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Differences in survival times, by gender, among those diagnosed with necrotizing fasciitis

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Walden University
2017

Abstract

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by

Ashley Hill

MPH, Walden University, 2012

BS, Everglades University, 2009

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Philosophy

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Abstract

Necrotizing fasciitis infections have high mortality rates especially when treatment is delayed. Despite the abundance of research in many areas of necrotizing fasciitis infection, there are limited and conflicting studies focusing on gender-related outcomes for those diagnosed and died with necrotizing fasciitis infection. The purpose of this study was to determine the association that gender plays on survival time of patients who have been diagnosed with necrotizing fasciitis using a cross-sectional study design. Succeeding the conceptual design of the life course model, the research question tested whether there was a significant difference in survival time between the genders while in the hospital. Additionally, the research questions tested whether gender-related survival was modified by sociodemographic factors or mediated by risk factors for survival of necrotizing fasciitis. Kaplan-Meir method was used to examine survival times between genders. The Cox Proportional Hazards model was used to examine effect modification and mediation. Secondary data from the State Inpatient Databases (SID) and the National Inpatient Sample (NIS) was obtained and used. The result illustrated that there is no difference in survival by gender. However, among men, survival is modified by age. Additionally, diabetes diagnosis tends to affect the survival time for both males and females. The research contributed to social change by increasing the knowledge and understanding of necrotizing fasciitis infections and mortality factors. The results of this study aid in the treatment of necrotizing fasciitis infections for health professionals and inform the health community with a better comprehension of the infection.

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Dedication

This dedication is for my family and friends who have guided, inspired, and encouraged me through my life. My grandmother who is the smartest person I know. My mother who reached her goals of a doctoral degree at 58 but also makes time for silliness. My father who first taught me curiosity but also patience. My daughter, Bailey, niece, Leah, and cousins who renew my passion for improving the world in a small way daily. My brother who continually teaches me, even if I don't care to hear it. My extended family and close friends who stay connected, motivate me, teach me, and help me enjoy all of life. There is everlasting thank you for all of them.

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Chapter 1: Introduction to the Study

Introduction

One of the rarest but deadliest infectious diseases, necrotizing fasciitis, also known as flesh eating bacteria, has a history that dates back to Hippocratic times while noted as a disease that made flesh, sinews, and bones fall away (Green et al., 1996). Necrotizing fasciitis is now described as a bacterial infection that affects the fascia and subcutaneous fat that results in death of the epidermis (Shimizu & Tokuda, 2010). Currently, the incident rate for necrotizing fasciitis is only at 0.40 per 100,000 people in United States with average incidence ranging from 500 to 1,500 new cases (Shimizu & Tokuda, 2010). Mortality rate of necrotizing fasciitis is as high as 32% to 65% (Mukhopadhyay, Saha, Biswas, & Biswas, 2011, p. 7). Many reports have noted a five-fold increase in necrotizing fasciitis in the last decade (Mukhopadhyay et al., 2011). Moreover, the average cost for treating necrotizing fasciitis per patient is roughly $50,000 to $100,000 (Faucher, Morris, Edelman, & Saffle, 2001; Widjaja, Tran, Cleland, Leung, & Millar, 2005). Accordingly, the length of stay in a hospital ranges from 13 days to 172 days depending on the numerous complications that can arise from necrotizing fasciitis infections (Mulla, Gibbs, & Aronoff, 2006).

In a study over long-term outcomes for necrotizing fasciitis patients, Light et al. (2010) who collected data from 1998 to 2006 from a single university-based Burn and Trauma Center found that 87 of the 377 patients in the study died within 10 years of being hospitalized for necrotizing fasciitis infection (p. 99). Light et al. (2010) noted a tendency of women having a higher mortality rate than men in long-term survival (p. 99).

Light et al. (2010) study included patients from age 1 to 89 with a median age range of 49 (p. 99). In a population-level study conducted by Oud and Watkins (2015) the investigators found, among woman hospitalized for necrotizing fasciitis, the odds of mortality were higher compared to similarly hospitalized men (p. 5). However, Oud and Watkins (2015) noted "conflicting data on the role of gender on patient outcomes in severe infectious" (p. 7) remain an issue. Thus, this study will provide information regarding the differences in gender and survival time for patients hospitalized for necrotizing fasciitis infections.

Chapter 1 is divided into 12 sections. All sections in this chapter convey relevant information regarding the topic. The introduction and background illustrate the gap in literature and give contextual information over the topic. The problem statement illustrates the evidence and meaning to the topic. The purpose of the study offers information regarding the study design. The research questions outline the variables being studied. The theoretical framework clarifies the approach of the study. The nature of the study outlines the variables, methodology, data collection procedures, and what type of data is being used. The definitions section describes the main variables in the study. The assumptions section addresses the suppositions of the study. The scope and delimitations section defines the boundaries of the study and gives insight into validity and generalizability of the study. The limitations section outlines the parameters of the study. Finally, the significance and social change of the study gives insight into positive social change aspects of the study.

Background

As early as the 1950s, infectious disease researchers noted connections between necrotizing fasciitis and other bacteria (McCloskey, 1973; Noble, 1969; Taviloglu & Yanar, 2007). Clinical research consistently found two main pathogenic causes of necrotizing fasciitis which included Staphylococcus aureus and Streptococcus bacteria (McCloskey, 1973; Noble, 1969). Research now separates necrotizing fasciitis into four types (Davoudian & Flint, 2012; Hassal, Fagan, Carson, & Currie, 2010). The first type, type 1, the most common type of infection, results from a polymicrobial infection with sources deriving from four different microbes, which are mixed anaerobe and aerobe organisms (Davoudian & Flint, 2012; Hassel et al., 2010). Type I necrotizing fasciitis infections commonly occurs on the trunk and perineal sites among immunocompromised and diabetic patients (Davoudian & Flint, 2012; Hassel et al., 2010). Type II necrotizing fasciitis is a monomicrobial infection resulting from Streptococcus pyogenes or Staphylococcus aureus, and is less common than type I necrotizing fasciitis (Davoudian & Flint, 2012; Hassel et al., 2010). Type II is linked to toxic shock and occurs frequently with people with addiction disorders (Davoudian & Flint, 2012; Hassel et al., 2010). Type III necrotizing fasciitis is uncommon but is associated with higher levels of mortality at 40% and is connected to Vibrio damselae, Vibrio Vulnificus, or other Vibrio species (Davoudian & Flint, 2012; Hassel et al., 2010). Type IV necrotizing fasciitis is connected to fungal infections and is very unusual (Davoudian & Flint, 2012; Hassel et al., 2010). Type IV necrotizing fasciitis is connected with traumatic injuries and burns (Davoudian & Flint, 2012; Hassel et al., 2010).

Diagnosis of necrotizing fasciitis

Researchers have focused fairly extensively on examining quick diagnosis and treatment of necrotizing fasciitis (Taviloglu & Yanar, 2007). When symptoms occur, early diagnosis is one of the key elements to decreasing morbidity and increasing survival among those infected with necrotizing fasciitis (Bair et al., 2009; Davoudian & Flint, 2012; Mukhopadhyay et al., 2011). Early diagnostics have proven to be complicated for necrotizing fasciitis. Some of the reasons for the complications include: many different types of bacteria causing necrotizing fasciitis infections, the location of the infected site or absence of portal entry, identification of symptoms, and risk factors associated with necrotizing fasciitis (Bair et al., 2009; Davoudian & Flint, 2012; Mukhopadhyay et al., 2011). The ideal criterion for diagnosis whether necrotizing fasciitis is present is through surgical exploration and tissue biopsy (Bair et al., 2009; Davoudian & Flint, 2012; Mukhopadhyay et al., 2011). However, if the patient is not severely ill then laboratory tests should be conducted. These laboratory tests include serum chemistry studies, imaging of infected site, and complete blood count with differentials, arterial blood gas measurement, and urinalysis (Kobayashi et al., 2011).

Moreover, color Doppler ultrasound, magnetic resonance imaging (MRI), or contrast-enhanced computed tomography (CT) scanning can aid in early diagnostics for people who necrotizing fasciitis (Kobayashi et al., 2011). If the patient is not severely ill and laboratory results have varying results, some studies have found that elevated white blood cells, increased blood urea nitrogen counts, and reduction in serum sodium levels are signs for necrotizing fasciitis (Bair et al., 2009; Davoudian & Flint, 2012;

Mukhopadhyay et al., 2011). Furthermore, needle aspiration and gram staining can be used to facilitate early diagnostics, as well (Bair et al., 2009; Davoudian & Flint, 2012; Mukhopadhyay et al., 2011). Research has indicated that needle aspiration needs to be taken at the edge of the tissue where the bacteria is plentiful. Gram staining can be more complicated due to the range of bacteria that can cause necrotizing fasciitis. However, gram staining can be highly effective if it is a polymicrobial infection which is frequently the case in necrotizing fasciitis infections (Bair et al., 2009; Davoudian & Flint, 2012; Mukhopadhyay et al., 2011). Lastly, there is a Laboratory Risk Indicator in Necrotizing Fasciitis (LRINEC) score. This diagnostic tool has capability of detecting necrotizing fasciitis early though sensitivity, specificity, and positive and negative predictive value have shown small effects in early diagnostic techniques (Holland, 2009).

