enter the actual body, and the intestinal epithelium provides a first-line defense by acting as a protective barrier; other factors to keep bacteria at bay include gut motility, mucin and chloride secretion by goblet cells, and defensins, which are "human antibiotics" (Biedermann & Rogler, 2015, p 153). Finally, the last line of defense occurs when a battle is fought between healthy and pathogenic bacteria, with imbalance in the flora allowing a pathway for bacterial invasion and acute illness (Biedermann & Rogler, 2015). CDI is an example of a pathogenic bacteria taking up residence in the GI system due to dysbiosis.

It is known that older adult microbiota composition is different than younger individuals (Claesson et al., 2011; Mariat et al., 2009; Meehan, Langille, & Beiko, 2015). The bacterial composition of the gastrointestinal tract has been shown to be affected by many entities to include physiological, dietary, environment, microbiological, and host factors (Tongeren, Slaets, Harmsen, Welling, 2005). The microbiota composition may change as the human body ages, and it is affected by mobility, nutrition, and psychosocial stressors (Biedermann & Rogler, 2015; Tongeren et al., 2005). When CDI is treated with antibiotics, healthy bacterial flora is also affected, potentially resulting in a cascade effect of dysbiosis (Meehan et al., 2015). Further research is needed to determine the etiology of this phenomenon, with potential factors including physiological reasons or additive changes over the lifespan (Biedermann & Rogler, 2015). Possible signatures of frailty found with microbiomes has been posited by frailty experts, with a call to further research of the microbiome (Meehan et al., 2015).

Milani et al. (2016) investigated the composition of gut microbiota in three cohorts of older adults, measuring frailty using the Clinical Frailty scale by Rockwood (Rockwood et al., 2005). The cohorts were divided into hospital-acquired CDI group, antibiotic-exposed group without CDI, and non-antibiotic exposed group without CDI. This sample was comprised of hospitalized adults older than age 65, more than two comorbidities, and hospitalized secondary to an illness other than gastrointestinal etiology. The frailty scores across the group were similar, without statistical significance noted. As this was a cross-sectional study, repeated frailty measures were not undertaken, and the implication of the frailty score was unable to be determined. However, findings

of altered gut microbiota were noted in those with CDI, which is a known pathophysiologic process during this infection. A similar finding regarding frailty scores between a CDI group and control group was noted in a separate study (Van Esch, Van Broeck, Delmée, & Catry, 2015). Van Esch et al. (2015) used a frailty index previously created by Drubbel et al. (2012) for the outpatient setting. No statistical difference was noted in frailty index scores between the two groups, nor were there any differences in BMI and mini mental status examination scores. However, total protein and prealbumin in the CDI group was significantly lower compared to the control group without CDI. Interestingly, hypoalbuminemia has been linked with frailty (Kim, Higgins, Canaday, Burant & Hornick, 2014; McMillan & Hubbard, 2012).

Jackson et al. (2016) utilized fecal samples to further investigate microbiota and its association with frailty. By creating a frailty index by Rockwood, 39 domains were used to create a proportion of deficits (Jackson et al., 2016). Data from the Healthy Aging Twin Study was used to assess frailty indices and correlation with fecal samples containing microbiota (Jackson et al., 2016). After adjusting for age, alcohol intake, dietary habits, smoking, and BMI, frailty was negatively associated with microbiota diversity, indicating that higher frailty indices were linked with less diverse microbiota present in the gut (Jackson et al., 2016). These findings do not establish frailty as a cause or effect related to microbiota diversity; however, the authors relay that imbalance of intestinal flora may have negative effects on the overall health of these frail individuals.

Higher frailty scores and reduced health flora was demonstrated by Tongeren et al. (2005). The Groningen Frailty Indicator (GFI) was used as a measurement of frailty,

with high frailty scores correlating with statistically significant reduced amount of lactobacilli (Tongeren et al., 2005). Lactobacilli is vital in immunological functions, assisting with digestion and absorption, and thwarts growth of harmful bacteria that may be present in the gut (Tongeren et al., 2005). Older adults with high frailty scores from the GFI also exhibited a statistically significant reduced percentage of hybridizable bacteria, meaning the overall bacterial flora was reduced in the GI tract (Tongeren et al., 2005). Interestingly, the sample was provided the same dietary menu during the study, had no exposure to antibiotics during the study or at least four weeks prior, and were 70 to 100 years old (Tongeren et al., 2005). Although this study does not include CDI exposure, the intestinal flora is examined, which is already known to be altered in individuals with CDI.

Behar and colleagues (2017), studied the prevalence of asymptomatic carriage of *Clostridium difficile* and discussed risk factors for colonization. The study used the MUST score (malnutrition measurement) and Barthel score (activities of daily living) to assess frailty (Behar et al., 2017). The patients were inpatient and recruited if over age 18 and no current diagnosis of CDI. Stool samples were collected on admission and weekly while hospitalized. Stool samples were assessed for toxin A, B, and PCR. The sample size was 727, with 410 testing positive for *Clostridium difficile*. Of the 410 who had positive stool samples, 9.8% were carriers. Participants who were carriers had a higher likelihood of prior CDI and were more frail compared to non-carriers. PPI was not associated with colonization (Behar et al., 2017). Mortality amongst the carriers was predicted by male gender, prior admission from a residential facility, increased co-

morbidities, and malnutrition as characterized by the MUST score, which was used to measure frailty in this population.

A modified frailty index (mFI) was used to identify frailty in patients who had undergone colectomy for CDI due to complicating/severe features (Venkat, Telemi, Oleksandr, & Nfonsam, 2016). A total of 356 patients had a total colectomy, with 127 patients undergoing partial colectomy; as the frailty index score increased, so did morbidity. The mFI independently predicted overall morbidity and mortality in this patient population (Venkat et al., 2016).

Functional Status and CDI

Functional status and severe CDI was explored by Kyne and colleagues (1999), by utilizing Barthel scores as a measurement for functional status. Severe CDI was associated with lower Barthel scores; however, these scores were not included in the final statistical modeling with multivariate logistic regression. Instead, an abbreviated mental test was used in place of the Barthel score, as both correlated with each other.

A study by Rao et al. (2013) investigating functional status and severity of CDI was undertaken to further explore what had previously been evaluated by Kyne and authors years before. Although frailty was not directly studied, the authors found that impaired functional status was actually an independent risk factor for CDI after adjusting for possible co-founding variables of comorbidities, immunosuppression, and acid suppression therapy. Behar and colleagues (2017) studied *Clostridium difficile* colonization in older adults, using the Barthel score (a measurement of activities of daily living), Waterlow score (risk of pressure ulcers), and MUST scores (risk of malnutrition)

to identify frailty. Carriers of the bacteria were more likely to have higher MUST and Barthel scores (p=0.001 and 0.036, respectively), which coincided with frailty as per study definitions.

CDI Recurrence

The knowledge gaps involving the relationship between frailty and CDI are numerous. The risk of CDI recurrence in the elderly is greater than the general population, but age alone has been found insufficient as explaining the higher risk of recurrence in the elderly. This was demonstrated by a retrospective national review of Medicare patients ages 65 and older (Collins et al., 2015). During the years 2009-2011, the ICD-9 code for CDI (008.45) was used as a marker to identify patients admitted to acute care facilities with a primary or secondary diagnosis of CDI. Patients were further separated into community-acquired and healthcare-acquired groupings. Readmission was defined by any second admission to an acute facility with CDI as a primary diagnosis, but nursing homes and long-term care facilities were excluded.

In this study, patients were usually readmitted within one month after the initial discharge. The readmissions had low mortality rates but 1 in 5 required intensive care monitoring during the second hospitalization (Collins et al., 2015). Of those patients readmitted, 20% were admitted an additional time, which confirms the risk of increased recurrence with each CDI event. This study did not find a statistically significant risk of readmission related to increased age. This research confirmed that although older adults are at risk for recurrence, chronological age does not completely explain this phenomenon.

D' Agostino, Collins, Pencina, Kean, and Gorbach (2014), developed a predictive model to evaluate the risk of recurrence for CDI. Multiple factors to include demographics, comorbidity, medications, vital signs, laboratory findings, severity of disease, and symptoms were placed into a logistic regression model. Four independent risk factors were identified as statistically significant as predictors for recurrence (D'Agostino et al., 2014). Predictors included dichotomous variables of age (greater than or less than 75), number of loose bowel movements in the past 24 hours (greater than 10 or less than 10), baseline serum creatinine (greater than 1.2 mg/dL or less than 1.2mg/dL), and a prior occurrence of CDI (yes or no) (Agostino et al., 2014).

In another study, the relationship between CDI and multiple co-morbidities was explored using a Cumulative Illness Rating Scale (CIRS) (Ticinesi et al., 2015). The findings showed that only the highest quartile of scoring on the CIRS was significantly associated with risk for CDI (Ticinesi et al., 2015). This study was limited due to retrospective qualities, and the use of anti-depressants, narcotic therapy, and functional status was not explored as possible cofounding variables (Ticinesi et al., 2015).

CDI and Mortality

Additional knowledge gaps reside in the mortality surrounding CDI. A prospective study over one year in a large community hospital in Austria supported the risk of death with CDI and hospitalized patients. The findings noted that regardless of age, sex, or co-morbidity severity, patients with CDI were twice as likely to die during hospitalization compared to other hospitalized patients (Wenisch et al., 2012). Differing findings were noted in a systematic review by Bloomfield et al (2012), as the authors

identified age as a marker for mortality with CDI for hospitalized patients. This review found that white blood cells, serum creatinine levels, and serum albumin levels were markers for mortality secondary to CDI (Bloomfield et al., 2012). The presence of prior corticosteroids was raised as a possibility to be utilized as a risk factor for adverse outcomes in CDI.

Summary

The topic of frailty, CDI, and the older adult is sparse and needs further evaluation with repeated measures of frailty. Several studies called for dedicated research regarding frailty and CDI, but this remains a knowledge gap that needs to be bridged. Some potential factors were identified as risk factors for recurrence in CDI. Further research should evaluate whether these factors are independently operating or synergistic in nature with the presence of CDI. Chronological age alone is unreliable in the recurrence of CDI (Collins et al., 2015). The presence of comorbidities alone does not explain the recurrence or severity of CDI (Wenisch et al., 2012). Finally, the constant factor that is known surrounding CDI is the leading independent role that antibiotics play. The intestinal microbiota may be an area that deserves further research, as the treatment for CDI alters colonic flora, leading to dysbiosis and decreased defenses against risk of recurrence.

The Accumulation of Deficits approach with frailty index has been used in multiple studies to include outpatient care, elective hospital surgical admissions, long-term care facilities, and community research. Exploration of the syndrome with the frailty index has been used in descriptive studies, frailty and falls, delirium, mobility, and

fractures (Dent, Chapman, Howell, Piantadosi, Visvanathan, 2014; Eeles, White, O'Mahony, Bayer, & Hubbard, 2012; Hatheway et al., 2017; Joseph et al., 2015; Krishnan et al., 2014; Patel, Brennan, Brennan, Jupiter, Shar, & Davis, 2014; Ridda, Lindley, & MacIntyre, 2008). Adverse outcomes related to frailty and rehab (Singh et al., 2012), assessment of predictive validity of a frailty index related to discharge, length of stay, and mortality (Evans et al., 2014), and comparison of the frailty index to other tools was explored (van Iersel & Rikkert, 2006; Ritt et al., 2016; Wou et al., 2013). Multiple studies have explored frailty using a modified index in relation to elective procedures such as colorectal surgery, esophagectomy, head and neck surgery, vascular surgery, tracheostomy, and gynecological surgery (Adams et al.,2013; Brahmbatt et al., 2015; Farhat et al., 2012; George et al., 2015; Johnson, Bailey, Schmid, Lydiatt, & Johanning, 2014; Hodari, Hammoud, Borgi, Tsiouris, & Rubinfield, 2013; Karam, Tsiouris, Shepard, Velanovich, & Rubinfeld, 2013; Keller, Bankwitz, Nobel, & Delaney, 2014; Obeid et al., 2012). Although the frailty index has been used with a population having CDI (Van Esche et al., 2015; Venkat et al., 2016), the literature is sparse regarding measurement of frailty and CDI in this patient population.

The relationship between frailty and CDI in the hospitalized older adult deserves further exploration. Frailty is a dynamic entity, and further research following hospital admission and recurrent CDI is lacking in the literature. The Accumulation of Deficits framework and model proposed in Chapter I was used to guide this study. As prior evidence has shown, the presence of frailty, as operationalized by the frailty index, will affect recovery time in an individual. The environmental stressor of CDI is hypothesized

to adversely affect a compromised system, ultimately leading to adverse outcomes to include readmission for recurrent CDI, morbidity, and mortality. Recognition of frailty in the older adult is vital in the inpatient setting, with this research addressing a known knowledge gap surrounding the relationship between CDI and the older adult, utilizing the Accumulation of Deficits framework as a guide throughout the study.

CHAPTER III

METHODOLOGY

The purpose of this study was to explore the relationship between frailty in older adults and the recurrence of CDI. The literature supports the risk of recurrence and severe CDI more prevalent in adults over the age of 65 (Keller & Surawicz, 2014; Louie et al., 2013; Surawicz et al, 2013). Frailty is also associated with hospitalization and even death (Fried et al., 2001; Mitnitski et al., 2001). Details regarding the research design, setting, research procedures, measurements, data analyses, and power and sample size are described.

Design

By using a retrospective cohort design, an analysis of existing data from electronic medical records was undertaken exploring the relationship between frailty in the older adult and recurrent CDI. The electronic medical record system provided demographic information, documented admissions, progress notes, laboratory studies, radiological data, and vital health history for each individual who was admitted through the hospital system in North Carolina. This analysis examined the association between frailty and CDI, specifically the presence of frailty during an index admission for CDI and readmission for recurrent CDI over the span of one year.

Setting

The setting for this research included three hospitals belonging to a large hospital system in North Carolina. The hospital system serves the triad region and surrounding 12 counties and 1.6 million people (Piedmont Triad Regional Council, 2012).

Sample

Inclusion criteria consisted of a) age 55 and older, b) diagnosis of CDI via ICD-9 code 008.45 and ICD 10 code A04.7 and c) inpatient hospitalization. Exclusion criteria consisted of any observation admission less than 24 hours. The target population dates included December 31, 2013 through December 31, 2015. The EHR was electronically queried for health system inpatient admissions from December 31, 2012 through December 31, 2016, capturing any admission or discharge ICD codes for CDI for the specified timeframe. The recurrence of CDI was ensured by a review of each index admission and any prior admissions from that point that could potentially be the initial admission. Each patient was followed for a year, to capture recurrence after initial admission; therefore, the cutoff date of query was December 31, 2016, ensuring any patients that were admitted during the inclusion timeframe were followed an entire year. Additionally, patients captured at the beginning of December 31, 2013 were reviewed for any prior admissions the year before, ensuring the true index admission was captured.. The minimum age of 55 was selected as chronologically advanced years do not equate to frailty (Morley et al., 2013), and hospitalization of the older adult with physiologic abnormal underpinnings that propel the pathway of frailty (Maxwell & Wang, 2017). The majority of frailty research in the hospitalized older adult focuses on those ages 65 and

older (Afilalo et al., 2012; Dent et al., 2014; Eeles et al., 2012; Evans et al., 2014; Joseph et al., 2015; Krishnan et al., 2014; Purser et al., 2006). Components of frailty may be present in middle-age adults (Pol et al., 2011) Although the literature supports recurrence within one to three weeks after antibiotic completion (Chopra & Krishna, 2014; Schmid et al., 2014), the timeframe of one year was reviewed in order to capture any repeat admissions for CDI, as development may occur months after discharge (Cohen et al., 2010).

Human Subjects Protection

The Institutional Review Board (IRB) guidelines at the University of North Carolina at Greensboro (UNCG) and hospital system were reviewed and followed during this study. Full application for IRB approval was submitted first to UNCG for approval. Once approved, this was submitted to the hospital's nursing research council, per protocol. IRB approval was then submitted and received by the hospital system. A Data Use Agreement was obtained per the hospital system policy and agreed upon by UNCG and the hospital system prior to data collection. De-identified data were stored in a safe, password protected system, following HIPPA compliant guidelines and accessed via a virtual desktop that was created by the hospital system for research purposes.