Treatment of necrotizing fasciitis

When diagnosis is confirmed, treatment should start immediately to increase rates of survival and decrease the damage done from the fleshing eating bacteria (Kobayashi et al., 2011). Evidence suggests that antibiotic treatment and surgical debridement are the key elements in increasing survival for the patients who have necrotizing fasciitis (Bucca et al., 2012; Davoudian & Flint, 2012; Taviloglu & Yanar, 2007). Surgical debridement is also necessary to minimize tissue loss and possibly prevent amputation of the infected areas (Bucca et al., 2012; Davoudian & Flint, 2012; Taviloglu & Yanar, 2007). There is controversy and conflicting evidence regarding how much tissue should be removed from the infected area for proper recovery and minimize loss of tissue thickness (Anaya & Dellinger, 2007; Meyers, 2012; Shimizu & Tokuda, 2010). In addition, antibiotics should

be started immediately using a broad-base antibiotic initially and a more specific targeted antibiotic after surgery to enhance rates of survival (Anaya & Dellinger, 2007; Meyers, 2012; Shimizu & Tokuda, 2010). Depending on the situation and accessibility, hyperbaric oxygen treatment could also be considered (Anaya & Dellinger, 2007; Meyers, 2012; Shimizu & Tokuda, 2010). Research has suggested that hyperbaric oxygen treatment could decrease mortality of necrotizing fasciitis patients after surgical debridement and antibiotics have been completed (Anaya & Dellinger, 2007; Meyers, 2012; Shimizu & Tokuda, 2010). Yet, many studies have varied on the need and effectiveness of hyperbaric oxygen treatment (Anaya & Dellinger, 2007; Meyers, 2012; Shimizu & Tokuda, 2010).

Management of Infection

Initial management of necrotizing fasciitis depends on specific course of action, which typically is: (1) organ support; (2) source limitation, and: (3) precise antimicrobial dosage (Anaya & Dellinger, 2007; Davoudian & Flint, 2012). Due to the rising rates of other infections, antimicrobial dosage is recommended for patient survival rates and dosage should be adjusted after proper culturing of wound (Anaya & Dellinger, 2007; Davoudian & Flint, 2012). Regardless of what which system—circulatory, respiratory, or other, organ support is a necessity until systems improvements are seen (Anaya & Dellinger, 2007; Davoudian & Flint, 2012). Daily wound care is needed, and this includes: (1) cleaning; (2) tropical ointment application, and; (3) dressing for the wound (Anaya & Dellinger, 2007; Davoudian & Flint, 2012). Research also recommends vacuum closure of the wounds to decrease infections (Anaya & Dellinger, 2007;

Davoudian & Flint, 2012). Often, skin replacement surgery is recommended for these patients, which can be performed typically a few weeks after the patient recovers from the initial incident (Anaya & Dellinger, 2007; Davoudian & Flint, 2012).

There are limited studies on hospital aftercare, or helping patients manage care while in the hospital after the initial management of necrotizing fasciitis. There are even fewer studies on survival factors during a hospital stay for patients with necrotizing fasciitis (Huang et al., 2011; Light et al., 2010). One researcher suggested teaching patients how to reduce a recurrence of this disease through patient education and by teaching patients about various components associated with this infection (Meyers, 2012). Factors associated with survival would aid in patient education, treatment, and management of necrotizing fasciitis. Moreover, patient education could include areas that have inadequate information, such as gender-related survival and factors associated with gender-related mortality for necrotizing fasciitis patients (Light et al., 2010; Oud & Watkins, 2015).

Problem Statement

Research suggests that gender difference in mortality due to necrotizing fasciitis infection is not well understood (Light et al., 2010; Oud & Watkins, 2015). To address this gap, this study aimed to examine whether there is a difference in survival times between men and women diagnosed with necrotizing fasciitis. Additionally, I examined whether there are differences in preexisting medical conditions between men and women that may have contributed to survival.

Purpose of the Study

I used a cross-sectional study to examine the association that gender plays on survival time of patients who have been diagnosed with and died from necrotizing fasciitis. The dependent variable is survival time. The independent variable is gender. The covariates for mediation include diabetes, obesity, and chronic renal disease. Covariates for effect modification include age, insurance type, and region of residence. Some of the confounding factors in this study include—race and/or ethnicity, education, type of necrotizing fasciitis, and inter-hospital transfer while initially admitted.

Research Questions

Research Question 1: For the people who have been diagnosed with and died from necrotizing fasciitis, is there a significant difference in mean survival time between the genders while in the hospital?

Ho1: There will be no significant difference in mean survival time between genders among those who have been diagnosed with and died from necrotizing fasciitis while in the hospital.

HA1: There will be a significant difference in mean survival time between genders among those who have been diagnosed with and died from necrotizing fasciitis while in the hospital.

Research Question 2: For the people who have been diagnosed with and died from necrotizing fasciitis, is any difference in mean survival time between genders while in the hospital modified by sociodemographic risk factors of age, insurance state, and region?

Ho1: The difference in mean survival time between genders while in the hospital is not modified by sociodemographic risk factors of age, insurance state, and region.

HA2: The difference in mean survival time between genders while in the hospital is modified by sociodemographic risk factors of age, insurance state, and region.

Research Question 3: For the people who have been diagnosed with and died from necrotizing fasciitis, is there any difference in mean survival time between genders while in the hospital mediated by pre-existing medical conditions of diabetes, obesity, and chronic renal disease?

Ho1: The difference in mean survival time between genders while in the hospital is not mediated by pre-existing conditions of diabetes, obesity, and chronic renal disease.

HA2: The difference in mean survival time between genders while in the hospital is mediated by pre-existing conditions of diabetes, obesity, and chronic renal disease.

Theoretical Framework

The conceptual framework this study used is the life course epidemiology approach. The origins of the life course approach root back to studies in history, psychology, sociology, public health, among other disciples (Ben-Shlomo & Kuh, 2002). The main beliefs of the life course approach are the analysis of individual and population lives through a multifaceted look into the organizational, cultural, and societal settings (Ben-Shlomo & Kuh, 2002). In the public health context, the life course approach has

had a major influence on chronic health conditions with an emphasis on the comprehension of an inter-relationship of direct and indirect exposure variables, in addition to genetic and psychosocial conduits (Ben-Shlomo & Kuh, 2002).

More recently, the life course approach has appeared in infectious disease studies (Hall, Yee, & Thomas, 2002; Halfon, Larson, Lu, Tullis, & Russ, 2014). The stages of the life course approach in infectious disease research are: (1) susceptibility; (2) infection; (3) disease; and (4) natural history, along with phases of generativity, acquisition of capacity, maintenance of function, and managing decline (Hall et al., 2002; Halfon et al., 2014). This collaboration of new concepts in the life course approach will aid in the understanding of the multidimensional nature of necrotizing fasciitis infection through the variations of influence on infectious disease (Hall et al., 2002; Halfon et al., 2014).

Nature of the Study

The cross-sectional study design was used in this inquiry. Cross-sectional design offers a snap shot of the variables of interest in a study (Schmidt & Kohlmann, 2008). There are a number of advantages in conducting a cross-sectional study. First, a cross-sectional study is advantageous for exploratory studies (Schmidt & Kohlmann, 2008). Second, cross-sectional studies are less costly and do not require follow-up which decreases collection time for large population studies (University of Michigan, 2010). Lastly, cross-sectional studies are beneficial for aiding in public health planning and interventions for target populations (Schmidt & Kohlmann, 2008). Even though there are noted strengths in the use of a cross-sectional study design, there are still limitations.

Some disadvantages in the use of a cross-sectional study include difficulty making causal inference, Neyman bias, and situation or outcomes of interest may change over time (Schmidt & Kohlmann, 2008). For clarity, Neyman bias, which is also known as incidence-prevalence bias, is regarded as bias that occurs in a study when a group of survivors are selected that are related to prognosis factors (Delgado-Rodriguez & Llorca, 2004).

Cross-sectional study was chosen over experimental and quasi-experiment study designs for several reasons. Though experimental studies are the golden standard with high internal validity, there is not a need to manipulate variables in this study to analyze long-term outcomes in necrotizing fasciitis (Frankfort-Nachmias and Nachmias, 2008). Additionally, quasi-experimental designs are similar to experimental designs without randomization with lower cost and higher external validity but was not appropriate for this study due to the nature and overall objective the study seeks to accomplish which is assessing the survival time for patients who live through the first initial 30 days of a necrotizing fasciitis infection (Frankfort-Nachmias and Nachmias, 2008).

This study examined secondary data from the State Inpatient Databases (SID) and the National Inpatient Sample (NIS). The SID is a family of databases which contains inpatient discharge abstracts of 97% of the United States community hospital discharges (Agency for Healthcare Research and Quality, 2015). The SID contain more than 100 clinical and nonclinical variables; examples of the data elements contained in SID include: primary and secondary diagnoses and procedures, admission and discharge

status, patient demographic characteristics, expected payment source, total charges, and length of stay (Agency for Healthcare Research and Quality, 2015).

The participants were defined by those who had been diagnosed with necrotizing fasciitis and died during their hospital stay for the years of 2008 through 2012. Due to the rarity of the disease, and to efficiently capture all possible cases of necrotizing fasciitis, I combined five years of data starting from 2008 from the National Inpatient Sample (NIS) to the SID (Charnot-Katsikas et al., 2009; Kobayaski et al. 2011; Zackarias et al., 2010). Additionally, participants included patients who have one of the following comorbidity conditions and/or risk factors: diabetic, obesity, and chronic renal disease.

All risk factors that were obtained through hospital discharge records were under the other diagnoses category of the data set (Centers for Disease Control and Prevention, 2011). All risk factors use the International Classification of Disease (ICD) 9 and/or 10. Diabetes were analyzed through the ICD-9 code of 250.00 to 250.93 on the hospital discharge data (ICD9DATA, 2014). Obesity will use ICD-9 code of 278 to 278.03. Lastly, the use of chronic renal failure will use ICD-10 code of 673-675 and 682-685 (ICD9DATA, 2014). Any missing data, incomplete data, unknown values, and duplicate record for any variable were excluded and removed.

The Kaplan-Meier survival curve was used to examine survival times between genders. The Cox Proportional Hazards model was used to examine effect modification and mediation. The Kaplan-Meier method can be employed to investigate differences in survival between men and women over time (Greenwood & Nikulin, 1996). The Cox Proportional Hazards model was used as the regression model to examine time to failure

of an event while examining whether failure was modified or mediated by a third order variable. IBM Statistical Packaging for Social Science (SPSS) 20 version will be used to analyze all the data.

Definitions

Survival time: the duration of time between one or more events happening, such as death.

Gender: the state of being female or male.

Necrotizing fasciitis: a bacterial infection of the fascia, the tissue that lines and separate muscle, and the surrounding organs.

Diabetes: a metabolic disease in which the body's inability to produce any or enough insulin causes elevated levels of glucose in the blood.

Obesity: weight that is higher than what is considered as a healthy weight for a given height is described as overweight or obese.

Chronic Renal Disease: more commonly classified as chronic kidney disease and is listed as stages based on the patient's level of glomerular filtration rate (GFR) which is a measure of filtering capacity of the kidneys.

Age: the length of time that a person has lived.

Insurance state: this is classified in the data as Medicaid, Medicare, private insurance, self-payed, no charge, or other.

Region of Residency: The United States Census Bureau defines four regions. Region 1: Northeast, which will include: New England, Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont, New Jersey, New York, and Pennsylvania. Region 2: Midwest, which will include: Illinois, Indiana, Michigan, Ohio, Wisconsin, Iowa,

Kansas, Minnesota, Missouri, Nebraska, North Dakota, and South Dakota. Region 3: South, which will include: Delaware, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, Washington D.C., West Virginia, Alabama, Kentucky, Mississippi, Tennessee, Arkansas, Louisiana, Oklahoma, and Texas. Region 4: West, which will include: Arizona, Colorado, Idaho, Montana, Nevada, New Mexico, Utah, Wyoming, Alaska, California, Hawaii, Oregon, and Washington. Puerto Rico and other US territories are not part of any census region or census division.

Assumptions

This study used secondary data from State Inpatient Databases (SID) from the Agency for Healthcare Research and Quality (AHRQ). SID contains universal inpatient discharge records from 97% of U.S. community hospital discharges. The SID contains core set of clinical and nonclinical information on all patients. This study made the following assumptions with the use of the secondary data from SID: (1) the data obtained are accurate; (2) the data obtained are precise; and (3) the data obtained have minimal measurement error.

Scope and Delimitations

This study used a cross-sectional design using secondary archived data. The study covered five years of hospital discharge data starting in 2008 to 2012. The secondary data was analyzed and coded accordingly. All patients have died during their hospital duration and no personal identifiers will be used. The target population was all patients diagnosed with necrotizing fasciitis in the United States and died during their hospital stay. The data included gender, races/ethnicity, age, primary and secondary diagnosis, expected

payment source, and length of stay (Agency for Healthcare Research and Quality, 2015). Generalization will be limited to US population who would have been captured by the NIS database.

Limitations

There are several limitations in this study. The overarching limitation of this cross-sectional study is misclassification. Misclassification may result from loss of record or improper classification. It is possible that a person's death from necrotizing fasciitis may not have been captured and may have been attributed to another cause. While difficulty in establishing directionality and temporality is a major limitation of the cross-sectional design, it may not be an issue in this study, since death is final outcome, and by default does not have to follow any previous outcome.

Significance and Social Change Implications

In 2012, the media highly publicized three cases of necrotizing fasciitis in Georgia (Castillo, 2012). Despite information and research on necrotizing fasciitis, there are very few studies that have examined risk factors for surviving necrotizing fasciitis (Huang et al., 2011; Light et al, 2010). Light et al. (2010) found 87 of the 377 or 25% had a 3-year morality rate while Khamnaum et al. (2015) found 290 of the 1504 or 19.3% of the patients died while in the hospital. Studies show that the underlying cause of death among those diagnosed with necrotizing fasciitis, 3 years after initial diagnosis, was pneumonia, sepsis, urinary tract infections, and choleystitis (Light et al., 2010). The average survival time for men and women after leaving the hospital was 10 years while

the average age of patients was 49 years old (Light et al., 2010). However, mortality tended to be higher among women.

There is the potential for several elements of positive social change in this dissertation. At a community level, this study can add to the knowledge of necrotizing fasciitis survival factors and give health practitioners and patients of necrotizing fasciitis a more comprehensive awareness of the infection. By using a cross-sectional study design, the researcher hopes to add to the body of literature on how necrotizing fasciitis differentially affects mortality among men and women. This study is unique in the manner that it is one of the initial endeavors in the United States to statistically measure necrotizing fasciitis in regard to gender, sociodemographic factors, and risk factors that can be associated with the survival time (Huang et al., 2011; Light et al., 2010). The third contribution is to clarify the differences in mortality for patients of necrotizing fasciitis in a study focused in the United States (Light et al., 2010; Oud & Watkins, 2015).

Summary

Necrotizing fasciitis is a rare but deadly bacterial infection. There is a high mortality among patients diagnosed with necrotizing fasciitis. Early diagnostics and quick treatment are key factors associated with surviving necrotizing fasciitis infection. Researchers have focused broadly in case-reports and literature and medical reviews to help in faster diagnostics, etiology of necrotizing fasciitis, common features through incidence of characteristics of necrotizing fasciitis, and treatment of necrotizing fasciitis but there is still conflict or lack of agreement among studies over gender-related survival analysis in necrotizing fasciitis patients. The next chapter will illustrate the seminal

articles related to necrotizing fasciitis while focusing on the study variables and the gap or gaps in the literature.

Chapter 2: Literature Review

Introduction

In this chapter, I illustrate the search strategies involved in the literature review. This review covers the theoretical foundation/conceptual framework as it is associated with infectious disease. I review a historical perspective of necrotizing fasciitis research. In this chapter, I also review the current research in necrotizing fasciitis while illustrating the gap in literature. Finally, I connect the variables of the study to research. The variables include; (1) gender with survival time analysis; (2) demographic features correlated to necrotizing fasciitis; (3) risk factors and survival time in necrotizing fasciitis.

Literature Search Strategy

This literature review included the evaluation of the following databases: the Academic Premier database of Walden University, Science Direct, Google Scholar, PUBMED, and MEDLINE. This approach generated hundreds of peer-reviewed articles over necrotizing fasciitis. Search terms consist of: *necrotizing fasciitis, necrotizing fasciitis* AND *etiology, necrotizing fasciitis* AND *diagnosis, necrotizing fasciitis* AND *clinical features, necrotizing fasciitis* AND *risk factors, necrotizing fasciitis* AND *treatment, necrotizing fasciitis* AND *prognosis, necrotizing fasciitis* AND *long-term outcomes, outcome measures* AND *necrotizing fasciitis, survival analysis* AND *necrotizing fasciitis, and gender* AND *necrotizing fasciitis*. Peer-reviewed journals were included that were published in English, focusing on data primarily to the variables in the study which include—gender with survival time analysis, demographic features

correlated to necrotizing fasciitis, and risk factors and survival time in necrotizing fasciitis. Additionally, studies will be included of necrotizing fasciitis that give more understanding, accuracy, and historical background. Despite the abundance of research in some areas of necrotizing fasciitis, many facets of research are limited.

Theoretical Framework

This study uses the life course approach for the theoretical framework. Initially, the life course approach in epidemiology was used for chronic health issues (Ben-Shlomo & Kuh, 2002; Hall, Yee, & Thomas, 2002). The life course approach has more recently been connected with infectious disease epidemiology (Halfon, Larson, Lu, Tullis, & Russ, 2014; Hall et al., 2002; World Health Organization, 2000). The life course approach in infectious disease focuses on four main influences, which are—susceptibility, infection, disease, and natural history (Figure 1; Hall et al., 2002).