Data Collection

The data were extracted from the medical record by approved personnel at the hospital system. A consolidated database was created using data obtained from the EHR. ICD-9 and ICD-10 codes were used as identifiers of *Clostridium difficile* infection-related admissions. The diagnosis codes for admission and discharge were included in the

report request, as individuals admitted for hospitalization may not have the diagnosis of CDI at time of admission, and, CDI may occur during hospital stay. Specific dates that corresponded to laboratory results included in the frailty index were derived in the study database. As stool tests require time to collection and reporting of results, including the final discharge diagnosis identified individuals with CDI. In addition, diagnosis of CDI may not occur on initial day of admission, as healthcare providers use clinical judgment when interpreting stool test results, assessing patients, and identifying signs and symptoms of potential CDI if stool tests are inconclusive. No personal identifiers were included with each grouping of individual data.

Hospital approved personnel transferred the data to the virtual desktop for data analyses and followed privacy laws. Randomized data audits were performed, ensuring the accuracy of data input.

Measurements

Basic demographic information was extracted from the medical record. This information had no personal identifying information. These variables are recorded on admission in the electronic medical record by nursing personnel, staff, and providers and located in Table 2. This demographic information was routinely captured on admission, with static measurements of sex, ethnicity, and race unchanging. Place of residence, living arrangements, and marital status was assumed unchanged during the hospital admission, as these are present prior to admission. PPI use prior to admission was captured, which is documented on outpatient medication record at time of admission. These medications included omeprazole (Prilosec), pantoprazole (Protonix),

esomeprazole (Nexium), dexlansoprazole (Dexilant), rabeprazole (Aciphex), lansoprazole (Prevacid) and omeprazole/sodium bicarbonate (Zegerid). PPI use was coded as "0" for no PPI use and "1" for PPI prescription on admission.

Clostridium difficile infection was defined by the presence of ICD- 9 codes and ICD-10 codes identified either on admission or as a discharge diagnosis. At times, a hospitalization evolves as the database on a patient expands, and CDI diagnosis may be obtained several days into a hospital admission. For purposes of this study, CDI was not classified as hospital-acquired or community-acquired, as the research focus is regarding frailty and the presence of CDI leading to a recurrence after hospitalization. The ICD-9 and ICD-10 codes are applied to the medical record once a diagnosis of CDI is confirmed via stool specimens during the hospitalization or at the discretion of the provider after review of clinical presentation, signs, and symptoms. The most widely used stool specimen during this timeframe was a *Clostridium difficile* polymerase chain reaction (PCR), defined as positive or negative in the medical record. An additional test for CDI for this timeframe could include stool samples for the presence of toxins A or B.

An initial admission was documented, with review of the medical record within the defined study period to ensure no previous admission for CDI was present. Once the initial admission was verified, the frailty index scores were created from the initial admission data, using the components for the frailty index as outlined in Table 3. The frailty index score was calculated by dividing the total number of deficits present in an individual by the total number of variables measured in the frailty index (36 in this study). Each frailty deficit component in the frailty index was coded into "0" for absent

or “1” for present. For laboratory indices, abnormal values derived from the literature were coded as “1”, with normal laboratory values coded as “0”, as defined in Table 3.

Health conditions were coded into “0” or “1”, corresponding to absent or present, respectively. Smoking status was documented with choices of “current every day smoker”, “current some day smoker”, “former smoker”, “heavy tobacco smoker”, “light tobacco smoker”, “never assessed”, “never smoker”, “passive smoke exposure”, and “smoker status unknown”. A value of “0” was given if “never assessed”, “never smoker”, and “smoker status unknown” and “1” otherwise. The psychosocial item of the frailty index included support system, physical abuse, verbal abuse, sexual abuse, and self-neglect as outlined in Table 3. A code of “0” was given if patient denied any physical, verbal, or sexual abuse, and denied self-neglect. Support system was coded as “1” if no support system was identified.

Decreased mobility was documented on admission with choices to include: completely immobile, very limited, slightly limited, and no limitation. A “0” was coded if “no limitation”, and a “1” otherwise. The decreased mobility component was documented by healthcare personnel as part of the Braden scale questionnaire, as this was the clearest information to obtain on mobility in the medical record in a retrospective fashion. The total Braden score was included in the frailty index, with a score of 18 or less determined as at risk for pressure ulcers, consistent with recommendations in the literature (Bergstrom & Braden, 2002). The Braden score of 18 or less was coded as a “1”.

Fall risk was documented in the medical record on admission by hospital staff, utilizing the Johns Hopkins Fall Risk Assessment and including variables of age, fall

history, bowel and urine elimination, medications, patient care equipment, mobility, and cognition. Scores included low fall risk (0-5 points), moderate (6-13 points), and high fall risk (greater than 13 points). A low fall risk was coded as "0", otherwise "1". Full outline of the frailty index with definitions is located in Table 3. As medical record documentation may contain multiple choices, coding of variables absent or present may be difficult. Searle and colleagues stated clinical judgment could be employed if no identified "cut-off" points are present. Clinical judgment was utilized in this study, as noted in coding of variables.

Frailty Index

The frailty index was derived systematically according to the guidelines set forth by Searle and colleagues (2008). The deficits included in the frailty index may include symptoms, signs, diseases, disabilities, laboratory abnormalities, radiographic or electrocardiographic findings. Any deficits included in an FI should meet strict criteria to include deficits associated with health, increases with age, should not saturate early such as a deficit that is commonly present early in the aging process, should cover a representation of organ systems and not only associated with one system, and items should be used the same on each individual in the cohort applied so that the measurement is the same universally.

Including a wide representation of organ systems in a frailty index helps to take into account the natural aging process (Howlett & Rockwood, 2013). Individuals, despite their age, may vary in the level of function for each organ system. By utilizing laboratory tests, possible abnormalities may be assessed prior to actual organ dysfunction, which

could give rise to frailty (Howlett &Rockwood, 2013). Howlett et al. (2014) used a frailty index consisting of routine laboratory findings that showed predictive validity in relation to risk of mortality. Further support for laboratory markers included in a frailty index was demonstrated by Blodgett and colleagues, noting that even with small laboratory changes accumulating together can increase risk of mortality (2017). For purposes of this research, the frailty index was created by following the guidelines set forth by Searle et al. (2008) and including laboratory measurements are discussed.

Development of frailty index. The frailty index for this study included 36 components. Clinical laboratory markers, diseases, disabilities, psychosocial variables, and polypharmacy were included as deficits. Laboratory markers included in this frailty index were as follows: Albumin, ALT, alkaline phosphatase, hemoglobin, creatinine, BUN, white blood cell count (WBC), glucose, sodium, and platelets. These were gathered due to known association with frailty, as outlined in Chapter 2. Chronic diseases included Vitamin D deficiency, arthritis, hypertension, stroke, cancer, diabetes mellitus (Type 1 and 2), COPD, asthma, BMI (<18 or >30), chronic kidney disease, depression, dementia, heart failure, and smoking status. Disability in functional status and activities of daily living was assessed by decreased mobility, independently performing ADLs, total Braden scale, incontinence, presence of falls within past 6 months, fall risk, and polypharmacy. Finally, psychosocial variables included support system, physical abuse, verbal abuse, sexual abuse, and self-neglect. These variables were chosen based on review of the literature as discussed in Chapter I and II, further outlined in the following table.

Table 3. Frailty Index for Older Adults with CDI (FI-CDI)

Variable	Positive Frailty Definition	Supportive Evidence
Laboratory		
Albumin	less than 3 g/dL	Kim et al., 2014 McMillan & Hubbard, 2012 Mitnitski et al., 2015
ALT	<17 or >30 U/L	Liu et al., 2014
Alkaline phosphatase	>140 U/L	Frith et al., 2009
Hemoglobin	<11.5 g/dL (male) < 11.0 g/dL (female)	Chaves et al., 2005 Mitnitski et al., 2015 Ng et al., 2014
Creatinine	>1.2 mg/dL	Howlett et al., 2014 Ng et al., 2014
BUN	>28 mg/dL	Howlett et al., 2014 Ng et al., 2014
WBC count	<3 or >9 K/uL	Fontana et al., 2013 Kanapuru & Ershler, 2009 Mitnitski et al., 2015
Glucose	<70 or >120 mg/dL	Fontana et al., 2013 Zaslavsky et al., 2016
Sodium	<135 or >145 mmol/L	Morley, 2015
Platelets	<150 or >400 K/uL	Mitnitski et al., 2015
Chronic Diseases		
Vitamin D deficiency	ICD-9 268 ICD-10 E55	FernÃ¡ndez-Garrido et al., 2014
Arthritis	ICD-9 715.0 ICD-10 M15-M19	Cacciatore et al., 2014
Hypertension	ICD-9 401 ICD-10 110-116	Theou et al., 2015
Stroke	ICD-9 430-438 ICD-10 I60-I69	Ng et al., 2014
Cancer	ICD-9 140-239 ICD-10 C00-D49	Pérez-Zepeda et al., 2016
Diabetes mellitus (Type 1 and Type 2)	ICD-9 250 ICD-10 E08-E13	Sinclair et al., 2012 Ulley & Abdelhafiz, 2017
COPD	ICD-9 491, 491.2, 492 ICD 10 J44	Galizia et al., 2011 Ng et al., 2014
Asthma	ICD-9 493 ICD 10 J45	Ng et al., 2014
BMI	<18 or >30	Cooper et al., 2012

Variable	Positive Frailty Definition	Supportive Evidence
		Waters et al., 2013
Chronic Kidney Disease	ICD-9 585 ICD-10 N18	Shilpak et al., 2004
Depression	ICD-9 311 ICD-10 F32.9	Almedia et al., 2014 King et al., 2017 Makizako et al., 2014 Ng et al., 2014
Dementia	ICD-9 290 ICD-10 F03.90	Boyle et al., 2010 Clegg et al., 2013 Rockwood et al., 2005
Heart Failure	ICD-9 428 ICD-10 I50-50.9	Afilalo, 2011 Ng et al., 2014
Smoking Status	Smoker status unknown (0) Never assessed (0) Never smoker (0) Current every day smoker (1) Current some day smoker (1) Former smoker (1) Heavy tobacco smoker (1) Light tobacco smoker (1) Passive smoke exposure (1)	Kojima, Iliffe, Jivraj, Liljas, & Walters, 2017 Ulley & Abdelhafiz, 2017
Functional Status and Activity of Daily Living		
Decreased Mobility	No limitation (0) Completely immobile (1) Very limited (1) Slightly limited (1)	Bandeen-Roche et al., 2006 Hatheway et al., 2017 Sanchez-Garcia et al., 2017
Independently performs ADLs	Yes (0) or no (1)	Sanchez-Garcia et al., 2017
Braden Scale	Score 18 or less (1)	Bergstrom & Braden, 2002 Ogg, 2016
Urinary Incontinence	Yes (0) or no (1)	Berardelli et al., 2013
Falls	Yes (1) or no (0)within past 6 months	Li et al., 2014 Liu et al., 2016 Sanchez-Garcia et al., 2017
Fall Risk (Johns Hopkins Fall	Low fall risk (0) Moderate (1)	Li et al., 2014 Liu et al., 2016

Variable	Positive Frailty Definition	Supportive Evidence
Risk Assessment)	High fall risk (1)	Sanchez-Garcia et al., 2017
Polypharmacy	Patient takes 7 or more medications at time of admission (1)	Inouye, 1998 McMillian & Hubbard, 2012 Morley et al., 2013 Rolland & Morley, 2016 Shapiro et al., 2017
Psychosocial		
Support System	Spouse/significant other, children, parent, other relatives, friends/neighbors, church/faith community, home care staff, case manager/social worker, organized support group, shelter, therapist (0) None (1)	Hoogendijk et al., 2014 Ng et al., 2014
Physical Abuse	Denies (0) Denies and provider concerned (1) Yes in past (1) Yes in present (1)	Cooper et al., 2008 Johannesen & LoGiudice, 2013
Verbal Abuse	Denies (0) Denies and provider concerned (1) Yes in past (1) Yes in present (1)	Cooper et al., 2008 Johannesen & LoGiudice, 2013
Sexual Abuse	Denies (0) Denies and provider concerned (1) Yes in past (1) Yes in present (1)	Cooper et al., 2008 Johannesen & LoGiudice, 2013
Self-Neglect	Denies (0) Denies and provider concerned (1) Yes in past (1) Yes in present (1)	J. Lee et al., 2016 Papaioannou et al., 2012

Laboratory reference ranges were chosen based on the known age-related changes that occur in the older adult. Reference ranges from standard laboratories are routinely derived from sampling well, younger individuals (Edwards & Baird, 2005). Therefore, the laboratory markers in this study were defined according to known changes that occur with the aging process, so as to more precisely identify any subtle changes that could be occurring in this population. Albumin levels will decline each decade after the age of 60, so this will be slightly more decreased than a younger counterpart (Beers & Berkow, 2000). ALT levels in ages 65 and older tend to be lower than those of younger adults (Kelso, 1990), and alkaline phosphatase increased with age and is linked with malabsorption, bone abnormalities, and liver and kidney abnormalities (Brigden & Heathcote, 2000). Hemoglobin and hematocrit may trend lower in the older adult for numerous reasons to include but not limited to anemia, chronic blood loss, renal insufficiency, nutritional inadequacy, and other chronic conditions (Edwards & Baird, 2005). Likewise, an increase in hemoglobin and hematocrit above normal would be concerning for dehydration.

As the adult ages, the BUN and creatinine will stay fairly close to standardized normal values; this is explained by reduced lean body mass and other factors that affect decreased BUN and creatinine (Brigden & Heathcote, 2000). Although lower white blood cell counts should not be attributed to age alone, immunity does slowly decline after the third decade of life (Rybka et al., 2003). Decreased WBC counts could indicate disease, infections/sepsis, medications, and increased WBC counts may indicate acute infection or stress response. Glucose ranges are wider for the older adult, and the serum

glucose levels slowly increase with age, yet glucose tolerance decreases (Edwards & Baird, 2005). Platelet function may be affected by age; however, the normal range value is not significantly changed in older adults when compared to younger counterparts (Brigden & Heathcote, 2000).

Although the frailty index score can be placed as a trichotomous variable (frail, pre-frail, and not frail or pre-frail), the use of a continuous frailty score has been recommended for more robust outcomes and higher statistical power (Theou & Rockwood, 2015). Operationalizing the definition of frailty is through the frailty index (Mitnitski, Mogilner, & Rockwood, 2001). The trajectory to frailty may be different for each individual, so multiple items that are linked with frailty may be used in a frailty index (Theou et al., 2015). A minimum of 30 deficits is estimated to be sufficient for appropriate estimation of frailty (Rockwood & Mitnitski, 2011).

The frailty index, even with varying deficits included in various indices, has noted an overall consistent average of 0.03 deficits accumulated per year after age 70 (Theou et al., 2015). A threshold has been consistently shown, whereby the most that any one individual will have in deficits equals ⅔ of the total deficits, approximately a score of 0.7 (Rockwood & Mitniski, 2007; Theou et al., 2015). Recent literature has supported an even lower limit of 0.5 (Armstrong, Mitnitski, Launer, White, & Rockwood, 2015). The threshold between fit and frail has been described as 0.25, with lower scores identifying fit and higher identifying frail (Hubbard et al., 2017).

Criterion validity. The FI has been shown to predict adverse outcomes in relation to frailty (Drubbel et al., 2014; Rockwood, 2005). The FI has been used primarily

in the outpatient setting extensively. A review by Drubbel et al. (2014) noted criterion validity was upheld in multiple studies that used the FI to predict mortality, hospitalization, length of hospital stay, emergency care, falls and fractures, changes in activities of daily living, and mental status changes. After adjusting for age, gender, and other comorbidities, the FI appropriately predicted these adverse outcomes. The FI has also been found to better predict risk of mortality in the older adult population versus the frailty phenotype (Kulminski et al., 2008). The FI helps to define frailty differences in people of similar ages, which can raise awareness for likely development of adverse outcomes (Drubbel et al., 2014).