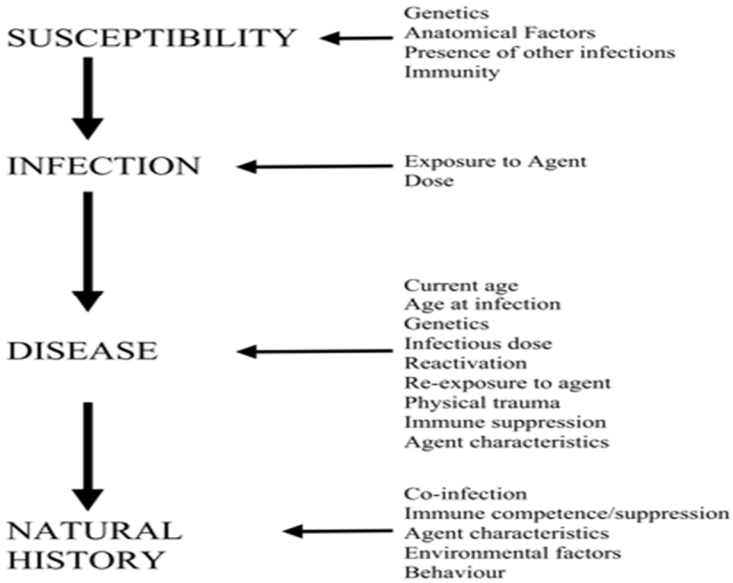


Figure 1. Simplified model of influences that may affect infectious disease. From "Life course epidemiology and infectious diseases," by A. Hall, L. Yee, & S. Thomas,

2002, *International Journal of Epidemiology, 31*, p. 300. Reprinted with permission (See Appendix A).

Often with regard to the life course model, researchers downplay the framework as a common sense approach. However, the framework has enormous implications for understanding the different stages of health in relation to specific disease process (World Health Organization, 2000). This collaboration of new concepts in the life course approach will aid in the understanding of the multidimensional nature of necrotizing fasciitis infection through the variations of influence on infectious disease (Halfon et al., 2014; Hall et al., 2002).

Historical Perspective

In 1871, a Confederate surgeon in the Army described necrotizing fasciitis as hospital gangrene with a mortality rate of 46% among 2,642 infected soldiers (Wilson, 1952, p.417). Research around necrotizing fasciitis has been sporadic and often the main research tool was through case-studies (Mukhopadhyay et al., 2011). As early as 1924, researchers started focusing on case reports of necrotizing fasciitis and the connection to other bacteria associated with the infection (Meleney, 1924). Meleney (1924) reported necrotizing fasciitis and its links to streptococcal infections (p.324). Fifty years later, necrotizing fasciitis was connected to staphylococcus aurous (Leppard & Seal, 1982; McCloskey, 1973). In the initial case reports for diagnosis of necrotizing fasciitis, researchers looked into bacteriology and serology. The researcher's main focus in early necrotizing fasciitis research was narrowing down the types of bacteria that contributed to the infection (Leppard & Seal, 1983). In 1995, research started to examine additional risk

factors for necrotizing fasciitis (Leibowitz & Ramakrishnan, 1995). There was evidence suggesting that age, local tissue factors, and immune status may be contributing factors to acquiring necrotizing fasciitis (Leibowitz & Ramakrishnan, 1995).

Current Trends

The bulk of necrotizing fasciitis research has focused in risk factors, diagnostics, treatment, and microbiology of necrotizing fasciitis since the mid-90s. Moreover, classification for people who are diagnosed with necrotizing fasciitis are getting more and more well-defined with the collective studies looking into these areas (Das, Baker, & Venugopal, 2012; Puvanendran, Huey, & Pasupathy, 2009). Another area of research that has started becoming refined is research over the risk factors for necrotizing fasciitis infection. Recent researchers are noting that the most common risk factor is diabetes; with ranges as high as 70% to 32% of patients having diabetes who are diagnosed with necrotizing fasciitis (Das et al., 2012, p. 2; Puvanendran et al., 2009, p. 982). Other risk factors for people who are diagnosed with necrotizing fasciitis include: obesity, patients taking immunosuppressive drugs, intravenous drug misuse/addiction problems, ages greater than 45 years old; chronic diseases, peripheral vascular disease, hypertension, and malnutrition (Das et al., 2012, p. 2; Puvanendran et al., 2009, p. 982). Necrotizing fasciitis occurs more often in males than females with rates ranging from 54% to 80% (Das et al., 2012, p. 2; Puvanendran et al., 2009, p. 982). Surgery and soft tissue infections are the most common precipitating events that have been linked to necrotizing fasciitis (Das et al., 2012; Puvanendran et al., 2009). These risk factors can aid in the

earlier diagnostics of necrotizing fasciitis, as well as the treatment prescribed for necrotizing fasciitis.

As stated previously, treatment that has proven beneficial is early diagnostics, surgical debridement, and broad-spectrum antibiotics that cover the commonly suspected organism that caused necrotizing fasciitis (Douglas, 1996; Puvanendran et al., 2009; Shimzu & Tokuda, 2010). The type of antibiotics used in necrotizing fasciitis treatment range from clindamycin to penicillin and combinations of other antibiotics (Douglas, 1996; Puvanendran et al., 2009; Shimzu & Tokuda, 2010). Surgical debridement is a necessity for survival of people who have been diagnosed with NF (Douglas, 1996; Puvanendran et al., 2009; Shimzu & Tokuda, 2010). Without surgical intervention than mortality rates rise to almost 100% of the patients with necrotizing fasciitis and still after surgical debridement mortality rates are at 36% for the patients with necrotizing fasciitis (Douglas, 1996; Puvanendran et al., 2009, p. 983; Shimzu & Tokuda, 2010, p. 1051). Additionally, the patients that present with the predisposing factors, especially diabetic patients have higher rates of mortality than the people outside of the predisposing factors for necrotizing fasciitis (Douglas, 1996; Puvanendran et al., 2009; Shimzu & Tokuda, 2010).

The microbiology of necrotizing fasciitis is refined with the growing body of case-studies that researchers include in their analysis of necrotizing fasciitis. Initially, researchers described necrotizing fasciitis through multiple terminologies, including: necrotizing erysipelas, acute infective gangrene, hemolytic Streptococcus, dermal gangrene, and supportive fasciitis (Douglas, 1996; Erstad et al., 1992). Currently, the

microbiology of necrotizing fasciitis is has a more straightforward description (Anaya & Dellinger, 2007; Hunter et al., 2011). Consequently, necrotizing fasciitis research in early diagnostics, risk factors, treatment, and the microbiology of necrotizing fasciitis have been well-established through a multitude of case-studies, retrospective reviews, and clinical evaluations over the infections (Das et al., 2012; Puvanendran et al., 2009). These studies help add to the literature of necrotizing fasciitis research, assist in understanding more about the bacterial infection, and aid in how practitioners respond to the infection.

Literature Review Related to Key Variables

When I started my review of the literature, I observed that there is a significant and concerning gap in the literature regarding survival analysis and gender of patients with necrotizing fasciitis in the United States. Only a small amount of quantitative studies found in the literature indicate attention to the study variables, survival analysis, and patients with necrotizing fasciitis. Even fewer studies have been conducted in the United States over the survival analysis, the study variables, and patients with necrotizing fasciitis. In order to support positive social change and increase knowledge of necrotizing fasciitis infections and the variables that contribute to survival and non-survival during hospital stay, this study was initiated. This next section will illustrate the seminal articles over the variables in this study and the gap in literature.

Mortality and Survival Analysis for Necrotizing Fasciitis

Recently, researchers have started focusing on predictors of mortality in necrotizing fasciitis patients. It has been helpful to examine the variables associated with survival and non-survival of patients with necrotizing fasciitis because it aids in quicker

diagnosis, shapes better treatment, and illuminates areas that need to be managed through long-term care options. In one of the first studies to look at mortality rate, the researchers examined the histopathologic stage of necrotizing fasciitis of 82 cases from January 1990 to December 2002 from the Mayo clinic (Bakleh et al., 2005). In this retrospective study, there were only 25 patients out of the 82 with a histopathologic classification scheme (Bakleh et al., 2005). The researchers found that patients with stage I findings had statistically significantly lower mortality than patients with stage III findings, with an odds ratio of 0.1; 95% CI, 0.001-0.8 (Bakleh et al., 2005, p. 413). Limitations in the study were the sample size and study design (Bahleh et al., 2005).