Construct validity. The FI has noted strength of correlation with the Consolice Study of Brain Ageing score with r=0.72 (Lucicesare, 2010), Frailty Phenotype ($r=0$.65) (Rockwood, Andrew, Mitnitski, 2007), and Edmonton Frail Scale (r = 0.61) (Armstrong, Stolee, Hirdes, Poss, 2010). When compared with the Mini Mental State exam, the FI showed a strong negative correlation (r = -0.58) (Rockwood et al., 2007). The FI has also been used with dichotomized variables, with the frailty phenotype as a reference for measuring frailty; the FI had a sensitivity of 45.9 to 60.7% and specificity of 83.5 to 90% (Cigolle, Ofstedal, Tian, & Blaum, 2009; Kulminski et al., 2008).

Inpatient FI. Inpatient use of the FI has been documented. Krishnan et al. (2014) noted patients with hip fracture and higher FI scores had increased mortality and greater lengths of stay. Delirium and frailty was studied with older adults admitted to a general medicine floor, with poor prognosis noted if frailty and delirium present in an individual, and delirium was associated with higher frailty indices (Eeles et al., 2012). Dent et al.

(2014) evaluated frailty and the ability to predict poor outcomes in a geriatric unit, with measurements at discharge and six months later. Several different measurements of frailty were utilized to include the FI and phenotypic measurements; however, only the frailty index was able to show good prediction of poor outcomes both at discharge and six months. Joseph et al. (2015) compared risk of fracture between frail older adults and non-frail, using an FI. After adjustment for age, sex, injury severity, vital signs, and fracture development, an FI of 0.25 or greater was an independent risk factor for post-discharge dedicated care. Singh et al. (2012) noted frailty as significantly correlating to length of stay and predictor of poor function. Hatheway et al. (2017) used an inpatient frailty index based on the comprehensive geriatric assessment to explore the relationship between mobility recovery time and frailty in acute inpatient admission for the older adult. Evans et al. (2014) used an FI to assess predictive validity in acute care related to discharge, length of stay, and risk of mortality. Increased FI was associated with increased risk of death, long-term care, and length of stay. As noted, the FI has been used in multiple inpatient arenas with the older adult. Song, Mitnitski, and Rockwood (2010) posited an FI score of ≤ 0.08 as non-frail, FI ≥ 0.25 as frail, and the remainder as pre-frail. For purposes of this study, frailty was measured on a continuous scale, with 0.25 as the minimum score for frailty in an individual.

Data Analyses

All data were examined for missing data or outliers after initial randomized accuracy checks. Descriptive statistics were used to describe the study sample and outcomes such as frequency (*n*) and percentage (%) for categorical measures and mean

(*M*), standard deviation (*SD*), median (*Med*) and range for continuous measures. All analyses were performed in R statistical software v3.4.2 (R Core Team, 2017). A two-sided *p*-value < 0.05 was considered statistically significant.

The following questions, guided by the Accumulation of Deficits framework, (Figure 1) will be used for this research:

1. What sociodemographic variables are related to recurrent CDI admission?
2. What sociodemographic variables are related to frailty during an initial admission for CDI?
3. What is the prevalence of the frailty index variables among members of the sample?
4. What proportion of the sample has a frailty index score of 0.25 and above indicating frailty?
5. What is the relationship between the frailty index score during the initial admission for CDI and documented recurrence of CDI within a year?
6. What is the relationship between proton pump inhibitor (PPI) use prior to admission, frailty, and recurrent hospitalization for CDI?

For RQ1, sociodemographic variables were tested for differences between CDI patients with and without any recurrent admissions using Chi-square tests or Fisher's exact tests (if any expected counts < 5) for categorical variables and independent-samples *t*-tests or Mann-Whitney *U* nonparametric tests (if within-group Normality cannot be assumed) in bivariate analysis. Logistic regression with any recurrent CDI admission vs. none as the dependent variable was performed to identify sociodemographic factors in a

multivariable framework. Adjusted odds ratios (AORs) and their 95% confidence intervals (CIs) were estimated and reported. Logistic regression assumptions were checked according to Osborne (2015), including overall goodness-of-fit using Hosmer-Lemeshow testing.

For RQ2, Pearson correlations (r) or Spearman rho rank correlations (r_s) (if Normality cannot be assumed or outliers exist) along with scatterplots with linear and local regression (LOESS) trend fits were examined first in bivariate analyses among continuous sociodemographic variables (e.g., age) and frailty index scores. For categorical sociodemographic variables, bivariate analyses were performed using *t*-tests and analysis of variance (ANOVA) or Mann-Whitney *U* and Kruskal-Wallis tests (if within-group Normality cannot be assumed). Linear regression with frailty index score as the dependent variable (transformed by multiplying by 100%) was performed to identify sociodemographic factors in a multivariable framework. Unstandardized (b) and standardized (β) coefficients and their 95% CIs were estimated and reported. Linear regression assumptions, including linearity, homoscedasticity, independence, and Normality, were assessed with knowledge of the study design, analysis of residuals and Durbin-Watson statistics. Multicollinearity was assessed and presence of multicollinearity was considered to be any variance inflation factor (VIF) > 10.

For RQs 3 and 4, the percentage of CDI patients experiencing each individual frailty index deficit component was estimated. In addition, the mean frailty index score and percentage of patients with index score ≥ 0.25, defining frailty in this study, were estimated along with 95% CIs.

Analyses similar to those used to address RQ1 were used to investigate RQ5 in comparing frailty index scores on CDI patients with and without recurrence. Logistic modeling adjusted for sociodemographic factors in RQ1 results was performed to assess the association of frailty and CDI recurrence after accounting for sociodemographic characteristics. Analysis assumptions were again checked as appropriate.

For RQ6, a Chi-square test or Fisher's exact test (if any expected count < 5) was performed to test the association of proton pump inhibitor (PPI) use prior to admission and recurrent CDI vs. no recurrence in bivariate analysis. Additionally, the final logistic regression modeling from RQ4 was expanded to include PPI use prior to admission, and associations with recurrent CDI tested accordingly. Changes in the adjusted association of frailty index scores and CDI recurrence was noted and discussed. Logistic regression assumptions were again checked according to Osborne (2015).

Power and Sample Size

It was anticipated that data extracted from the electronic medical record from approximately 800 patients will be available over the study period. Further, it was anticipated that approximately 20% of patients will experience at least one CDI recurrence during this time-period (approximately 160 patients with ≥1 recurrent CDI admission). Statistical power and sample size considerations were therefore evaluated with these assumptions in mind along with exploring alternative scenarios. Among all planned analyses, the multivariable logistic regression analyses for RQ6, "What is the relationship between outpatient PPI therapy prior to admission, frailty, and recurrent hospitalization for CDI?", dictates the overall sample size requirement for the current

study as it is the most complex. The following table illustrates model size (number of independent variables (IVs) based on the required number of CDI recurrence events and total sample size (depending upon the prevalence of recurrent CDI) according to sample size guidelines evidence of 5 to 9 events per predictor variable (EPV) from Vittinghoff and McCulloch (2007):

Table 4. Required Number of Events and Sample Size by Prevalence of CDI Recurrence and Model Complexity

No. events	CDI recurrence prevalence (%)	Total sample size required	Total No. IVs using 5 EPV	Total No. IVs using 9 EPV
80	10%	800	16	8
80	20%	400	16	8
80	40%	200	16	8
160	10%	1,600	32	17
160	20%	800	32	17
160	40%	400	32	17
240	10%	2,400	48	26
240	20%	1,200	48	26
240	40%	600	48	26

Assuming 17 total independent variables (IVs) in a logistic regression, modeling frailty index score and PPI use prior to admission would leave 13 independent variables to accommodate sociodemographic characteristics, including hospital site. As evidenced in Table 4, this model size is appropriate given the measured characteristics and planned analyses for the study research questions of interest. With 17 IVs and conservatively assuming the stricter requirement of 9 events per IV (EPV) based on Vittinghoff and McCulloch (2007), a total of 153 CDI recurrence events are required. If the prevalence of CDI recurrence is 20% and conservatively rounding up to 160 events, a total sample size

of 800 patients is required under these assumptions. In particular for the adjusted association between frailty index score and CDI recurrence, an adjusted odds ratio (AOR) of 1.35 can be detected with sufficient power (≥80%), assuming a two-sided Type I error = .05, normal distribution of frailty index scores, and a squared correlation (ρ^2) of frailty index scores with other model included IVs of .20 and under similar other assumptions. If the squared correlation is higher, $\rho^2 = .50$, then an AOR = 1.46 can be detected with ≥80% power under all other similar assumptions.

Limitations

Due to the retrospective nature of this study, chart documentation was not complete or consistent on each individual. With older populations, the possibility remained that individuals may be deceased prior to a recurrence of CDI and for this study were considered as non-recurrent CDI cases. The assumption was made that routine laboratory studies, nursing care documentation, and admitting history and physicals would provide sufficient data for the frailty index to be calculated retrospectively. However, missing data was a limitation and resulted in the inability to apply the frailty index to the entire sample. In this case, those with all variables accounted for in the frailty index were used for analyses with questions specifically pertaining to frailty. Care was taken to ensure that once ICD-9 and ICD-10 codes were identified, that the individual's initial admission was verified and not a subsequent admission. Multiple admissions for the same individual required detailed and specific reports to be run using the specific diagnostic identifiers. All of these factors were considered while obtaining data and reporting the final study outcome in order to ensure validity.

Summary

The relationship between CDI in the frail older adult and recurrent CDI has not been explored extensively in the literature. The Accumulation of Deficits framework was used to guide this research study to explore the relationships proposed. The FI-CDI served as operationalization of frailty, including many variables that were easily attained from the electronic medical record. These findings contributed to a known knowledge gap in the literature regarding the relationship between frailty in the older adult and CDI.

CHAPTER IV

RESULTS

The findings from the retrospective cohort of existing medical record data are given in this chapter. This study explored the relationship between frailty and recurrent CDI in adults ages 55 years and older who were hospitalized for CDI infection in the acute care setting. The FI-CDI was used to measure frailty. Results for preliminary data analysis, sample characteristics, and research questions are given in this chapter.

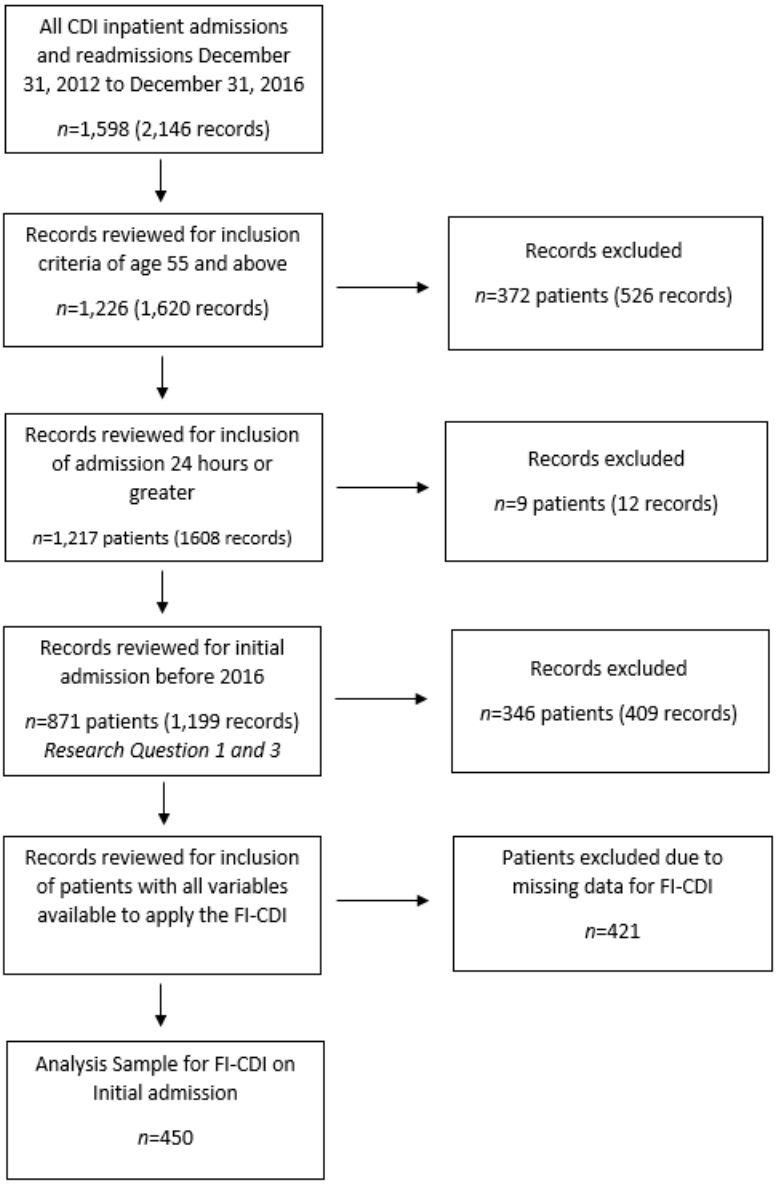
Preliminary Analysis

All CDI admissions and readmissions from December 31, 2012 to December 31, 2016 were extracted from the participating hospitals' database by hospital personnel. Three hospitals, serving the Triad area and surrounding counties, were sites of care for the study. After extraction, 1,598 patients had presented during this timeframe with 2,146 total admission records. Records were reviewed for inclusion and exclusion criteria, resulting in a final analysis sample of 1,199 admissions on 871 patients (see Figure 2). First, 372 patients under 55 years old were excluded. Next, nine patients had admissions that lasted less than one day and were additionally excluded. Finally, 346 patients presenting in 2016 were excluded from the final analysis sample, as these patients had less than a year of follow-up. Approximately half of the sample had data available for application of the FI-CDI on admission (*n*=450, 51.7%) and discharge (*n*=468, 53.7%). Due to missing data, FI-CDI was applied to 51.7% (n=450) of the original analysis

sample for specific research questions pertaining to frailty. Logistic regression for analyses was performed for those with non-missing data, as outlined in Table 16. Logistic regression used FI-CDI on initial admission for analyses, as this is the most accurate representation of initial frailty status upon initial presentation for CDI, prior to possible healthcare interventions.

Missing data was expected in this retrospective study, as not all laboratory markers may be indicated for each individual presenting. Furthermore, data for functional status/ADLs and psychosocial variables were not included for some individuals as documentation varies with healthcare staff. Documentation by healthcare staff was completed in the EHR with availability of multiple choices as noted in Table 3. The first availability of laboratory markers on admission were used as initial data for admission laboratory data, and the last recorded laboratory measures were used to indicate discharge laboratory markers. Non-missing data for analyses is documented further in the outlined tables per variable as indicated.

Figure 2. Study Flow Chart



Sample Characteristics

Among the 871 patients, the total number of admissions over the study period (between 12/31/2012 to 12/31/2016) ranged from one to ten, with 663 admitted just once (76.1% of 871; see Table 5). Additionally, there were 79 deaths during first admission (9.1%), where these patients were unable to be subsequently followed for CDI recurrence. The number of deaths by admission number are described in Table 6. The average age on initial admission for those who expired was 75.1 (*SD*=9.5), with the majority of those expired age 65 and older (*n*=67, 84.8%). Over half of those who expired were female (*n*=44, 55.7%), and the majority were White (*n*=56, 70.9%) followed by Black/African-American (*n*=19, 24.1%). The non-Hispanic population (*n*=78, 98.7%) was largely represented in those who expired (see Table 7).

Table 5. Number of Admissions by Year of Admission

Admissions	**2012**	**2013**	**2014**	**2015**	**2016**	**Total**
1	2	209	201	251	0	663
2	0	88	75	97	10	270
3	0	20	40	53	16	129
4	0	28	22	26	8	84
5	0	7	10	10	3	30
6	0	3	1	2	0	6
7	0	3	2	2	0	7
8	0	0	0	0	0	0
9	0	0	0	0	0	0
10	0	2	3	2	3	10
Total	2	360	354	443	40	1,199

**Note*. Total of 1,199 admissions among *N*=871 patients.

Table 6. Number of Deaths (Expired) by Admission

Admission #	No. with Admission	No. Deaths (%)
1	871	79 (9.1%)
2	208	10 (4.8%)
3	73	7 (9.6%)
4	30	4 (13.3%)
5	9	2 (22.2%)
6	3	0
7	2	0
8	1	0
9	1	0
10	1	0

Table 7. Demographic Characteristics of Patients who Expired on Initial Admission (*n*=79)

Characteristic	*M* ± *SD* or *n* (%)
Age at initial admission (years)	75.1 ± 9.5
55 to < 65	12 (15.2)
≥ 65	67 (84.8)
Sex	
Female	44 (55.7)
Male	35 (44.3)
Race	
American Indian	0
Asian	0
Black/African American	19 (24.1)
White	56 (70.9)
Other	3 (3.8)
unavailable	1 (1.3)
Ethnicity	
Hispanic	0
Non-Hispanic	78 (98.7)
unavailable	1 (1.3)

The prevalence of CDI recurrence over the study period was 23.9% (*n*=208) among the 871 patients (95% CI = [21.2%, 26.8%]). The average age on index admission was 73.6 years (*SD*=10.7), where 77.8% (*n*=678) were ages 65 and older. Females

comprised over half of the sample (*n*=510, 58.6%). The majority of the sample was White (*n*=609, 69.9%), followed by Black/African American (*n*=234, 26.9%), and only 0.9% (*n*=8) were Hispanic. The largest proportion of the patients were married (*n*=363, 41.7%), followed by widowed (*n*=245, 28.1%), single (*n*=122, 14.0%) and divorced (*n*=120, 13.8%) with respect to marital status.

Almost two-thirds (*n*=576, 66.1%) resided in a private residence prior to initial admission, followed by skilled nursing facility (*n*=125, 14.4%). About one-third of the patients were discharged to either home/self-care (*n*=279, 32.0%) or a skilled nursing facility (*n*=261, 30.0%) after initial admission. CDI recurrence was more prevalent for those discharged to a skilled nursing facility (37.5% vs. 27.6% with no recurrence) and home health care (24.5% vs. 15.2% no recurrence) ($p<0.001$). The average length of stay for an index admission was 8.8 days (*SD*=8.6), with average length of stay at index admission for those with eventual recurrent CDI admission was 8.9 days (*SD*=8.3). The average number of days from first discharge to first recurrent admission was 71.2 days (*SD*=41.7). Here, 77.9% of patients with any recurrence over the study period had greater than or equal to 30 days between first discharge and first recurrent admission (*n*=159). Sample characteristics are detailed further in Table 8 overall and by recurrence status.

Table 8. Patient Characteristics of the *Clostridium difficile* (CDI) Sample

Characteristic ***n* (%) or *M* ± *SD***	**Overall (*N* = 871)**	**Recurrent CDI (*n* = 208; 23.9%)**	**No recurrence (*n* = 663;76.1%)**	***P*-value**
Age at initial admission (years)	73.6 ± 10.7	73.3 ± 11.1	73.7 ± 10.5	0.640
55 to < 65	193 (22.2)	57 (27.4)	136 (20.5)	0.046
≥ 65	678 (77.8)	151 (72.6)	527 (79.5)	
Sex				0.712
Female	510 (58.6)	119 (57.2)	391 (59.0)	
Male	361 (41.4)	89 (42.8)	272 (41.0)	
Race[1]				0.797
American Indian	6 (0.7)	1 (0.5)	5 (0.8)	
Asian	3 (0.3)	1 (0.5)	2 (0.3)	
Black/African American	234 (26.9)	60 (28.8)	174 (26.2)	
White	609 (69.9)	144 (69.2)	465 (70.1)	
Other	16 (1.8)	2 (1.0)	14 (2.1)	
unavailable	3 (0.3)	0	3 (0.5)	
Ethnicity				0.317
Hispanic	8 (0.9)	0	8 (1.2)	
Non-Hispanic	856 (98.3)	207 (99.5)	649 (97.9)	
unavailable	7 (0.8)	1 (0.5)	6 (0.9)	
Marital status at 1st admission				0.247
Divorced	120 (13.8)	38 (18.3)	82 (12.4)	
Legally separated	15 (1.7)	2 (1.0)	13 (2.0)	
Married	363 (41.7)	80 (38.5)	283 (42.7)	
Single	122 (14.0)	33 (15.9)	89 (13.4)	
Unknown	6 (0.7)	1 (0.5)	5 (0.8)	
Widowed	245 (28.1)	54 (26.0)	191 (28.8)	
Residence prior to admission				0.791
Assisted living	28 (3.2)	9 (4.3)	19 (2.9)	
Group home	3 (0.3)	1 (0.5)	2 (0.3)	
Nursing home	5 (0.6)	1 (0.5)	4 (0.6)	
Other	15 (1.7)	3 (1.4)	12 (1.8)	
Private residence	576 (66.1)	129 (62.0)	447 (67.4)	
Skilled nursing facility	125 (14.4)	27 (13.0)	98 (14.8)	
missing	119 (13.7)	38 (18.3)	81 (12.2)	
Living arrangements *(all that apply)*				n/a
Spouse/significant other	287 (33.0)	63 (30.3)	224 (33.8)	
Alone	140 (16.1)	32 (15.4)	108 (16.3)	
Children	147 (16.9)	31 (14.9)	114 (17.2)	
Other	98 (11.3)	27 (13.0)	71 (10.7)	

Characteristic ***n* (%) or *M* ± *SD***	**Overall (*N* = 871)**	**Recurrent CDI (*n* = 208; 23.9%)**	**No recurrence (*n* = 663;76.1%)**	***P*-value**
missing	244 (28.0)	65 (31.3)	179 (27.0)	
Discharge plan at 1st admit				<0.001
Home/Self Care	279 (32.0)	65 (31.3)	214 (32.3)	
Short Term Hospital	10 (1.1)	0	10 (1.5)	
Skilled Nursing Facility	261 (30.0)	78 (37.5)	183 (27.6)	
Intermediate Care Facility	5 (0.6)	1 (0.5)	4 (0.6)	
Home Health Care Svc	152 (17.5)	51 (24.5)	101 (15.2)	
Left against/without/Elope	2 (0.2)	1 (0.5)	1 (0.6)	
Expired	79 (9.1)	0	79 (11.9)	
Federal Hospital	1 (0.1)	0	1 (0.6)	
Hospice/Home	19 (2.2)	0	19 (2.9)	
Hospice/Medical Facility	29 (3.3)	2 (1.0)	27 (4.1)	
Rehab Facility	14 (1.6)	3 (1.4)	11 (1.7)	
Long Term Care	18 (2.1)	7 (3.4)	11 (1.7)	
Another Institution (n.d.)	1 (0.1)	0	1 (0.2)	
Inpt rehab/Acute care hosp	1 (0.1)	0	1 (0.2)	
Proton pump inhibitor (PPI) use prior to admission	454 (52.1)	114 (54.8)	340 (51.3)	0.419
LOS in-hospital (days)	8.8 ± 8.6	8.9 ± 8.3	8.7 ± 8.7	0.369
No. CDI recurrences	0.4 ± 0.8	1.6 ± 1.0	-	n/a
0	663 (76.1)	0	663 (100)	
1	135 (15.5)	135 (64.9)	0	
2	43 (4.9)	43 (20.7)	0	
3	21 (2.4)	21 (10.1)	0	
4	6 (0.7)	6 (2.9)	0	
5	1 (0.1)	1 (0.5)	0	
6	1 (0.1)	1 (0.5)	0	
7	0	0	0	
8	0	0	0	
9	1 (0.1)	1 (0.5)	0	
Days from 1st discharge to 1strecurrent admission	71.2 ± 41.7	71.2 ± 41.7		n/a
< 30 days	45 (5.2)	45 (22.1)	-	
≥ 30 days	159 (18.3)	159 (77.9)		

**Note*. n/a = Not available. Left against/without/elope = left against medical advice, left without being seen, elopement. Another Institution n.d. = not defined.

Research Question 1

What sociodemographic variables are related to recurrent CDI admission?

In bivariate analyses, only age group at initial admission was statistically significantly related to recurrent CDI admission (p=0.046). Here, recurrent CDI was more prevalent (27.4% of those with recurrent CDI vs. 20.5% of no recurrence) in those 55 to 64 years old (22% of the sample) relative to patients ages 65 and older (72.6% with recurrent CDI vs. 79.5% of no recurrence). Interestingly, age at initial admission continuously was not significantly different between recurrence groups (73.3 years ± 11.1 vs. 73.7 ± 10.5, p=0.640). All other sociodemographic variables were not statistically significantly related to recurrent CDI admission (all p>0.100), and are subsequently detailed further next.

Sex, race, ethnicity, and marital status were not significantly related to recurrent CDI admission (see Table 8). Marital status was not statistically significantly related to recurrence, where some differences between recurrence groups were noted for those divorced (18.3% vs. 12.4% with no recurrence) and married (38.5% vs. 42.7% non-recurrence) but were not significant (p = 0.247). Composition of the recurrence groups were not significantly difference between those having a private residence prior to admission (62.0% of recurrent CDI vs. 67.4% without any recurrence, p=0.791). Multiple combinations of living arrangements prior to admission were available in the medical record, and the most common documented living arrangements included with spouse/significant other (n=287, 33.0%), alone (n=140, 16.1%), and with children (n=147, 16.9%). After multivariable logistic regression for recurrent CDI (see Table 16),

age continued to be an independent predictor for recurrent CDI when adjusting for other sociodemographics, frailty as measured by the FI-CDI, and PPI use prior to admission ($p < 0.05$ in all models). Specifically, the adjusted odds ratio for 55 to 64 years vs. ≥ 65 varied from 2.123 (in Model 2) to 2.088 (in Model 3). In Model 3 with all sociodemographic, frailty using FI-CDI, and PPI use, the odds of any CDI recurrence increased by 108.8% for those in the 55 to 64 year age group relative to ≥ 65, adjusting for frailty and all other variables in this model (AOR = 2.088, 95% CI = [1.216, 3.583], $p = 0.007$)

Research Question 2

What sociodemographic variables are related to frailty during an initial admission for CDI?

For purposes of this study, frailty was measured by the FI-CDI, with a cut-off of 0.25 and above indicating frailty. Analyses were performed with the FI-CDI (*n*=450, 51.7%). Sample characteristics of those with all variables for the FI-CDI are outlined in Table 9. The majority of this analysis sample was age 65 and older (*n*=334, 74.2%) and over half were female (*n*=256, 56.9%). White (n=316, 70.2%) and Black/African-American (*n*=118, 26.2%) races were predominant, and the Non-Hispanic population was largely represented (*n*=442, 98.2%).

In bivariate analyses for frailty indices (see Table 10), continuous age on initial admission was weakly but significantly positively correlated with frailty as measured by the FI-CDI (r_s =0.096, p = 0.043). When divided into clinically meaningful age groups,

patients of ages 55 to 64 had an average FI-CDI score of 0.34 (*SD*=0.11) relative to 0.38 (*SD*=0.10) for patients 65 and older (p=0.003).

Sex, ethnicity, and marital status were not significantly related to frailty during an initial admission for CDI as measured by the FI-CDI (see Table 10). The average female FI-CDI score was 0.37 (*SD*=0.11), similar to 0.37 (*SD*=0.09) for males. The average FI-CDI score was 0.40 (SD=0.07) among the 8 Hispanic patients.

Frailty scores were significantly higher for Black/African-American patients (0.40 ± 0.10) relative to White patients (0.36 ± 0.10) (overall p = 0.030, Holm adjusted pairwise comparison p = 0.029). Mean frailty scores for residence prior to admission were significantly different (p < 0.001); where skilled nursing facility (0.44 ± 0.07) and assisted living (0.43 ± 0.10) had the highest average FI-CDI scores. Those who expired at initial admission had an average FI-CDI score of 0.40 (*SD*=0.08).

Additionally, PPI use prior to admission was significantly related to FI-CDI (0.39 ± 0.10 vs. 0.35 ± 0.10 non-use, p<0.001). Length of stay in hospital was weakly-to-moderately positively significantly correlated with frailty for the FI-CDI (r_s = 0.239, p <0.001). The number of CDI recurrences was not significantly correlated with frailty by the FI-CDI (r_s= 0.056, p=0.236). The average frailty score for those without recurrence was 0.37 (*SD*=0.11) as measured by the FI-CDI. Average frailty scores for subsequent recurrences were similar (see Table 10). Days from first discharge to first admission showed low, non-significant correlation with frailty scores for the FI-CDI (r_s=0.110, p=0.250).

Table 9. Demographic Characteristics of Patients with FI-CDI (*n*=450)

Characteristic	***M* ± *SD* or *n* (%)**
Age at initial admission (years)	72.3 ± 10.6
55 to < 65	116 (25.8)
≥ 65	334 (74.2)
Sex	
Female	256 (56.9)
Male	194 (43.1)
Race	
American Indian	5 (1.1)
Asian	1 (<1.0)
Black/African American	118 (26.2)
White	316 (70.2)
Other	9 (2.0)
unavailable	1 (<1.0)
Ethnicity	
Hispanic	4 (<1.0)
Non-Hispanic	442 (98.2)
unavailable	4 (<1.0)

Table 10. Bivariate Analysis of Patient Characteristics and Frailty Index Scores (*n*=450)

Characteristic ***n* (%) or *M* ± *SD***	**FI-CDI** **(*n*=450; 51.7%)**	***P*-value**
Age at initial admission (years)	r_s = 0.096	0.043
55 to < 65	0.34 ± 0.11	0.003
≥ 65	0.38 ± 0.10	
Sex		0.941
Female	0.37 ± 0.11	
Male	0.37 ± 0.09	
Race[1]		0.030
American Indian	0.36 ± 0.11	
Asian	n/a	
Black/African American	0.40 ± 0.10	
White	0.36 ± 0.10	
Other	0.34 ± 0.16	

Characteristic ***n* (%) or *M* ± *SD***	**FI-CDI** **(*n*=450; 51.7%)**	***P*-value**
Marital status at 1st admission		0.072
Divorced	0.38 ± 0.10	
Legally separated	0.47 ± 0.06	
Married	0.36 ± 0.10	
Single	0.37 ± 0.11	
Widowed	0.38 ± 0.10	
Residence prior to admission		<0.001
Assisted living	0.43 ± 0.10	
Group home	0.39 ± 0.13	
Nursing home	n/a	
Other	0.39 ± 0.09	
Private residence	0.35 ± 0.10	
Skilled nursing facility	0.44 ± 0.07	
Discharge plan at 1st admit		<0.001
Home/Self Care	0.32 ± 0.11	
Transferred ST Hospital	n/a	
Skilled Nursing Facility	0.42 ± 0.08	
Intermediate Care Facility	n/a	
Home Health Care Svc	0.36 ± 0.09	
Left against/without/Elope	n/a	
Expired	0.40 ± 0.08	
Federal Hospital	n/a	
Hospice/Home	0.42 ± 0.08	
Hospice/Medical Facility	0.42 ± 0.08	
Rehab Facility	0.36 ± 0.08	
Long Term Care	0.40 ± 0.06	
Another Institution (n.d.)	n/a	
Inpt rehab/Acute care hosp	n/a	
Proton pump inhibitor (PPI) use prior to admission (Yes)	0.39 ± 0.10	<0.001
No	0.35 ± 0.10	

Characteristic ***n* (%) or *M* ± *SD***	**FI-CDI** **(*n*=450; 51.7%)**	***P*-value**
LOS in-hospital (days)	$r_s = 0.239$	<0.001
No. CDI recurrences	$r_s = 0.056$	0.236
0	0.37 ± 0.11	
1	0.38 ± 0.10	
2	0.37 ± 0.08	
3	0.39 ± 0.08	
4	n/a	
5	n/a	
6	n/a	
7	n/a	
8	n/a	
9	n/a	
Days from 1st discharge to 1st recurrent admission	$r_s = 0.110$	0.250
< 30 days	0.37 ± 0.10	0.184
≥ 30 days	0.40 ± 0.08	

**Note*. n/a = Not available. Left against/without/elope = left against medical advice, left without being seen, elopement. Another Institution n.d. = not defined.