After Bakleh et al. (2005), more researchers started looking into outcomes and probability of mortality (Golger, Ching, Goldsmith, Pennie, & Bain, 2007; Yaghoubian, de Virgilio, Dauphine, Lewis, & Lin, 2007). Golger et al. (2007) retrospectively reviewed necrotizing fasciitis patients from hospitals in Ontario, Canada from 1994 to 2001. The researchers analyzed demographic, comorbid illness, and disease-specific data with the association of mortality (Golger et al., 2007). The researchers found that age with an odds ratio of 1.04, 95 percent confidence interval, 1.01 to 1.08; $p = 0.012$, immune status with an odds ratio of 3.97, 95 percent confidence interval, 1.04 to 15.19; $p = 0.044$, and streptococcal toxic shock syndrome with an odds ratio of 10.54, 95 percent confidence interval, 2.80 to 39.44; $p < 0.001$, were independent predictors of mortality in patients with necrotizing fasciitis (Golger et al., 2007). Limitations in Golger et al. study is the retrospective study design (p. 1807). Yaghoubian et al. (2007) examined simple admission laboratory values in Los Angeles Biomedical Institute from 1997 to 2006 to

try to predict mortality in patients with necrotizing fasciitis. The variables that were used in their study included: age, race, medical history, physical examination findings, radiographic findings, cause of infection, primary site infection, vital signs, levels of serum sodium, potassium, chloride, bicarbonate, urea nitrogen, creatinine, glucose, lactic acid, albumin (base excess or base deficit), white blood cell count, and anion gap to analyze and classify patients into high and low risk groups for mortality (Yaghoubian et al., 2007). The researchers found that history of cancer, intravenous drug abuse, being transferred outside the hospital, admissions temperature, low systolic blood pressure on admissions, base deficit, and elevated white blood cell count were factors associated with mortality in patients with necrotizing fasciitis (Yaghoubian et al., 2007). Additionally, the researchers found that admission serum lactate greater than 54.1mg/dL had a mortality rate of 32% and patients with serum lactate level less than 54.1 mg/dL combined with a serum sodium level less than 135 mEq/L had a mortality of 19% during their time in the hospital (Yaghoubian et al., 2007, p. 3). Limitations in Yaghoubian et al. (2007) study were the retrospective design and limited studies using the CART analysis tool (p.846).

Su et al. (2008) used a retrospective cohort study in two hospitals in Taiwan during 2002 to 2005. The researchers used the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC score) to predict outcomes of patients who had necrotizing fasciitis (Su et al., 2008). The LRINEC included the following variables: C - reactive protein, total white cell count, hemoglobin, sodium, creatinine, and glucose to score a patient on a scale of 0 to 13 (Su et al., 2008). A score of less than or equal to 6 on the LRINEC test and amputation was associated with higher mortality (Su et al., 2008, p. 970). Su et al.

(2008) was the first to look into the LRINEC score and mortality. Limitations in this study include—LRINEC scores for diagnosis should be used cautiously, missing information through hospital discharge records, influence of therapies in patients, and use of retrospective study design (Su et al., 2008).

Following Su et al. (2008), two other researchers found further innovative approaches to assess mortality in necrotizing fasciitis patients (Lee et al., 2011; Fann, Chiang, Hsiao, Hong, & Chen, 2011). Lee et al. (2011) retrospectively examined 46 patients with monomicrobial necrotizing fasciitis from Chang Gung Memorial Hospital. The researchers classified patients into either gram-positive cocci or gram-negative bacillus (Lee et al., 2011). The group that was gram-positive for cocci had a higher prevalence of gouty arthritis whereas the group put into gram-negative bacillus had higher incidence of hemorrhagic bullae, septic shock, thrombocytopenia, and chronic liver dysfunction (Lee et al., 2011). The non-survivors of necrotizing fasciitis were patients with chronic liver dysfunction, chronic renal failure, reduced serum albumin values, thrombocytopenia, and immature leukocyte more than 10% (Lee et al., 2011, p. 4). Though, Lee et al. (2011) found no statistical difference in LRINEC score, age, gender infection location, or isolated pathogenic bacterium between survivors and non-survivors (Lee et al., 2011). Limitations in Lee et al. were small sample size, use of consecutive serious of patients for cohort, and the grouping of patients in cohort study (p. 7).

Similar to Yaghoubian et al. (2007), Fann et al. (2011) used a retrospective review of two hospitals in Taiwan from 2002 to 2005. The researchers identified clinical

admission characteristics and laboratory findings to differentiate between high and low morality risk groups in patients with necrotizing fasciitis (Fann et al., 2011). Additionally, parallel to Yaghoubain et al. (2007) the researchers used a C4.5 decision tree to analyze 23 clinical characteristics and laboratory tests to examine outcome measures (Fann et al., 2011). Differing from Yaghoubain et al. (2007), these researchers found three independent predictors of mortality for patients with necrotizing fasciitis, which are: increase in immature neutrophils, hypotension, and left shift in the differential white blood cell count (Fann et al., 2011). Weaknesses in the Fann et al. study were study design and prior antibiotic treatment in patients (p. 107).

Gender Associated with Survival of Necrotizing Fasciitis

Researchers have examined the incidence of male-to-female ratio of who acquires necrotizing fasciitis (Ryseel et al., 2010; Shukry & Ommen, 2013; Vijayakumar, Pullagura, & Thimmappa, 2014). However, there have been relatively limited studies that have looked into gender as one of the factors for survival or non-survival after diagnosed with necrotizing fasciitis. Light et al. (2010) found that there was a trend toward higher mortality among woman than men in long-term survival after diagnosed with necrotizing fasciitis (p. 99). Though, Light et al. (2010) did not concentrate on gender as a variable in their study.

Khamnuan et al. (2015) retrospectively reviewed three hospitals in Thailand during 2009 to 2012. Khamnuan et al. (2015) looked for clinical predictors of mortality of patients with necrotizing fasciitis (p.1). There were 1,504 patients included in the study (Khamnuan et al., 2015). The researchers found being female with a risk ratio of 1.37

was one of the factors associated with mortality (Khamnuan et al., 2015). Among the other findings, chronic heart disease with risk ratio of 1.64, cirrhosis with a risk ratio of 2.36, age greater than 60 with a risk ratio of 1.39, skin necrosis with a risk ratio of 1.22, pulse greater than 130/min with a risk ratio of 2.26, systolic blood pressure less than 90 mmHg with a risk ratio of 2.05, and serum creatinine of greater than or equal to 1.6 mg/dL with a risk ratio of 3.06 were associated with mortality among necrotizing fasciitis patients (Khamnuan et al., 2015). Limitations in Khamnuan et al. study were omission of LRINEC and APACHE II scoring systems to patients, retrospective study design, insufficient medical records (p.6). Wang and Lim (2013) retrospectively reviewed hospital records from 2004 to 2011 at Mackay Memorial Hospital in Taitung. Wang and Lim (2013) found a risk factors associated with death were gender, hospital days, and albumin level (p. 139). Wang and Lim (2013) found men having a lower risk of death than females with an odds ratio of 0.18 (p. 139). Weaknesses in Wang and Lim study were the retrospective study design and small sample size (p.143).

Consequently, and as previously mentioned, Lee et al. (2011) found no statistical difference in gender between survivors and non-survivors (Lee et al., 2011). Because there are conflicting results from Khamnuan et al. (2015), Wang and Lim (2013), and Lee et al. (2011) studies and none of the studies have been conducted in the United States, there is a need to further investigate how gender is associated with survivor and non-survivors of people diagnosed with necrotizing fasciitis in the United States.

Diabetes, Obesity, and Chronic Renal Disease Association with Survival of Necrotizing Fasciitis

Diabetes and being obese have been identified as leading risk factors associated with acquiring necrotizing fasciitis (Lee et al., 2011; Oud & Watkins, 2015; Wang & Lim, 2013). Chronic renal disease has varied between studies for being a predominant risk factor for necrotizing fasciitis infection but often stays at the forefront of characteristics of necrotizing fasciitis patients (Lee et al., 2011; Oud & Watkins, 2015; Wang & Lim, 2013). In a cohort study from 2001 to 2010 using Texas Inpatient Public Use Data File, the researchers performed ~~a~~ one of the largest population-based examination of patterns of necrotizing fasciitis (Oud & Watkins, 2015). There were 12,172 patients included in the study who were hospitalized for necrotizing fasciitis (Oud & Watkins, 2015). Oud and Watkins (2015) discovered that 47.6% of the patients who were diagnosed with necrotizing fasciitis had diabetes, 15.2% of the patients with necrotizing fasciitis were obese, and 15.5% of patients with necrotizing fasciitis had chronic renal failure (p.3). Oud and Watkins found that diabetes had an odds ratio of 0.75 and a p-value of 0.0023 of predicting mortality among patients with necrotizing fasciitis (p. 5). Oud and Watkins (2015) also found that obesity had an odds ratio of 0.532 and a p-value of <0.0001 of predicting mortality among patients with necrotizing fasciitis patients (p.5). Additionally, Oud and Watkins (2015) found that chronic renal disease had an odds ratio of 1.738 with a p-value of <0.0001 for predicting mortality with patients of necrotizing fasciitis (p. 5). Oud and Watkins (2015) did not statistically evaluate if survival and non-survival of necrotizing fasciitis patients with diabetes, obesity, and/or

chronic renal disease was mediated by gender. Though, Oud and Watkins (2015) did note that the "findings of reduced risk of death among males with necrotizing fasciitis contrast the lack of gender-related prognostic impact reported by others" (p. 7). Weakness in Oud and Watkins study include use of administrative data excluded timeliness of diagnosis, details, source control, resuscitative interventions in institutional outcomes, and generalizability was only to Texas population (p.8).