Research Question 3

What is the prevalence of the frailty index variables among members of the sample?

The frailty index (FI) was comprised of laboratory markers, chronic diseases, functional status and activity of daily living, and psychosocial components. The laboratory markers comprising the FI for initial admission and discharge laboratory values are described in Table 11. Further description of the frailty index variables and comparisons between patients with and without recurrent CDI are outlined next. Overall sample characteristics were performed with non-missing data.

Laboratory Characteristics

Hypoalbuminemia, defined for this study as albumin less than 3 g/dL, was present on 54.6% of the sample at time of initial admission (*n*=443), and 75.1% (*n*=609) had an albumin less than 3 g/dL at initial discharge. The average albumin on admission was 2.86 g/dL (*SD*=0.68). Abnormal ALT was defined as less than 17 U/L or greater than 30 U/L, and over two-thirds (*n*=553, 70.2%) had abnormal ALT values as described at time of initial admission, and likewise at initial discharge (*n*=602, 74.6%). The average ALT on admission was 30.6 U/L (*SD* = 61.6*).* An elevated alkaline phosphatase, described as greater than 140 U/L on initial admission, was noted in 17.1% of the sample (*n*=138), with similar elevation noted in 14.3% of the sample at initial discharge (*n*=115). For those with at least one CDI recurrence, 15.4% (*n*=32) were elevated at initial admission and 11.1% (*n*=23) at initial discharge; there was no significant findings related to elevated alkaline phosphatase and recurrent CDI admission (all $p>0.100$). The average alkaline phosphatase on admission for the sample was 108.8 U/L (*SD*=78.5), and were similar for recurrent and non-recurrent CDI (see Table 11).

A low hemoglobin was defined as less than 11.5 g/dL for males and less than 11.0 g/dL females, respectively. The average hemoglobin (Hgb) for the sample on initial admission was 11.6 g/dL (*SD* =2.3), with an average Hgb 10.3 g/dL (*SD*=1.7) at discharge. There was no significant difference in the hemoglobin values for recurrent CDI versus non-recurrent CDI patients ($p=0.316$). About one-fifth of the male sample (*n*=181, 20.8%) had a low hemoglobin on initial presentation, where as 22.6% of females had similar presentation on admission with low hemoglobin (*n*=196).

An elevated creatinine, defined as greater than 1.2 mg/dL, was found in 52.1% (*n*=453) of the sample for initial admission. The average creatinine on admission was 2.1 mg/dL (*SD*=2.3), where the recurrent and non-recurrent groups were similar on average. There were no significant differences between groups related to elevated creatinine (all *p*> 0.100). BUN was also measured, with elevated BUN defined as greater than 28 mg/dL. The average BUN for the sample at initial admission was 33.5 mg/dL (*SD*=28.0), and were similar between the recurrent and non-recurrent groups. No significant finding was found related to elevated BUN and recurrent CDI at initial admission (*p*=0.846) or initial discharge (*p* = 0.143).

Leukocytosis defined as white blood cells greater than 9 K/uL or leukopenia, defined as white blood cells less than 3 K/uL, respectively, was noted in 64.1% (*n*=544) of the sample on initial admission. Specifically, leukocytosis was more prominent in the sample (*n*=518, 61.0%) on initial admission, and leukopenia was noted in 3.1% (*n*=26) on admission. The average WBC count was 12.8 K/uL on initial admission (*SD*=10.3) There was no statistically significant difference between recurrent and non-recurrent CDI patients for abnormal white blood cells (leukocytosis and leukopenia) at initial admission (*p*=0.757) or initial discharge (*p*=0.644).

Glucose levels averaged 144.9 mg/dL (*SD*=79.4) on initial presentation, with the majority of the sample (*n*=467, 53.9%) having greater than 120 mg/dL on initial admission. Over half of the sample was also found to have abnormal glucose levels (less than 70 mg/dL or greater than 120 mg/dL) on initial admission (*n*=496, 57.2%). No

significant differences were found with abnormal glucose levels at initial admission for recurrent and non-recurrent CDI patients (p=0.340).

Hyponatremia (sodium less than 135 mmol/L) and hypernatremia (sodium greater than 145 mmol/L) was noted in 35.4% of the sample on initial admission (n=308). Approximately one-third of the sample (n=277, 31.9%) were classified with hyponatremia on initial admission, and only a small proportion had hypernatremia (n=31, 3.6%) on admission. Sodium levels were not statistically significant by recurrent CDI status (all p> 0.100).

The average platelet count for the sample on initial admission was 241.6 K/uL (SD=115.1). Thrombocytopenia, defined as a platelet count less than 150 K/uL, was present in 19.3% (n=165) on initial admission. Thrombocytosis, defined as platelets greater than 400 K/uL, was noted in only 8.8% (n=75) on admission. No significant differences were noted in platelet counts by recurrent CDI status (all p> 0.100).

Table 11. Laboratory Characteristics of the *Clostridium difficile* (CDI) Sample

Characteristic ***n* (%) or *M* ± *SD***	**Overall (*N* = 871)**	**Recurrent CDI (*n* = 208; 23.9%)**	**No recurrence (*n* = 663; 76.1%)**	***P*-value**
1. Albumin (g/dL)				
At 1st admit (*n*=811; 93.1%)	2.86 ± 0.68	2.89 ± 0.67	2.85 ± 0.68	0.440
At 1st discharge (*n*=811; 93.1%)	2.53 ± 0.64	2.52 ± 0.59	2.53 ± 0.65	0.766
<3.0 at admit	443 (54.6)	103 (49.5)	340 (51.3)	0.750
<3.0 at discharge	609 (75.1)	142 (68.3)	467 (70.4)	0.643
2. ALT (U/L)				
At admit (*n*=788; 90.5%)	30.6 ± 61.6	28.7 ± 41.9	31.1 ± 66.5	0.815
At discharge (*n*=807; 92.7%)	30.6 ± 103.3	22.7 ± 24.8	33.0 ± 117.4	0.652
<17 at admit	405 (51.4)	103 (49.5)	302 (45.6)	0.247
>30	148 (18.8)	39 (18.8)	109 (16.4)	0.444
<17 or >30	553 (70.2)	142 (68.3)	411 (62.0)	0.044
<17 at discharge	453 (56.1)	116 (55.8)	337 (50.8)	0.167
>30	149 (18.5)	33 (15.9)	116 (17.5)	0.706
<17 or >30	602 (74.6)	149 (71.6)	453 (68.3)	0.252
3. Alkaline phosphatase (U/L)				
At admit (*n*=806; 92.5%)	108.8 ± 78.5	111.4 ± 87.5	108.0 ± 75.5	0.947
At discharge(*n*=806; 92.5%)	108.3 ± 100.9	109.3 ± 120.8	108.0 ± 94.0	0.975
>140 at admit	138 (17.1)	32 (15.4)	106 (16.0)	0.965
>140 at discharge	115 (14.3)	23 (11.1)	92 (13.9)	0.374
4. Hemoglobin (g/dL)				
At admit (*n*=870; 99.9%)	11.6 ± 2.3	11.5 ± 2.3	11.7 ± 2.3	0.316
At discharge(*n*=870; 99.9%)	10.3 ± 1.7	10.2 ± 1.6	10.4 ± 1.8	0.155
Male <11.5 at admit	181 (20.8)	49 (23.6)	132 (19.9)	0.301
Female <11.0	197 (22.6)	48 (23.1)	149 (22.5)	0.905
Male <11.5 at discharge	265 (30.5)	67 (32.2)	198 (29.9)	0.579
Female < 11.0	330 (37.9)	86 (41.3)	244 (36.8)	0.252
5. Creatinine (mg/dL)				
At admit (*n*=869; 99.8%)	2.1 ± 2.3	2.1 ± 2.2	2.1 ± 2.3	0.948
At discharge (*n*=869; 99.8%)	1.6 ± 1.8	1.6 ± 1.7	1.6 ± 1.8	0.711
>1.2 at admit	453 (52.1)	106 (51.0)	347 (52.3)	0.823
>1.2 at discharge	317 (36.5)	72 (34.6)	245 (37.0)	0.618
6. BUN (mg/dL)				
At admit (*n*=867; 99.5%)	33.5 ± 28.0	33.3 ± 26.8	33.5 ± 28.4	0.599
At discharge (*n*=869; 99.8%)	23.9 ± 23.6	21.4 ± 17.4	24.7 ± 25.2	0.701
>28 at admit	374 (43.1)	91 (43.8)	283 (42.7)	0.846
>28 at discharge	216 (24.9)	43 (20.7)	173 (26.1)	0.143

Characteristic *n* (%) or *M* ± *SD*	Overall (*N* = 871)	Recurrent CDI (*n* = 208; 23.9%)	No recurrence (*n* = 663; 76.1%)	*P*-value
7. White blood cells (K/uL)				
At admit (*n*=849; 97.5%)	12.8 ± 10.3	12.3 ± 6.9	13.0 ± 11.2	0.945
At discharge (*n*=849; 97.5%)	10.6 ± 9.5	9.6 ± 4.9	10.9 ± 10.5	0.892
<3 at admit	26 (3.1)	4 (1.9)	22 (3.3)	0.408
>9	518 (61.0)	125 (60.1)	393 (59.3)	1.000
<3 or >9	544 (64.1)	129 (62.0)	415 (62.6)	0.757
<3 at discharge	22 (2.6)	3 (1.4)	19 (2.9)	0.360
>9	402 (47.3)	96 (46.2)	306 (46.2)	0.927
<3 or >9	424 (49.9)	99 (47.6)	325 (49.0)	0.644
8. Glucose (mg/dL)				
At admit (*n*=867; 99.5%)	144.9 ± 79.4	144.2 ± 77.9	145.1 ± 79.9	0.946
At discharge (*n*=869; 99.8%)	127.5 ± 53.6	130.2 ± 53.9	126.7 ± 53.5	0.666
<70 at admit	29 (3.3)	3 (1.4)	26 (3.9)	0.129
>120	467 (53.9)	109 (52.4)	358 (54.0)	0.750
<70 or >120	496 (57.2)	112 (53.8)	384 (57.9)	0.340
<70 at discharge	12 (1.4)	1 (0.5)	11 (1.7)	0.312
>120	335 (38.6)	78 (37.5)	257 (38.8)	0.832
<70 or >120	347 (39.9)	79 (38.0)	268 (40.4)	0.608
9. Sodium (mmol/L)				
At admit (*n*=869; 99.8%)	136.5 ± 5.8	136.4 ± 4.7	136.5 ± 6.1	0.757
At discharge (*n*=869; 99.8%)	138.2 ± 4.8	137.7 ± 4.0	138.3 ± 5.0	0.177
<135 at admit	277 (31.9)	60 (28.8)	217 (32.7)	0.349
>145	31 (3.6)	5 (2.4)	26 (3.9)	0.419
<135 or >145	308 (35.4)	65 (31.3)	243 (36.7)	0.190
<135 at discharge	160 (18.4)	42 (20.2)	118 (17.8)	0.487
>145	49 (5.6)	7 (3.4)	42 (6.3)	0.150
<135 or >145	209 (24.1)	49 (23.6)	160 (24.1)	0.958
10. Platelets (K/uL)				
At admit (*n*=855; 98.2%)	241.6 ± 115.1	240.8 ± 121.7	241.8 ± 113.1	0.703
At discharge(*n*=868; 99.7%)	234.1 ± 113.5	234.9 ± 111.9	233.9 ± 114.1	0.943
<150 at admit	165 (19.3)	38 (18.3)	127 (19.2)	0.860
>400	75 (8.8)	13 (6.3)	62 (9.4)	0.213
<150 or >400	240 (28.1)	51 (24.5)	189 (28.5)	0.303
<150 at discharge	191 (22.0)	40 (19.2)	151 (22.8)	0.332
>400	77 (8.9)	17 (8.2)	60 (9.0)	0.809
<150 or >400	268 (30.9)	57 (27.4)	211 (31.8)	0.269

**Note*. All laboratory values correspond to the first available at admission and last available at discharge. Percentages overall are calculated with non-missing data. *P*-value is for comparing groups using *t*-test or Mann-Whitney *U* test for continuous variables and Chi-square or Fisher's exact test for categorical variables.

Chronic Disease Characteristics

Chronic diseases most common in this sample included hypertension (*n*=703, 80.7%), arthritis (*n*=384, 44.1%), cancer (*n*=362, 41.6%), and diabetes (Type 1 and Type 2) (*n*=356, 40.9%), as shown in Table 12. The chronic diseases found to be significantly more prevalent in recurrent CDI included hypertension (88.0% vs. 78.4%; *p*=0.003), heart failure (36.1% vs. 25.6%; *p*=0.005), and chronic kidney disease (34.1% vs 24.9%; p=0.011). Smoking status was assessed at time of admission, where 43.7% of the sample classified as former smoker (*n*=381), and 39.3% (*n*=342) classified as never smoker. More than half of the sample had ever smoked (*n*=515, 60.1%), with 63.9% of those with recurrent CDI (*n*=133) ever smoking relative to 57.8% without (*n*=383; *p*=0.169). The average BMI for the sample at initial admission was 27.0 kg/m^2 (*SD*=7.5), with 26.9% of the sample (*n*=199) having BMI greater than 30 kg/m^2 on initial admission. The recurrent and non-recurrent group had similar proportions of BMI greater than 30 kg/m^2, with 23.1% (*n*=48) of the recurrent group and 22.8% (*n*=151) of non-recurrent group (*p*=0.890).

Table 12. Chronic Diseases of the *Clostridium difficile* (CDI) Sample

Characteristic ***n* (%) or *M* ± *SD***	**Overall (*N* = 871)**	**Recurrent CDI (*n* = 208; 23.9%)**	**No recurrence *n* = 663; 76.1%)**	***P*-value**
11. Vitamin D deficiency	36 (4.1)	10 (4.8)	26 (3.9)	0.719
12. Arthritis	384 (44.1)	103 (49.5)	281 (42.4)	0.084
13. Hypertension	703 (80.7)	183 (88.0)	520 (78.4)	0.003
14. Stroke	223 (25.6)	63 (30.3)	160 (24.1)	0.092
15. Cancer	362 (41.6)	95 (45.7)	267 (40.3)	0.194
16. Diabetes (type 1 or 2)	356 (40.9)	95 (45.7)	261 (39.4)	0.125
17. COPD	228 (26.2)	55 (26.4)	173 (26.1)	0.993
18. Asthma	118 (13.5)	29 (13.9)	89 (13.4)	0.941
19. BMI (kg/m^2)				
At admit (*n*=740; 85.0%)	27.0 ± 7.5	26.9 ± 7.2	27.1 ± 7.6	0.782
At discharge (*n*=740; 85.0%)	27.2 ± 7.6	26.9 ± 6.9	27.3 ± 7.9	0.756
<18 at admit	41 (5.5)	11 (5.3)	30 (4.5)	0.745
>30	199 (26.9)	48 (23.1)	151 (22.8)	0.890
<18 or >30	240 (32.4)	59 (28.4)	181 (27.3)	0.702
<18 at discharge	43 (5.8)	10 (4.8)	33 (5.0)	1.000
>30	200 (27.0)	45 (21.6)	155 (23.4)	0.766
<18 or >30	243 (32.8)	55 (26.4)	188 (28.4)	0.762
20. Chronic Kidney Disease	236 (27.1)	71 (34.1)	165 (24.9)	0.011
21. Depression	221 (25.4)	63 (30.3)	158 (23.8)	0.076
22. Dementia	91 (10.4)	15 (7.2)	76 (11.5)	0.105
23. Heart Failure	245 (28.1)	75 (36.1)	170 (25.6)	0.005
24. Smoking Status				0.598
Current daily smoker*	110 (12.6)	27 (13.0)	83 (12.5)	
Current someday smoker*	16 (1.8)	6 (2.9)	10 (1.5)	
Former smoker*	381 (43.7)	97 (46.6)	284 (42.8)	
Never assessed	6 (0.7)	0	6 (0.9)	
Never smoker	342 (39.3)	74 (35.6)	268 (40.4)	
Passive smoke exposure*	2 (0.2)	0	2 (0.3)	
Smoker status unknown	11 (1.3)	3 (1.4)	8 (1.2)	
Ever smoking (*n* =857)	515 (60.1)	132 (63.5)	383 (57.8)	0.169

**Note*. *P*-value is for comparing groups using *t*-test or Mann-Whitney *U* test for continuous variables and Chi-square or Fisher's exact test for categorical variables. Overall percentages are calculated with non-missing data.