Parallel to the Oud and Watkins study, Lee et al. (2011) found mortality to be higher among patients with chronic renal failure with a p-value of 0.015 (p.4). Lee et al. (2011) did not find a statistical difference in diabetes between survivors and non-survivors of necrotizing fasciitis (p.139). Obesity was not statistically evaluated in this study (Lee et al., 2011). Wang and Lim (2013) found diabetic mellitus to be a risk factor associated with death among necrotizing fasciitis patients (p.139). However, Wang and Lim (2013) showed that chronic renal disease was not statistically significant in risk factors associated with death and obesity was not statistically evaluated in this study (p.140). Oud and Watkins (2015), Lee et al. (2011), and Wang and Lim (2013) studies illustrate that further investigation of diabetes, obesity, and chronic renal disease as risk factors associated with necrotizing fasciitis patients and if the risk factors are mediated by gender and survival time.

Age, Insurance, and Region of Residence Association with Survival of Necrotizing Fasciitis

Older age has been one of the factors that has emerged in research as a risk factor for necrotizing fasciitis (Krieg, Dizdar, Verde, & Knoefel, 2014; Oud & Watkins, 2015;

Ryseel et al., 2010; Vijayakumar et al., 2014). Insurance type and place of residency has not been well examined in survival analysis in necrotizing fasciitis patients. Krieg et al. (2014) retrospectively reviewed records from 1996 and 2011 at a single university hospital (p. 334). The researchers found 64 cases of necrotizing fasciitis infection (Krieg et al., 2014). The researcher's results illustrated that age greater than 60 was a demographic characteristic that effected mortality among the patients with necrotizing fasciitis (Krieg et al., 2014). Krieg et al. (2014) did not analyze insurance type or place of residency in their study. Limitations in Krieg et al. study were retrospective study design and small sample size (p. 35). As previously mentioned, Oud and Watkins (2015) retrospectively reviewed Texas Inpatient Public Use Data Files from 2001 to 2010 (p. 2). The researchers found that age greater than 65 was a predictor of mortality among hospitalizations with necrotizing fasciitis (Oud & Watkins, 2015). Moreover, Oud and Watkins (2015) found that zip code of residence was not associated with increased risk of death after controlling for covariates (p. 4). Oud and Watkins (2015) did not look into insurance type for statistical analysis. However, the researchers did analyze income level, which was found to not be an association for mortality among patients with necrotizing fasciitis (Oud & Watkins, 2015). Khamnuan et al. (2015) retrospective review of three hospitals in Thailand found age greater than 60 and patients with no education had a greater risk for mortality using a univariable analysis (p.3). Khamnuan et al. (2015) did not analyze place of residency as a factor associated with mortality in their study. Krieg et al. (2014), Oud and Watkins (2015), and Khamnuan et al. (2015) studies illustrate that

further investigation in the United States of how age, education, and place of residency is warranted and if the factors are moderated by gender in a survival analysis.

Summary and Conclusion

Chapter 2 provided information over necrotizing fasciitis literature and research. Necrotizing fasciitis infections have high mortality (Golger et al., 2007; Oud & Watkins, 2015). Survival analysis and statistical evaluation of medical charts in necrotizing fasciitis research has illustrated that predictors of mortality fluctuate marginally depending on each study (Bakleh et al., 2005; Golger et al., 2007; Lee et al., 2011; Yaghoubian et al., 2007). The predominant factors associated with mortality in necrotizing fasciitis patients while in the hospital were: moderate-to-severe neutrophilic infiltration with infected necrotizing fasciitis tissue, age, immune status, obesity, streptococcal toxic shock syndrome, history of cancer, intravenous drug abuse, elevated white blood cell count, being transferred outside the hospital, admissions temperature, low systolic blood pressure upon admissions, LRINEC score less than or equal to 6, chronic liver dysfunction, chronic renal failure, reduced serum albumin values, thrombocytopenia, immature leukocyte more than 10%, hypotension are associated with mortality in necrotizing fasciitis patients while in the hospital (Bakleh et al., 2005; Fann et al., 2011; Golger et al., 2007; Lee et al., 2011; Su et al., 2008; Yaghoubian et al., 2007).

The relationship of how gender is associated with mortality is still limited in research (Khamnuan et al., 2015; Light et al., 2010; Oud & Watkins, 2015; Wang & Lim, 2013). Two researchers found females having a lower survival rate compared to men with

necrotizing fasciitis infection (Khamnuan et al., 2015; Wang & Lim, 2013). Additionally, two other research groups noticed conflicting data associated with gender and survival of necrotizing fasciitis patients (Lee et al., 2011; Oud & Watkins, 2015). Though, only one study was conducted in the United States. Statistically evaluating current patients who have been diagnosed with necrotizing fasciitis through a survival analysis specifically looking into gender will aid in the ability for hospitals, doctors, and practitioners to better care for these individuals. This study will provide the first in the United States to statistical measure the association of gender on survival time for necrotizing fasciitis patients. Furthermore, this study will determine if the gender is mediated from diabetes, obesity, and chronic renal disease in the survival analysis as well as if gender has an effect modification from age, education, and region of residence.

In Chapter 3, I will give the details of the study, including the research design and the rationale. I will give details over the dependent and independent variables, and the rationale for the research questions. I will give details over sampling, the population, and how the data was collected. I will also give details over the software used for analysis, threats to validity of the study, and ethical issues that may arise.

Chapter 3: Research Method

Introduction

Necrotizing fasciitis is an uncommon but highly fatal infection. Mortality can be as high as 65% (Mukhopadhyay et al., 2011). Many factors associated with mortality in patients with necrotizing fasciitis has been well-defined (Bakleh et al., 2005; Fan et al., 2011; Golger et al., 2007; Lee et al., 2011; Su et al., 2008; Yaghoubian et al., 2007). Though, research in gender-related mortality is still misunderstood. The purpose of this study was to examine the association that gender plays on survival time of patients who have been diagnosed with necrotizing fasciitis while still in the hospital. Additionally, this research examined factors that can be mediated and moderated by gender-related survival of necrotizing fasciitis infections. A number of reasons influenced this research, including the minimal studies looking into gender-related survival in necrotizing fasciitis patient and no current research at population-level conducted in the United States over this area. Furthermore, there are no studies that use gender to examine if there is modification in survival while in the hospital by sociodemographic risk factors or mediated by risk factors.

In Chapter 3, I give the particulars of the study, including the rationale why the research design was chosen over other research designs. I present details over the dependent and independent variables, and the rationale for the research questions. I provide information over sampling, the population, and how the data was collected. I also give specifics over the software used for analysis, threats to validity of the study, and ethical issues that may arise.

Research Design and Rationale

In this quantitative investigation, I used a cross-sectional design for the study. Cross-sectional study design was the most appropriate choice for this study because it allows for data to be analyzed at a single point in time to answer the research questions. In this study, gender and survival analysis were measured through the State Inpatient Database (SID). The outcomes for the research questions signify an outline of the frequency and association of components under examination over a 5-year period, 2008-2012.

Justification for Using the Design

The rationalization for the design of this study is founded on previous studies done (Khamnuan et al., 2015; Light et al., 2010; Oud & Watkins, 2015; Wang & Lim, 2013). These researchers used a type observational study to analyze several variables in necrotizing fasciitis patients as will my study. Oud and Watkins (2015) and Khamnuan et al (2015) both used a cohort study design to examine variables associated with mortality and necrotizing fasciitis patients. Cohort study design is advantageous when looking into several outcomes of interest in one study (Mann, 2003). A cohort study was not chosen for this research because there was not a need to follow the group of participants for any period of time to answer the research questions. Light et al. (2010) and Wang and Lim (2013) used retrospective chart reviews to describe clinical features and outcome measures of necrotizing fasciitis patients. Retrospective chart reviews are valuable in gathering study results (Vassar & Holzmann, 2013). However, there is lower

generalizability than cross-sectional studies since they are typically done in a limited number of clinics or hospital settings.

Additionally, experimental study designs were not chosen for this research because there is not a need to manipulate the variables in the study. Nor was there a need for pre-testing or post-testing to examine the relationship between the variables. Quasi-experimental designs were not chosen because the length of time to match many of the cases to proper controls, the cost of increasing years of data usage, and the complexity is not needed for this study's research questions to be examined. The pre-experimental study designs were not chosen because they do not fit the research questions or study parameters. For the purposes of this research, a cross-sectional study is the most beneficial. Cross-sectional studies look at whole populations and/or subset of the population at a particular point in time (University of Michigan, 2010).The cross-sectional design is specifically linked to the research questions that I seek to see if there is a relationship between. The main research question is: is there a difference in survival, by gender, for patients hospitalized for necrotizing fasciitis infections. Using the cross-sectional design, I can focus on the linkage between the independent variable, gender, and the dependent variable, survival time. Additional analysis can be made of the mediating and moderating variables through the cross-sectional design.

Operational Use of the Conceptual Framework

Researchers are taking the life course theory in a new direction by looking at specific points in a person's life. This is particularly useful in this cross-sectional study to understand the specific time period of survival for each individual case of necrotizing

fasciitis while still encompassing the many other factors that influence a person's survival after the infection of the disease (Mayer, 2009). As applied in this study, the life course approach can focus on the outcomes in necrotizing fasciitis with the physical and social exposures (i.e. gender, sociodemographic factors, and risk factors) that play into the outcome measures of surviving necrotizing fasciitis (Hall, Yee, & Thomas, 2002). The life course approach indicates that there is an interplay of biological, social, and psychological factors that influence the life course of each individual (Hall, Yee, & Thomas, 2002). This applies to this study through the age of the participants acquiring necrotizing fasciitis infection and the time after acquiring necrotizing fasciitis infection possibly could influence the risk factors that are associated with necrotizing fasciitis infections along with survival of the infection (Hall, Yee, & Thomas, 2002; Light et al., 2010).

Moreover, the life course approach implies an insight of the effects of the environment while allowing the assumption that individuals change in a changing environment (Kuh et al., 2003). Furthermore, time is one of the key issues in the life course approach and denotes in the life course model that the individual at the time of a particular risk (necrotizing fasciitis infection) is assumed to affect the outcome (survival) (Kuh et al. 2003). The life course model also includes the understanding that health-related outcomes (risk factors) are dependent on the time of the events and each individual's characteristics (Kuh et al., 2003). One of the main reasons that the life course model is a fitting theoretical model is because the multifaceted nature of the model. The life course model correlates well with how outcomes of necrotizing fasciitis patients

interact with their environment, biological elements that are associated with demographic, risk factors of necrotizing fasciitis infection, and survival time after the initial infection (Kuh et al., 2003; Light et al., 2010). Lastly, the cross-sectional nature of this study collaborates time sensitive data collection which is fitting in this model. The life course model offers a perspective of the life course of the individuals in the study and a prediction of the age-graded, time-relevant data that is gathered to examine the gender differences along with risk factors that may be associated with survival time of necrotizing fasciitis patients (Kuh et al., 2003; Light et al., 2010).

Methodology

Population

The population of the study was made up of the patients from the SID which is a part of the family of databases and software tools developed for the Healthcare Cost and Utilization Project (HCUP) (Healthcare Cost and Utilization Project, 2015). SID includes inpatient discharge records from community hospitals in that 48 states (Healthcare Cost and Utilization Project, 2015). SID contains the universe of the inpatient discharge abstracts in all participating states (Healthcare Cost and Utilization Project, 2015). SID encompasses 97% of all U.S. community hospital discharges (Healthcare Cost and Utilization Project, 2015). The core set of information in the dataset from SID is clinical and nonclinical information on all patients, including principle and secondary diagnoses and procedures, admission and discharge status, patient demographic characteristics, expected payment source, total charges, and length of stay (Healthcare Cost and Utilization Project, 2015).

The participants were defined by those who had been diagnosed with necrotizing fasciitis between 2008 and 2012 and died in the hospital. Due to the rarity of the disease, and to efficiently capture all possible cases of necrotizing fasciitis, I combined five years of data starting from 2008 from the National Inpatient Sample (NIS) to the SID (Charnot-Katsikas et al., 2009; Kobayaski et al. 2011; Zackarias et al., 2010). Additionally, participants were included who had one of the following comorbidity conditions and/or risk factors: diabetic, obesity, and chronic renal disease.

Sampling and Sampling Procedure

Through secondary data collection, the sample size was drawn. The sampling strategy that was used in this study is a nonprobability sampling procedure. It does not involve randomization. A primary feature of non-probability sampling is that samples are chosen by the personal judgment of the investigator, rather than random choice. While certain researchers might see non-probability sampling procedures as substandard to probability sampling procedures, there are solid theoretical and sensible rationale for the application of non-probability sampling (Canada Statistics, 2013). A chief goal of non-probability sampling is to look at the intricacies of the sample being studied. In addition, non-probability sampling is beneficial for concealed and/or hard-to-reach subsets of the populations (Frankfort-Nachmias, & Nachmias, 2008).

Necrotizing fasciitis has a very small incidence rate for annual occurrence. For the adult group of participants, the incident rate has been calculated to be around 0.4 per 100,000 cases (Edlick, 2013, para.6). Due to the very small population for the study, purposive sampling would best fit the study parameters. This means that all patients

during the 5-year time period were purposively sought out and sampled with the recognition that this sample may not be a direct representation of national makeup. The aim of purposive sampling is to spotlight on specific distinctiveness of a population which best match the research question(s) (FAO Corporate Document Repository, 2011, para. 5). The chief advantage of purposive sampling is the comparative simplicity for the study to include participants. The primary disadvantage for this kind of sample is generalization to external people is difficult to do since the inclusion criteria that are used in the sampling techniques and is prone to research bias (FAO Corporate Document Repository, 2011).

The inclusion criteria will include all participants in the study period that have been diagnosed with necrotizing fasciitis and died while in the hospital. The exclusion criteria will include missing data on any of the cases. A G*Power analysis was ran for the sample size. The large sample, z-test, logistic regression, a priori was chosen with one tail, power at 80 percent, and alpha at 0.05. The G*Power test illustrates there should be 396 participants in the study for 80 percent power.

Data Collection

This study did not involve any recruitment of participants as it was conducted with secondary data collection methods. Though, it is important to explain how data was recruited into the study for further statistical analysis. I undertook the secondary data collection through the SID dataset, which is includes inpatient discharge records from community hospitals in that state (Healthcare Cost and Utilization Project, 2015). The SID files encompass all patients, regardless of payer, providing a unique view of

inpatient care in a defined market or state over time (Healthcare Cost and Utilization Project, 2015). Moreover, distinctions with respect to mediating and moderating variables was collected and was subject to thorough analysis to help establish further understanding of gender-related mortality in necrotizing fasciitis patients. The main clinical outcome that was measured is mortality. The mediating variables that were included diabetes, obesity, and chronic renal disease. The moderating variables in this study which were included are age, education, and region of residence.

Since this is a cross-sectional study using secondary data from the SID, there was no need to provide informed consent, nor was there a need for participants to exit the study or any follow-up procedures needed. Any data that was collected that was missing variables was excluded from this study. Additionally, this study was subject to Walden University IRB approval.

Use of Archival Data

Secondary data collection is the re-investigation of data that have been collected by another source through raw or published data (Doolan & Froelicher, 2009; Smith et al., 2011). Secondary data collection and analysis have similar phases to primary data collection methods. The phases include: (1) describing the research subject and questions; (2) choosing the dataset to be used; (3) familiarizing yourself with the data that were selected; and (4) presenting your findings (Doolan & Froelicher, 2009; Smith et al., 2011). There are several reasons to conduct a secondary data collection and analysis. First, the research is less obtrusive than other types of collection methods (Doolan & Froelicher, 2009; Smith et al., 2011). The time spent on collection is less and the cost of

secondary data analysis is minimal compared to many primary data collection methods (Doolan & Froelicher, 2009; Smith et al., 2011). The research can cover a wider demographic of people and increase the sample size used in the study (Doolan & Froelicher, 2009; Smith et al., 2011). Even though there are several advantages to collecting data through secondary sources there are still limitations of this type of data collection method. A major limitation in secondary data collection is that there is less control over the sampling population than primary data collection methods (Doolan & Froelicher, 2009; Smith et al., 2011). Additionally, secondary data can have limited access or be difficult to obtain, modification of the data may have already occurred, there may be poor documentation of the data, and confidentiality still needs to be considered for the usefulness in the research (Doolan & Froelicher, 2009; Smith et al., 2011).

For the use of the SID, each research is required to take the online HCUP Data Use Agreement Training Course, and users of the SID must read and sign the Data Use Agreement for State Databases prior to the purchase of the data (Healthcare Cost and Utilization Project, 2015). A copy of the data use agreement is in the appendix of the study.

Table 1

Research Questions and Variables

Research Questions	Hypothesis	Dependent variable	Independent variable	Mediating or Moderating Variable	Data analysis
Research Question 1: "For the people who have been diagnosed with and died from	Null Hypothesis: There will be no significant difference in survival time between genders among those who have	Survival time	Gender		Kaplan-Meier survival curve

necrotizing fasciitis, is there a significant difference in survival time between the genders while in the hospital?"	been diagnosed with and died from necrotizing fasciitis while in the hospital.				
Research Question 2: "Is any difference in survival time between genders while in the hospital modified by sociodemographic risk factors which is defined as age, insurance state, and region?	Null Hypothesis: The difference in survival time between genders while in the hospital is modified by sociodemographic risk factors which is defined as age, insurance state, and region.	Survival time	Gender	Moderating Variables: age, insurance state, and region	Cox proportional hazards
Research Question 3: "Is there any difference in survival time between genders while in the hospital mediated by pre-existing medical conditions, which is defined as diabetes, obesity, and chronic renal disease?	Null Hypothesis: The difference in survival time between genders while in the hospital is mediated by pre-existing conditions, which is defined as diabetes, obesity, and chronic renal disease.	Survival time	Gender	Mediating Variables: diabetes, obesity, and chronic renal disease	Cox proportional hazards

Data Analysis Plan

IBM Statistical Package for the Social Sciences (SPSS) Statistics 21 (SPSS 21) was used to run the analysis of the data. IBM SPSS 21 is a systematic tool that aids in understanding for data examination with precise results and allows one to assess all outcomes of interest (IBM, 2015). This statistical software is a suitable choice due to its

ability to conduct descriptive and inferential analysis over the dataset that was used in this study. SPSS 21 was loaded on the researcher's personal computer and password protected.