Functional Status and Activity of Daily Living Characteristics

Functional status and activity of daily living characteristics are given in Table 13. Over half of the sample was slightly limited with mobility (*n*=467, 57.4%) on initial admission, followed by very limited (*n*=239, 29.4%). The recurrent group had 60.1% (*n*=125) as slightly limited, compared to the non-recurrent group of 51.6% (*n*=342). About one-fifth of patients with recurrence (*n*=44, 21.2%) were very limited, compared to 29.4% very limited in the non-recurrent group (*n*=195). Performing Activities of daily living (ADLs) independently was noted in 51.1% (*n*=386) of the sample on initial admission, with no significant difference (*p*=0.836) in ADL performance for recurrent (*n*=89, 42.8%) and non-recurrent groups (*n*=297, 44.8%).

A score of 18 or less on the Braden scale is interpreted for individuals as at risk for pressure ulcers, and the average Braden scale score on initial admission for the sample was 16.3 (*SD*=3.1) in this study, with similar average scores for the recurrent (16.3 ± 2.9) and non-recurrent groups (16.3 ± 3.1). Over two-thirds of the sample (*n*=579, 71.1%) had a Braden scale score ≤ 18 on admission. There were no significant differences in prevalence of admission Braden score ≤ 18 by recurrent CDI status (*p*=0.948). Over one-quarter of the sample (*n*=236, 32.5%) had incontinence, and no significant difference in incontinence prevalence was noted for the recurrent group on admission (27.9% vs 26.8%, *p*=0.710).

Falls within the past six months were documented on 20.0% (*n*=131). No significant difference was noted in prevalence of falls within past six months for by recurrent CDI status (13.9% vs. 15.4% no recurrence, *p*=0.738). Fall risk at admission

was documented as low fall risk, moderate fall risk, and high fall risk. Over half of the sample (*n*=482, 59.1%) was classified as high fall risk. For those with recurrent CDI, the prevalence of high fall risk was 58.2% (*n*=121), similar when compared to non-recurrent group with 54.4% (*n*=361) (*p* = 0.306).

Polypharmacy, defined as seven medications or more on admission, was indicated for almost two-thirds of the sample on initial admission (*n*=569, 65.3%). The prevalence of polypharmacy was close to being significantly different by recurrence groups on admission (66.8% vs. 64.9%, p=0.060) and at discharge (66.8% vs. 64.6%, *p*=0.050).

Table 13. Functional Status and Activity of Daily Living of the *Clostridium difficile* (CDI) Sample

Characteristic ***n* (%) or *M* ± *SD***	**Overall (*N* = 871)**	**Recurrent CDI (*n* = 208; 23.9%)**	**No recurrence (*n* = 663; 76.1%)**	***P*-value**
25. Decreased Mobility,				
At admit (*n*=814; 93.5%)				0.059
Completely immobile*	27 (3.3)	7 (3.4)	20 (3.0)	
Very limited*	239 (29.4)	44 (21.2)	195 (29.4)	
Slightly limited*	467 (57.4)	125 (60.1)	342 (51.6)	
No limitation	81 (10.0)	15 (7.2)	66 (10.0)	
At discharge (*n*=814; 93.5%)				0.002
Completely immobile*	44 (5.4)	3 (1.4)	41 (6.2)	
Very limited*	214 (26.3)	46 (22.1)	168 (25.3)	
Slightly limited*	469 (57.6)	129 (62.0)	340 (51.3)	
No limitation	87 (10.7)	13 (6.3)	74 (11.2)	
26. Independently performs ADLs				
At admission (*n*=756; 86.8%)				0.836
Yes	386 (51.1)	89 (42.8)	297 (44.8)	
No	370 (48.9)	82 (39.4)	288 (43.4)	
At discharge (*n*=756; 86.8%)				0.911
Yes	384 (50.8)	88 (42.3)	296 (44.6)	
No	372 (49.2)	83 (39.9)	289 (43.6)	
27. Braden scale (points)				
(*n*=814; 93.5%)	16.3 ± 3.1	16.3 ± 2.9	16.3 ± 3.1	0.961
At discharge (*n*=814; 93.5%)	16.6 ± 3.5	16.9 ± 2.8	16.5 ± 3.7	0.904
≤ 18 at admission	579 (71.1)	135 (64.9)	444 (67.0)	0.948
≤ 18 at discharge	492 (60.4)	127 (61.1)	365 (55.1)	0.061
28. Incontinence (any yes)				
At admit (*n*= 727; 83.5%)	236 (32.5)	58 (27.9)	178 (26.8)	0.710
At discharge (*n*= 727; 83.5%)	216 (29.7)	53 (25.5)	163 (24.6)	0.746
29. Falls within past 6 mos.				
At admission (*n*=656; 75.3%)	131 (20.0)	29 (13.9)	102 (15.4)	0.738
At discharge (*n*= 656; 75.3%)	148 (22.6)	36 (17.3)	112 (16.9)	0.907
30. Fall Risk				
At admission (*n*=816; 93.7%)				0.306
Low fall risk (0-5)	163 (20.0)	38 (18.3)	125 (18.9)	
Moderate (6-13)*	171 (21.0)	33 (15.9)	138 (20.8)	
High fall risk (>13)*	482 (59.1)	121 (58.2)	361 (54.4)	
At discharge (*n*=816; 93.7%)				0.334
Low fall risk (0-5)	87 (10.7)	18 (8.7)	69 (10.4)	
Moderate (6-13)*	222 (27.2)	46 (22.1)	176 (26.5)	
High fall risk (>13)*	507 (62.1)	128 (61.5)	379 (57.2)	

Characteristic *n* (%) or *M* ± *SD*	Overall (*N* = 871)	Recurrent CDI (*n* = 208; 23.9%)	No recurrence (*n* = 663; 76.1%)	*P*-value
31. Polypharmacy (≥7 meds)				
At admit (*n*=748; 85.9%)	569 (76.1)	139 (66.8)	430 (64.9)	0.060
At discharge (*n*= 748; 85.9%)	567 (75.8)	139 (66.8)	428 (64.6)	0.050

**Note*. *P*-value is for comparing groups using *t*-test or Mann-Whitney *U* test for continuous variables and Chi-square or Fisher's exact test for categorical variables. Overall percentages are calculated with non-missing data.

Psychosocial Characteristics

Support systems for the sample were predominantly children (*n*=452, 51.9%), spouse/significant other (*n*=340, 39.0%), other relatives (*n*=173, 19.9%), and friends/neighbors (*n*=128, 14.7%). Those with and without recurrence had similar findings for support system on initial admission. Physical abuse was denied by 99.3% of the sample on initial admission (*n*=739), with no statistically significant findings for physical abuse by recurrent CDI status (*p*=0.172). Physical abuse was confirmed by 0.3% (*n*=2) on admission. Verbal abuse was also denied by 99.6% on initial admission (*n*=742), with no statistically significant findings for verbal abuse by recurrent CDI groups (*p*=0.534). Verbal abuse and sexual abuse were confirmed by 0.1% (*n*=1) on initial admission. Sexual abuse and self-neglect were denied by 99.9% (*n*=744) and 99.3% (*n*=740), respectively, on initial admission. Self-neglect was confirmed by 0.1% (*n*=1) on admission. No statistical significant findings were noted for sexual abuse or self-neglect by recurrent CDI status (both $p > 0.100$).

Table 14. Psychosocial Characteristics of the CDI Sample

Characteristic ***n* (%) or *M* ± *SD***	**Overall (*N* = 871)**	**Recurrent CDI (*n* = 208; 23.9%)**	**No recurrence (*n* = 663; 76.1%)**	***P*-value**
32. Support System				
At initial admission				n/a
(all that apply)				
Spouse/significant other	340 (39.0)	64 (30.8)	276 (41.6)	
Children	452 (51.9)	103 (49.5)	349 (52.6)	
Parent	20 (2.3)	8 (3.8)	12 (1.8)	
Other relatives	173 (19.9)	52 (25.0)	121 (18.3)	
Friends/neighbors	128 (14.7)	22 (10.6)	106 (16.0)	
Church/faith community	53 (6.1)	11 (5.3)	42 (6.3)	
Home care staff	14 (1.6)	2 (1.0)	12 (1.8)	
Case manager/social worker	1 (0.1)	0	1 (0.2)	
Other	20 (2.3)	19 (9.1)	1 (0.2)	
none*	7 (0.8)	1 (0.5)	6 (0.9)	
At discharge				n/a
Spouse/significant other	305 (35.0)	65 (31.3)	240 (36.2)	
Children	399 (45.8)	105 (50.5)	294 (44.3)	
Parent	21 (2.4)	8 (3.8)	13 (2.0)	
Other relatives	188 (21.6)	50 (24.0)	138 (20.8)	
Friends/neighbors	130 (14.9)	26 (12.5)	104 (15.7)	
Church/faith community	51 (5.9)	10 (4.8)	41 (6.2)	
Home care staff	6 (0.7)	2 (1.0)	4 (0.6)	
Case manager/social worker	1 (0.1)	0	1 (0.2)	
Other	37 (4.2)	19 (9.1)	18 (2.7)	
none*	8 (0.9)	2 (1.0)	6 (0.9)	
33. Physical Abuse				
At admit (*n*=744; 85.4%)				0.172
Denies	739 (99.3)	165 (79.3)	574 (86.6)	
Denies and provider concerned*	3 (0.4)	2 (1.0)	1 (0.2)	
Yes in past*	0	0	0	
Yes in present*	2 (0.3)	0	2 (0.3)	
At discharge (*n*=744; 85.4%)				0.172
Denies	739 (99.3)	165 (79.3)	574 (86.6)	
Denies and provider concerned*	3 (0.4)	2 (1.0)	1 (0.2)	
Yes in past*	0	0	0	
Yes in present*	2 (0.3)	0	2 (0.3)	

Characteristic *n* **(%) or** *M* ± *SD*	**Overall (*N* = 871)**	**Recurrent CDI (*n* = 208; 23.9%)**	**No recurrence (*n* = 663; 76.1%)**	***P*-value**
34. Verbal Abuse				
At admit (*n*=745; 85.5%)				0.534
Denies	742 (99.6)	166 (79.8)	576 (86.9)	
Denies and provider concerned*	1 (0.1)	1 (0.5)	0	
Yes in past*	1 (0.1)	0	1 (0.2)	
Yes in present*	1 (0.1)	0	1 (0.2)	
At discharge (*n*=745; 85.5%)				0.534
Denies	742 (99.6)	166 (79.8)	576 (86.9)	
Denies and provider concerned*	1 (0.1)	1 (0.5)	0	
Yes in past*	1 (0.1)	0	1 (0.2)	
Yes in present*	1 (0.1)	0	1 (0.2)	
35. Sexual Abuse				
At admit (*n*=745; 85.5%)				1.000
Denies	744 (99.9)	167 (80.3)	577 (87.0)	
Denies and provider concerned*	0	0	0	
Yes in past*	1 (0.1)	0	1 (0.2)	
Yes in present*	0	0	0	
At discharge (*n*=745; 85.5%)				
Denies	744 (99.9)	167 (80.3)	577 (87.0)	1.000
Denies and provider concerned*	0	0	0	
Yes in past*	1 (0.1)	0	1 (0.2)	
Yes in present*	0	0	0	
36. Self-Neglect				
At admit (*n*= 745; 85.5%)				0.159
Denies	740 (99.3)	166 (79.8)	574 (86.6)	
Denies and provider concerned*	4 (0.5)	0	4 (0.6)	
Yes in past*	0	0	0	
Yes in present*	1 (0.1)	1 (0.5)	0	
(*n*= 745; 85.5%)				1.000
Denies	742 (99.6)	167 (80.3)	575 (86.7)	
Denies and provider concerned*	3 (0.4)	0	3 (0.5)	
Yes in past*	0	0	0	
Yes in present*	0	0	0	

**Note*. *P*-value is for comparing groups using *t*-test or Mann-Whitney *U* test for continuous variables and Chi-square or Fisher's exact test for categorical variables. Overall percentages are calculated with non-missing data.

Research Question 4

What proportion of the sample has a frailty index score of 0.25 and above indicating frailty?

The FI-CDI was used to measure frailty in the sample. Due to missing data, the FI-CDI was available for calculation for 51.7% of the original sample (*n*=450) on admission and 53.7% of the original sample (*n*=468 at discharge).The FI-CDI revealed 89.1% (*n*=401) classified as frail at admission with an index score of ≥0.25 and 88.5% (*n*=414) at discharge, with 10.9% (n=49) non-frail at admission and 11.5% (*n*=54) non-frail at discharge. The FI-CDI average frailty scores were 0.37 (*SD*=0.10) on admission and 0.36 (*SD*=0.11) at discharge (see Table 15).

Figure 3 shows the distributions of FI-CDI by CDI recurrence status, with majority of those who recurred with an FI-CDI of 0.25 or greater (in overlapping purple). Boxplots of FI-CDI by CDI recurrence status are displayed in Figure 4. The median Fi-CDI score is higher than for those with CDI recurrence versus without recurrence. A few index score outliers are noted for patients with both non-recurrence and CDI recurrence.

Figure 3. Histograms of FI-CDI Measure by No Recurrence (Red) and CDI Recurrence (Purple)

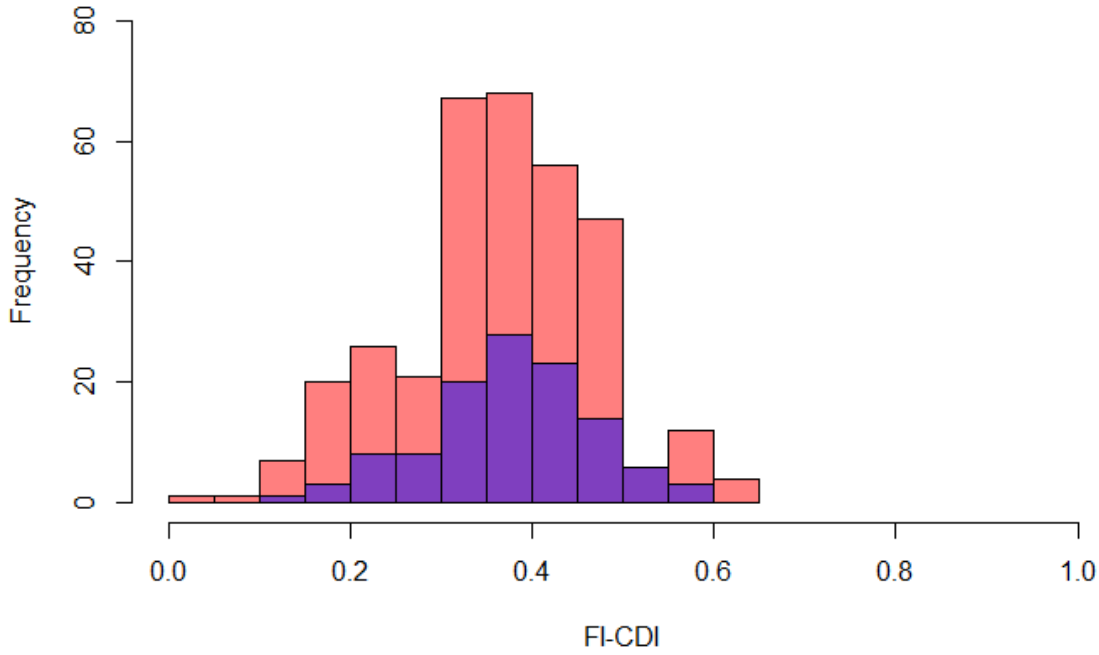
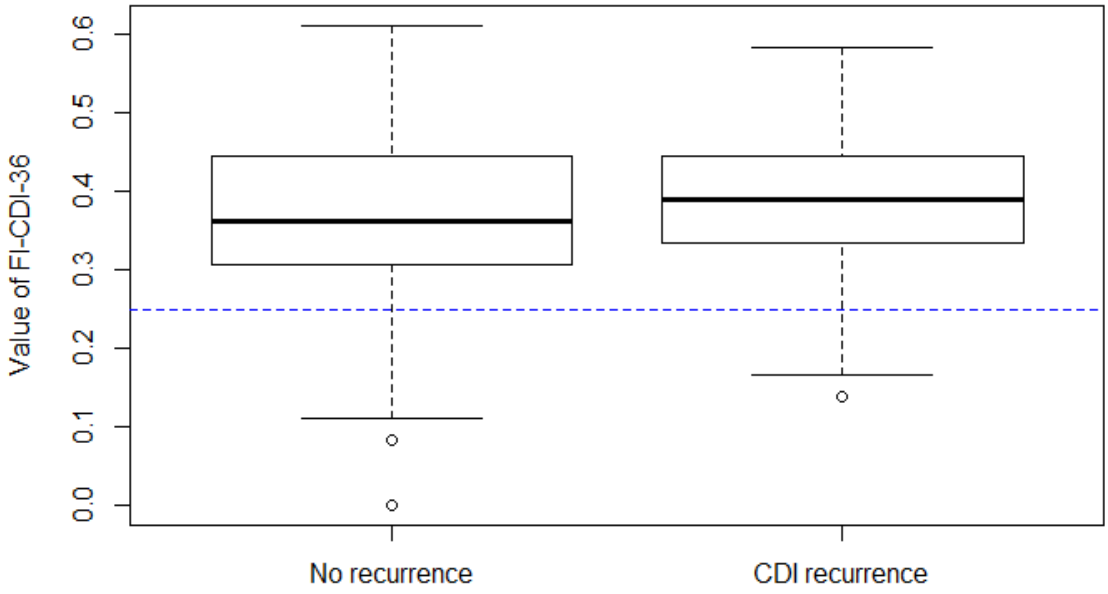


Figure 4. Boxplots of FI-CDI Measure by CDI Recurrence Status



Research Question 5

What is the relationship between the frailty index score during the initial admission for CDI and documented recurrence of CDI within a year?

The FI-CDI scores for recurrent CDI group on admission and discharge were both 0.38 (*SD*=0.09), compared to admit FI-CDI for patients without any recurrence (0.37 ± 0.11) and discharge (0.36 ± 0.11) (p = 0.223). The FI-CDI was able to be applied to 51.7% of the sample (n=450) at admission and 53.7% of the sample (n=53.7%) at discharge. For those with FI-CDI applied, 95.7% (n=111) of the recurrent CDI group had frailty scores ≥0.25 compared to 86.1% (n=303) of non-recurrent group at discharge, which was statistically significantly higher (p=0.008). While frailty was not found to be associated with CDI recurrence in these bivariate analyses at initial admission (p = .087), increased FI-CDI at initial admission was associated with increased odds of CDI recurrence after adjusting for sociodemographic factors. (AOR = 14.4, 95% CI = [1.120, 198.0], p = 0.043 (see Table 16).

Table 15. Bivariate Analysis of Frailty Index and Recurrent CDI Status

Characteristic ***n* (%) or *M* ± *SD***	**Overall (*N* = 871)**	**Recurrent CDI (*n* = 208; 23.9%)**	**No recurrence (*n* = 663; 76.1%)**	***P*-value**
FI-CDI at admit				
(*n*=450; 51.7%)	0.37 ± 0.10	0.38 ± 0.09	0.37 ± 0.11	0.223
At discharge (*n*=468; 53.7%)	0.36 ± 0.11	0.38 ± 0.09	0.36 ± 0.11	
≥ 0.25 (frailty) at admit	401 (89.1)	107 (93.9)	294 (87.5)	0.087
< 0.25	49 (10.9)	7 (6.1)	42 (12.5)	
≥ 0.25 (frailty) at discharge	414 (88.5)	111 (95.7)	303 (86.1)	0.008
< 0.25	54 (11.5)	5 (4.3)	49 (13.9)	

Research Question 6

What is the relationship between proton pump inhibitor (PPI) use prior to admission, frailty, and recurrent hospitalization for CDI?

Bivariate analyses and logistic regression for recurrent CDI was performed to assess the relationship between PPI use prior to admission, frailty and recurrent hospitalization for CDI. From logistic regression findings, PPI use prior to admission was not found to be significantly associated with recurrent CDI, when adjusting for frailty and sociodemographics (AOR=1.183, 95% CI=[0.727, 1.934], p=0.500).

Table 16. Logistic Regression from Hierarchical Model Building for Recurrent CDI (*N* =871)

AOR **(AOR 95% CI)** ***Z* value** ***P*-value**	**Model 1.** **Sociodemographics** **(*n* = 625)**	**Model 2.** **+FI-CDI** **(*n* = 383)**	**Model 3.** **+PPI use** **(*n* = 383)**
Age 55 to < 65 vs. ≥ 65 years	1.596 (1.014, 2.491) 2.044 0.041	2.123 (1.238, 3.637) 2.745 0.006	2.088 (1.216, 3.583) 2.676 0.007
Female vs. Male	0.963 (0.648, 1.437) -0.184 0.854	1.165 (0.711, 1.924) 0.603 0.547	1.140 (0.692, 1.890) 0.511 0.609
Non-White vs. White	0.988 (0.635, 1.516) -0.056 0.955	1.029 (0.592, 1.762) 0.105 0.917	1.050 (0.602, 1.804) 0.176 0.860
Not married vs. Married	1.131 (0.723, 1.770) 0.540 0.589	0.993 (0.558, 1.762) -0.023 0.981	1.006 (0.564, 1.785) 0.020 0.984
Private residence vs. Not private	1.041 (0.535, 2.162) 0.112 0.910	1.052 (0.470, 2.547) 0.119 0.905	1.082 (0.481, 2.629) 0.184 0.854
Live Alone vs. Otherwise	0.934 (0.558, 1.544) -0.263 0.793	0.969 (0.498, 1.858) -0.094 0.925	0.952 (0.489, 1.829) -0.145 0.884
Discharged Home/Self-care vs. Otherwise	0.734 (0.483, 1.106) -1.465 0.143	1.010 (0.594, 1.704) 0.036 0.971	0.997 (0.585, 1.684) -0.013 0.990
FI-CDI frailty index	-	14.4 (1.120, 198.0) 2.028 0.043	11.9 (0.873, 173.1) 1.843 0.065
PPI use prior to admission	-	-	1.183 (0.727, 1.934) 0.675 0.500

Summary

This chapter described the statistical analyses results for the exploration between frailty and recurrent CDI in the older adult. The sample was comprised of 871 patients ages 55 years and older who were hospitalized for CDI infection. The prevalence of recurrence for the study period was 23.9% (*n*=208), where patients in the sample had an average age of 73.6 years (*SD*=10.7) on admission and 9.1% expired during first hospitalization. Age remained significantly associated with recurrent admission in both bivariate analyses and logistic regression. Common co-morbidities included hypertension, arthritis, cancer, and diabetes for the sample. The FI-CDI measure of frailty applied to 450 patients on admission and 468 at discharge resulted in a prevalence of 89.1% frail on admission and 88.5% of patients at discharge.

FI-CDI scores were statistically significantly related to CDI recurrence after adjusting for sociodemographics. PPI use was found to not be associated in bivariate analysis or logistic modeling.

CHAPTER V

DISCUSSION

The purpose of this retrospective cohort study was to examine the relationship between frailty and recurrent CDI, specifically measuring frailty on an index admission with the researcher-derived FI-CDI. This chapter will discuss findings, limitations of study, implications for nursing, and recommendations for future research.

Accumulation of Deficits Framework

This study used the Accumulation of Deficits framework by Mitnitski, Mogilner, and Rockwood (2001), with operationalization of frailty performed through the researcher-derived frailty index, FI-CDI. This application of the FI-CDI is consistent with the clear guidelines by Searle and colleagues (2008), using variables associated with health, increasing with age, do not present early in the aging process, cover wide representation of organ systems, and used serially in the sample for measurement.

For purposes of this study, CDI was an acquired infection from the environment, illustrated as an external stress that results in physiological changes for the individual. The frailty index variables were interdependent deficits that could accumulate in a person. Due to the number of deficits affecting potential recovery time of an individual, higher frailty scores were hypothesized to result in impairment and affect recovery time, potentially increasing the risk of recurrent CDI and hospital readmission. The FI-CDI, applied to 51.7% (*n*=450) of the original sample, revealed frailty prevalence of 89.1%

frail on admission. After adjusting for sociodemographics, frailty was statistically significantly related to CDI recurrence. This finding supported the framework, as the presence of the external stressor CDI on a frail individual was significantly associated with recurrence. This finding is consistent with impairment to fully recover in the presence of frailty, with subsequent recurrence and actual hospital admission. Furthermore, although older adults are at risk for recurrent CDI, chronological age does not completely explain this phenomenon (Collins et al., 2015).

Sample

All CDI admission and readmission from December 31, 2012 to December 31, 2016 were extracted from the participating hospital database by approved hospital personnel, and 871 patients qualified for the study with a total of 1,199 admissions. The sample size of this study was higher than three recently reported studies that examined the relationship between frailty and CDI. Milani et al. (2016) reported 84 subjects, while Venkat et al. (2016) reported 483 subjects. Behar and colleagues (2017) had a total sample size of 727 participants, but 410 were carriers without active CDI. The average age on initial admission for this study was 73.6 years (SD=10.7), similar to other studies (Milani et al., 2016; Van Esch et al., 2015; Venkat et al., 2016). Females comprised 58.6% (n=510) of the overall sample, which is close to national trends of 64-65% female representation for CDI (Shrestha, Bime, & Taleban, 2018).

CDI recurrence over the study period was 23.9%, which is consistent with estimate recurrence rates of 10-40% after initial admission (Collins et al., 2015; Garey et al., 2008; Kelly & LaMont, 2008). The majority of the sample had recurrences greater

than or equal to 30 days between first discharge and subsequent recurrent admission. Although recurrent CDI usually happens within one to three weeks after antibiotic completion, recurrence can be months later (Cohen et al., 2010; Chopra & Krishna, 2014; McDonald et al., 2007), as found in this study.

CDI recurrence was more prevalent for those discharged to a skilled nursing facility and home health care services. Collins et al. (2015) reported differing results that skilled nursing facility, hospice, and long-term care actually decreased the odds of CDI readmission. The average length of stay for an index admission was 8.8 days, with average length of stay at index admission for those with eventual recurrent CDI admission 8.9 days; this is slightly higher than a recent national estimate of 5.8 days for CDI admission (Shrestha, Bime, & Taleban, 2018).

Interpretation of Findings

Research Question 1

What sociodemographic variables are related to recurrent CDI admission?

Sociodemographic variables and recurrent CDI admission were examined for the initial 871 patients. Sex, race, ethnicity, and marital status were not associated with recurrent CDI admission. Interestingly, literature supports African-American race as an independent risk factor for recurrent CDI (Argamany et al., 2016; Freedberg et al., 2013), which was not found in this research study. Age was the only sociodemographic variable related to recurrent CDI admission. Recurrent CDI was more prevalent in the ages 55 to 64 years old compared to patients ages 65 and older. Age also remained an independent predictor for recurrent CDI after multivariable logistic regression for recurrent CDI

(Table 16). The odds of any CDI recurrence in the 55 to 64 year age group increased by 108.8% compared to age 65 and older, after adjusting for sociodemographics, frailty, and PPI use. This finding is in contrast to literature which supports increased risk of recurrence with increasing age (Louie et al., 2013). Collins et al. (2015) also did not find increasing age related to CDI readmission in a sample of persons ages 65 and older.

Research Question 2

What sociodemographic variables are related to frailty during an initial admission for CDI?

Continuous age on initial admission weakly correlated with frailty. Frailty prevalence is known to increase with age (Clegg et al., 2013). The frailty index of an individual increases an average of 10-fold between ages of 20 and 90 (Theou et al., 2015). In prior research, frailty scores have shown to be higher in women versus men regardless of the variable combination (Mitnitski & Rockwood, 2015). Moreover, in this study, the average FI-CDI score for females was similar to males. Sex, ethnicity, and marital status were not significantly associated with frailty. However, frailty scores were significantly higher for African-American patients compared to Caucasian patients. This is consistent with literature that frailty prevalence is higher (65-85% more) among those African-American versus Caucasian (Bandeen-Roche et al., 2015). Statistically significant differences were noted with place of residence prior to admission, as patients living in skilled nursing facility and assisted living facilities had the highest average frailty scores, which is also consistent with increased frailty prevalence for institutional care (Bandeen-Roche et al., 2015).

The average FI-CDI score for those who expired on initial admission for CDI was 0.40. A frailty score of 0.40 and above has shown sensitivity and specificity for adverse outcomes including inpatient mortality (Hubbard et al., 2017). The frailty index is associated with poor health outcomes, with a maximum possible frailty score around 0.7 (Theou et al., 2015). The length of stay was weakly to moderately positively significantly correlated with frailty; yet the number of CDI recurrences showed no significant correlation with frailty. Frailty has been correlated with length of stay in the literature, similar to findings in this retrospective study (Drubbel et al., 2014; Evans et al., 2014; Singh et al., 2012). Interestingly, no significant correlation was noted with frailty and days between admissions for CDI. Murphy and colleagues (2012) noted that the risk of readmission for CDI after all-cause hospitalization was highest within 12 weeks after discharge, with risk of readmission decreasing thereafter. Hospital presentation for reasons other than CDI was not included in this study.

Research Question 3

What is the prevalence of the frailty index variables among members of the population?

The most prevalent co-morbidities in the sample included hypertension, arthritis, cancer, and diabetes; diabetes is known as a risk factor for frailty, and it also is an independent risk factor for treatment failure of CDI (Jung et al., 2010; Zaslavsky, et al. 2016). Cancer and arthritis are both known for association with frailty and subsequent adverse effects (Cacciatore et al; 2014; Perez-Zepeda et al., 2016). In this study, hypertension, heart failure, and chronic kidney disease was found to be significantly more

prevalent in recurrent CDI. The burden of diseases and co-morbidities have been predictive of increased risk for CDI recurrence (Collins et al., 2015). Severe CDI has also been associated with heart failure (Rao et al., 2013). Although this study did not include severity of CDI, the significant prevalence of heart failure in those who recurred should prompt thorough investigation into other co-existing co-morbidities at time of admission. Thorough assessment of the patient with a known history of heart failure may serve to decrease risk of recurrence if co-existing health conditions are closely monitored while inpatient and in follow-up.

As the average Body Mass Index (BMI) was 27.0 kg/m^2 and 26.9% had a BMI greater than 30 kg/m^2, nutritional needs remain a concern. The obese patient has also been found frail as well, with concerns for sarcopenic obesity in the setting of increased body fat and decreased skeletal muscle (Cooper et al., 2012). Sarcopenic obesity is linked with impaired mobility in the older adult, contributing to frailty.

Over half of the sample had a history of smoking at some point during the lifespan, and 12.6% of the sample endorsing daily smoking. As known in the literature, this lifestyle behavior contributes to frailty progression (Kojima et al., 2017; Ulley & Abdelhafiz, 2017). Although prevalence of current daily smokers, former smokers, and ever smoking in lifetime was similar for recurrent and non-recurrent group, this lifestyle habit contributes to the potential for frailty over time.

Laboratory abnormalities most present in the sample included hypoalbuminemia, abnormal ALT, low hemoglobin, elevated creatinine, elevated BUN, leukocytosis, elevated glucose level, and hyponatremia. Leukocytosis and hypoalbuminemia are

biomarkers that are not only contributors to the development of frailty but strongly associated with mortality in the hospitalized older adult (Fontana et al., 2013). Low or low normal hemoglobin has been shown to be an independent risk factor for frailty (Chaves et al., 2005). Sodium imbalances may be a culprit for hospitalization, falls, and mental status changes, contributing to frailty (Morley, 2015). Elevated creatinine is considered a risk factor for 30-day mortality in the older adult with CDI, and individuals with chronic kidney disease were more likely to have CDI recurrence.

Although over half of the population had slightly limited mobility, over half of the sample was high fall risk, increasing risk for future falls. In addition, 20.0% of the sample had fallen within the past six months at time of admission; with frailty as a predictor of future fall risk, the notable prevalence of fall risk in the sample is concerning (Li et al., 2014; Liu et al, 2016; Sanchez-Garcia et al., 2017). Over two-thirds had a Braden score ≤ 18, which is a reflection of multiple domains that contribute to the frailty trajectory (Ogg, 2016). The combination of increased fall risk, mobility impairment, and nutritional issues are factors that contribute to frailty and decline. Recognition of these deficits are imperative in the hospital setting.

Support systems were documented as present in the majority of the sample, including children, spouse/significant other, other relatives, and friends/neighbors, and less than one percent reported physical and verbal abuse in present. Self-neglect was reported in less than one percent in present. The psychosocial domain should be recognized, as the lack of psychosocial support is a known contributor to frailty (Hoogendijk et al., 2014a). Those with solitary living arrangements have been associated

with frailty (Ng et al., 2014), while those with increased social support have been associated with decreased frailty Woo et al., 2005). Physical abuse, verbal abuse, sexual abuse, and self-neglect were largely denied by the sample but recognition of elder abuse is paramount in providing care. Risk factors for elder abuse including frailty, physical decline, and difficulty with ADLs, should be assessed during acute hospitalizations of this vulnerable population, as literature has approximated 6% of older community-dwelling adults as victims of abuse (Cooper et al., 2008). Self-neglect, also leading to greater likelihood of frailty, has been shown to be an independent risk factor for early demise (Papaioannaou et al., 2012). Frailty may precipitate worsening self-neglect; therefore, careful assessment of the older adult is necessary for intervention as appropriate.

Research Question 4

What proportion of the sample has a frailty index score of 0.25 and above indicating frailty?

The FI-CDI was used to measure frailty of those in the sample with all FI-CDI variables available (n=450), with 89.1% frail on admission. Prior research utilizing various frailty indices have estimated a wide range of frailty prevalence, depending on outcome and population studied. When using a frailty index for acutely hospitalized older adults, prevalence of frailty ranged from 27% to 87.1% (Chong et al., 2017; Dent et al., 2014; Eeles et al., 2012; Joseph et al., 2015; Krishan et al., 2014; Patel et al., 2014). The majority of the analysis sample with FI-CDI applied was frail, which was consistent with the upper limits of frailty prevalence already reported in the literature for hospitalized

older adults. However, reported frailty prevalence in the specific population of those with acute hospitalization for CDI is sparse. Known existing studies using a frailty index with CDI patients have been in the outpatient setting or utilizing a modified frailty index in the post-surgical setting for complicated CDI; these did not report frailty prevalence of the sample in findings (Van Esch et al., 2015; Venkat et al., 2016).

Research Question 5

What is the relationship between the frailty index score during the initial admission for CDI and documented recurrence of CDI within a year?

The majority of those who had recurrent CDI admission were classified as frail on initial admission, without a significant difference in average continuous FI-CDI scores for recurrent and non-recurrent group. However, there was a significant difference in frailty prevalence for the recurrent CDI group at discharge compared to the non-recurrent group at discharge. Additionally, although initial admission frailty was not associated with CDI recurrence in bivariate analyses, an increased continuous frailty score was associated with increased odds of CDI recurrence after adjusting for sociodemographic variables, which contributes to the knowledge gap of the relationship between frailty and recurrent CDI. This research study provides new knowledge, as prior studies examining CDI and frailty have not examined recurrent CDI and frailty (Behar et al., 2017; Milani et al., 2016; Van Esch et al., 2015; Venkat et al., 2016). Behar et al. (2017) reported asymptomatic carriage of *Clostridium difficile* had a higher likelihood of prior CDI and were more frail than non-carriers, but frailty was described by assessing malnutrition and activities of daily living. Milani et al. (2016) measured frailty in older adults (65 and

older) with the Clinical Frailty Scale, noting similar frailty scores in those with CDI and those without CDI. Van Esch et al. (2015) used a frailty index that showed no difference in frailty index scores between CDI group and non-CDI group. Finally, Venkat et al. (2016) reported increased modified frailty index scores predicting morbidity and mortality of those who had undergone colectomy for CDI due to complicated/severe features. These studies did not examine recurrent CDI and frailty, which this study has done and contributed to a knowledge gap in the literature.

Research Question 6

What is the relationship between proton pump inhibitor (PPI) use prior to admission, frailty, and recurrent hospitalization for CDI?

PPI use prior to admission was found to be significantly associated with frailty on admission in bivariate analysis; however, PPI use prior to admission was not significantly associated with recurrent CDI, adjusting for frailty and sociodemographics. PPI use has been associated with increased risk for CDI incidence and recurrence (Linsky et al., 2010; McDonald et al., 2015; Roughead, Chan, Choi 2016; Trifan et al., 2017), but literature is mixed regarding findings. As PPI use was not significantly associated with recurrent CDI in this study, further research is needed to assess relationship and possible confounding variables.

Limitations of the Study

There are several limitations of this study due to the retrospective design of this cohort study and use of electronic health record. Laboratory values were assessed with the first available value and last value at discharge; however, timing of laboratory

analysis could vary across the sample with time obtained and resulted. The majority of laboratory values for the FI-CDI are obtained when providing care for acute presentation to the hospital, including complete blood count, comprehensive metabolic panel or basic metabolic panel. When using EHR data, specific patient characteristics may not always be accurately and completely documented by clinical staff and providers. Patients who expired during the initial admission were excluded from further analyses regarding recurrence. Information about antibiotic exposure prior to presentation for initial and recurrent admission was not obtained, as this was not available for this study. During hospitalization, the severity of CDI was not able to be determined, nor was the level of care such as intensive care, general admission, and treatment regimen. Discharge disposition was captured for the sample, but this does not describe events after discharge such as compliance with outpatient treatment, appropriate sanitization of the living environment, presentations to other hospital system, support system at home, and even death. Additionally, it is unknown if discharge locations for individuals were the same as pre-admission, as the prevalence of recurrent CDI was greater in those discharged to skilled nursing facility or home health care after initial admission. Hospital-acquired or community-acquired CDI was unable to be determined from this study, which could affect recurrence and morbidity. Although care was taken to define an initial admission, the researcher does not know if it was truly their first lifetime admission for CDI; however, the study period allowed review of admissions to determine presentation. If an individual had been admitted several years before the data that was used for this study,

the CDI presentation was likely from a different strain and would not be defined as a recurrence due to significant span of time between admissions.

Implications for Nursing

Nursing staff and advanced practice nurses have the opportunity to recognize the presence of frailty on admission for an acutely hospitalized patient with CDI. Hospitalized frail older adults are at risk for prolonged recovery during and after hospitalization, increased length of stays, need for higher acuity of care, and have an increased mortality rate compared to non-frail individuals (Hatheway et al., 2017; Muscedere et al., 2017; Vermeiren et al., 2016). The deficits that comprised the FI-CDI noted multiple clinical domains and laboratory values that were abnormal, capturing a snapshot of function for organ systems, which could be intervened upon to promote health and recovery and mitigate frailty (Howlett & Rockwood, 2013). Specifically, a large portion of the sample displayed hypoalbuminemia, raising concern for malnutrition and need to address nutrition during hospitalization and post-discharge. Hypoalbuminemia is associated with the development of frailty and mortality, thus attention to this is warranted (Fontana et al., 2013). Addition of nutritional supplementation and palatable flavors could be used to improve calorie intake and stimulate appetite (Lucas & Kennedy-Malone, 2014). BUN and creatinine were elevated in approximately half the sample, which is likely multifactorial in the setting of acute diarrheal illness, and this improved through hospitalization. However, close attention to laboratory markers during admission are vital to care of the whole patients, as

hypoalbuminemia and elevated creatinine are risk factors for 30-day mortality in the older adult with CDI (Bloomfield et al., 2012; Leibovici-Weissman et al., 2017).

Approximately two-thirds of the sample had a Braden scale less than 18, raising concern for pressure ulcer risk (Braden & Bergstrom, 1994), and bedside nursing has the opportunity to intervene directly with mobility measures, frequent turning, serial assessment and detailed documentation. Intervention to reduce pressure ulcer risk will in turn address an aspect that is one of many contributors to frailty.

Frailty recognition is vital to provide care and intervention as appropriate. Use of the FI-CDI includes multiple potential deficits that are associated with the frailty trajectory, consistent with the Accumulation of Deficits approach. Instead of focusing only on individual domains such as fall risk and Braden scale scores, incorporating multiple domains provides a larger range of intervention opportunity to potentially change the frailty pathway. Identifying an FI-CDI score of 0.25 and greater provides a classification for frailty. In addition, using a continuous score provides more precise measurements of frailty and prediction of adverse outcomes. Scores of 0.4 and above raise concern for ADL dependence and a significantly higher risk of mortality (Hubbard et al., 2017). Each increase of 0.1 has been shown to be associated with increased incidence of adverse outcomes (Hubbard et al., 2017). Identifying FI-CDI scores on admission will guide interventions and care throughout the hospitalization and post-discharge.

Interestingly, initial frailty prevalence on admission was not associated with recurrent CDI, but discharge frailty prevalence was significant for recurrent CDI. This

finding raises the need for identification of frailty throughout hospitalization instead of only on admission. Utilization of EHR may calculate a frailty score quickly, as this data is readily available on admission. The FI-CDI may be efficiently calculated with existing EHR data, triggering interventions from a multidisciplinary standpoint. For instance, variables in the FI-CDI that are abnormal could trigger nutrition consults, physical therapy, psychological support, pharmacy support, and internists support through awareness of chronic diseases present that may be overlooked due to focusing on acute illness.

Proper sanitization of living arrangements must be reviewed with individuals returning home, as spores are known to survive up to months on surfaces, even in harsh environments (Keller & Surawicz, 2014). Patient education is paramount in preventing the spread of CDI. Education should begin during hospitalization, as proper hand washing and sanitization while inpatient may help decrease health-care acquired infections. Transport from hospital to other facilities via hospital-approved transport or emergency medical services should exercise contact precautions to decrease risk of CDI transmission of a known or suspected infected individual.

During inpatient admission, patients should be placed in a private room with dedicated bathroom and equipment; however, in nursing homes or other facilities, private rooms may not be available. If private rooms are not available for those infected or known colonized status, patients should be grouped together with same infecting organism (McDonald et al., 2018). Contact precautions should be followed, and discontinuation of precautions may be considered if resolution of diarrhea is documented

for at least 48 hours (McDonald et al., 2018). Cleaning of rooms and any reusable equipment must be performed with a United States Environmental Protection Agency appropriate sporicidal bleach disinfectant (McDonald et al., 2018). Disinfecting with "no-touch" methods such as ultraviolet radiation or hydrogen peroxide vapor has been employed by facilities but limited data exists and further research is needed. Daily inpatient disinfecting of surfaces is recommended, coupled with appropriate contact precautions, washing of hands with soap and water, and dedicated equipment (McDonald et al., 2018). As an outpatient, all surfaces should be cleaned with bleach, hand washing with soap and water, and dedicated bathroom if possible.

Since 2013, hospitals that participate in the Centers for Medicare and Medicaid Services (CMS) Hospital Inpatient Quality Reporting Program have reported CDI infection data to the National Healthcare Safety Network, with the goal of movement towards prevention of CDI (Centers for Disease Control and Prevention, 2015b). The U.S. Department of Health and Human services also have target reductions of 30% for facility onset of CDI and CDI hospitalizations by 2020 (Centers for Disease Control and Prevention, 2015b). Therefore, as increased frailty scores on admission is associated with increased odds of CDI recurrence, findings suggest that assessment and targeted intervention for the frail older adult may decrease the possibility of readmission for CDI recurrence. Ensuring nutritional and hydration needs are met and early mobilization of hospitalized individuals is recommended as necessary interventions to decrease geriatric syndromes that contribute to frailty (Hatheway et al., 2017; Hubbard et al., 2017).

Recommendations for Future Research

This study confirms the need for future research regarding recurrent CDI, age, and frailty. The present study noted a significant finding of younger age (55 to 64) related to recurrent CDI relative to patients 65 and older. When age was measured continuously, no significant difference between recurrence and non-recurrence groups were noted. Yet, age (55-64) remained an independent predictor for recurrent CDI when adjusting for other sociodemographics, frailty, and PPI prior to admission. Future studies could explore other variables such as severity of course, acuity level, hospital-acquired or community-acquired infection, and discharge follow-up to assess compliance with treatment regimen.

Frailty prevalence in hospitalized older adults with CDI needs further research, as existing literature is sparse. Applying the FI-CDI on admission and discharge is necessary to capture this patient population and determine overall frailty prevalence. Further replication of the FI-CDI could be used in prospective studies to determine risk of adverse outcomes beyond CDI recurrence and readmission. In this study, the FI-CDI was an assessment of frailty status, whereby future research could employ the FI-CDI as a tool to predict adverse outcomes to include readmission for other reasons, institutionalization, and emergency room presentation, as the deficit accumulation approach has been shown to significantly predict mortality and hospitalization (Vermeiren et al., 2016). A meta-analysis by Vermeiren et al. (2016), reviewed 31 articles for frailty measurements and prediction of adverse outcomes. The deficit accumulation approach was used in seven of these articles, with findings of significantly

predicting mortality and hospitalization (Vermeiren et al., 2016). Therefore, using the FI-CDI for purposes beyond prediction of CDI recurrence needs further exploration.

Future research is also needed to explore PPI use and CDI risk and recurrence, as this remains controversial in the literature (Freedberg et al., 2013; Linksy et al., 2010; McDonald et al., 2015; Roughead et al., 2016; Trifan et al., 2017). Although PPI use prior to admission was significantly associated with frailty in bivariate analyses, PPI use was not significantly associated with recurrent CDI. Prospective studies capturing other possible cofounders such as antibiotic exposure prior to admission, choice of antibiotic during admission, post-discharge events, length of therapy on PPI, choice of PPI, and continuation of PPI after discharge should be undertaken.

Finally, healthcare costs both inpatient and outpatient are a concern, as the United States burden of CDI is approximately 500,000 cases annually (Lessa et al., 2015). Inpatient costs for CDI are over 4.8 billion, and costs for care in long-term care facilities still deserves further research (Dubberke & Olsen, 2012). Yu and colleagues (2016) performed a retrospective cohort study exploring costs for care of adults age 65 and older with Medicare of Medicaid residing in nursing homes with CDI. The authors estimated $15,000 expended per case and ultimately 800 million in healthcare costs for those in nursing homes with CDI (Yu, Baser, & Wang, 2016). Further research utilizing the FI-CDI to predict adverse outcomes should be undertaken, with exploration of resulting healthcare cost implications resulting from FI-CDI application during acute hospitalization.

Summary

This retrospective cohort study has explored the relationship between CDI and frailty by using a researcher-derived FI-CDI, with frailty scores significantly related to CDI recurrence after adjusting for sociodemographics. The age group 55 to less than 65 remained significantly associated with recurrent admission, compared to 65 and older members of the sample. PPI use was not associated with recurrent CDI prior to admission, but PPI use was significantly related to frailty with bivariate analysis. PPI use prior to admission was not significantly associated with recurrent CDI, when adjusted for frailty and sociodemographics. This study has helped narrow the knowledge gap regarding frailty and recurrent CDI. The use of the EHR offers the opportunity to aggregate existing clinical data to estimate risk and vulnerability that requires further assessment and targeted intervention beyond usual care. The older adult hospitalized with CDI should be assessed for frailty, as findings from this study confirm a relationship between frailty and recurrent CDI. Further research is needed to advance understanding of CDI and frailty to build the science base for implementing best practices for person-centered care.

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