Research Question 1: "For the people who have been diagnosed with and died from necrotizing fasciitis, is there a significant difference in mean survival time between the genders while in the hospital?" The dependent variable is survival time and the independent variable is gender. *Research Hypothesis 1:* There will be a significant difference in mean survival time between genders among those who have been diagnosed with and died from necrotizing fasciitis while in the hospital. Kaplan-Meier method will be used to analyze this relationship. Kaplan-Meir probability is calculated through the number of subjects surviving living at the start minus the number of subjects who died divided by the number of patients living at the start (Goel, Khanna, & Kishore, 2010). Subjects that are censored, dropped out, and/or excluded are not counted in the denominator.

Research Question 2: "Is any difference in mean survival time between genders while in the hospital modified by sociodemographic risk factors which is defined as age, insurance state, and region?" The null and alterative hypotheses associated with Research Question 2 are as follows:

$H2_{o1}$: The difference in mean survival time between genders while in the hospital will not be modified by age.

$H2_{a1}$: The different in mean survival time between genders while in the hospital will be modified by age.

$H2_{o2}$: The difference in mean survival time between genders while in the hospital will not be modified by insurance state.

$H2_{a2}$: The different in mean survival time between genders while in the hospital will be modified by insurance state.

$H2_{o3}$: The difference in mean survival time between genders while in the hospital will not be modified by region.

$H2_{a3}$: The different in mean survival time between genders while in the hospital will be modified by region.

To test these hypotheses, bivariate analysis was used. Moderating variables change the strength of an effect or relationship between two variables (i.e. survival time and gender). Thus cox proportional hazards was used to examine the effect of each moderating variables. The exponential of the coefficients from the Cox model gives the rapid relative risk for a rise of one unit for each covariate in question.

Research Question 3: "Is there any difference in mean survival time between genders while in the hospital mediated by pre-existing medical conditions, which is defined as diabetes, obesity, and chronic renal disease?" The null and alterative hypotheses associated with Research Question 3 are as follows:

$H3_{o1}$: The difference in mean survival time between genders while in the hospital will not be mediated by diabetes.

$H3_{a1}$: The difference in mean survival time between genders while in the hospital will be mediated by diabetes.

$H3_{o2}$: The difference in mean survival time between genders while in the hospital will not be mediated by obesity.

$H3_{a2}$: The difference in mean survival time between genders while in the hospital will be mediated by obesity.

$H3_{o3}$: The difference in mean survival time between genders while in the hospital will not be mediated by chronic renal disease.

$H3_{a3}$: The difference in mean survival time between genders while in the hospital will be mediated by chronic renal disease.

To test these hypotheses, bivariate analysis was used. Mediating variables specific how or why a particular effect or relationship may have occurred. For example, obesity may be associated with males to have a lower survival time for those diagnosed with and died from necrotizing fasciitis. Therefore, Cox proportional hazards was used to examine if there is an association through unadjusted estimates of the association between each mediating variable: diabetes, obesity, and chronic renal failure. Next, the research tested through Cox proportional hazards if there was an association between each mediating variable and the independent variable and each mediating variable and the dependent variable. If the independent and/or dependent variable is not associated with the mediating variable then the research can conclude that the variable is not mediated.

Threats to Validity

External validity refers to the generalizability of the study (Frankfort-Nachmias & Nachmias, 2008). People, places, and time can be threats to external validity (Frankfort-Nachmias & Nachmias, 2008). This study is cross-sectional study design which is

contingent on the study years of 2008-2012. Thus, the generalizability of time can only be assumed in this time frame. Misclassification is the main external threat to validity and temporal relationships cannot be established. Additionally, since this study is cross-sectional in nature, there cannot be a cause-and-effect relationship assumed for the population and study variables for other researchers (Frankfort-Nachmias & Nachmias, 2008). Though, the use of a large population that covers 97% of the of all U.S. community hospital discharges aids in the external generalizability of people and place in the United States with necrotizing fasciitis during the study period.

Internal validity is the extent the results of the study are true ((Frankfort-Nachmias & Nachmias, 2008). Purposive sampling is a limitation in internal validity. However, and as mentioned previously, necrotizing fasciitis is a rare disease and purposive sampling is the best method to focus on specific characteristics of the population and have a robust population under study (Frankfort-Nachmias & Nachmias, 2008).

Ethical Procedures

Ethical standards will be upheld in this study. Secondary data collection does not include informed consent. However, data usage is restricted to this particular research, online HCUP data use agreement training course was taken, and prevention of other researchers obtaining this data has been safeguarded. I have completed a human subject data handling agreement through the Walden University. All data have excluded personal identifiers and data will remain confidential to the researcher. The data will be stored on this researcher's personal computer, password protected, and in an Excel spreadsheet.

Summary

This research is a cross-sectional, quantitative research study with the use of secondary data from the HCUP and SID that will explore the relationship between gender-related mortality among patients who have been diagnosed with and died from necrotizing fasciitis. The data used was collected during the years of 2008 to 2012 with a total number of patients being roughly 396 to have 80 percent power and 0.05 alpha. Purposive sampling was used due to the rare nature of necrotizing fasciitis infections in the population. Analysis was through IBM Statistical Package for the Social Sciences (SPSS) Statistics 21 using Kaplan-Meir method and Cox proportional hazards to analyze the research questions and data. Chapter 4 will review the purpose of the study, research questions, and collection of the data. Chapter 4 will also give results of the study.

Chapter 4: Results

Introduction

The purpose of this cross-sectional study is threefold. First, it was to analyze the association of gender on survival time for cases who had necrotizing fasciitis and died while in the hospital. The second part was to analyze the relationship between survival time, gender, and the modifying variables in the study, which include: age, insurance state, and region for patients who have been diagnosed with and died from necrotizing fasciitis. Third, was to analyze the relationship between survival time, gender, and the mediating variables for this study, which are: obesity, diabetes, and chronic renal failure. Descriptive statistics were used to illustrate basic information over the patients that where included in the study. In this chapter, I provide a better understanding of the association between survival time, gender, along with the modification of age, insurance state, and region, and the mediation of obesity, diabetes, and chronic renal failure using Kaplan-Meier and Cox proportional hazards for inferential statistics. The following research questions and their connected hypothesis guided this study:

1. For the people who have been diagnosed with and died from necrotizing fasciitis, is there a significant difference in mean survival time between the genders while in the hospital?

Ho1: There will be no significant difference in mean survival time between genders among those who have been diagnosed with and died from necrotizing fasciitis while in the hospital.

HA1: There will be a significant difference in mean survival time between genders among those who have been diagnosed with and died from necrotizing fasciitis while in the hospital.

2. For the people who have been diagnosed with and died from necrotizing fasciitis, is any difference in mean survival time between genders while in the hospital modified by sociodemographic risk factors of age, insurance state, and region?

Ho1: The difference in mean survival time between genders among those who have been diagnosed with and died from necrotizing fasciitis while in the hospital is not modified by sociodemographic risk factors of age, insurance state, and region.

HA2: The difference in mean survival time between genders among those who have been diagnosed with and died from necrotizing fasciitis while in the hospital is modified by sociodemographic risk factors of age, insurance state, and region.

3. For the people who have been diagnosed with and died from necrotizing fasciitis, is there any difference in mean survival time between genders while in the hospital mediated by pre-existing medical conditions of diabetes, obesity, and chronic renal disease?

Ho1: The difference in mean survival time between genders among those who have been diagnosed with and died from necrotizing fasciitis while in the hospital is not mediated by pre-existing conditions of diabetes, obesity, and chronic renal disease.

HA2: The difference in mean survival time between genders among those who have been diagnosed with and died from necrotizing fasciitis while in the hospital is mediated by pre-existing conditions of diabetes, obesity, and chronic renal disease.

Data Collection

Data for this study was obtained through the Healthcare Cost Utility Project (HCUP). The national-inpatient sample (NIS) is one of seven databases offered through HCUP. The NIS data was collected after IRB approval; IRB approval number is 07-22-16-0196601. Once IRB approval was acquired, data from the NIS database was bought for the years of 2008-2012. After the payment of the NIS 2008-2012 dataset, HCUP attached ASC II files to convert to SPSS. Online HCUP data use agreement training course was taken prior to approval of IRB and the collection of data. I completed a human subject data handling agreement through the Walden University. All data have excluded personal identifiers and data will remain confidential to the researcher. The data will be stored on this researcher's personal computer, password protected, and in an Excel spreadsheet.

Data Analysis

There were roughly 8 million cases in the NIS dataset for each year from 2008-2012. The data was cleaned to include only participants who had a diagnosis one or diagnosis two of the 15 diagnosis offered through ICD-9 coding of necrotizing fasciitis and whom had died in the hospital. Diagnosis one of ICD-9 code for necrotizing fasciitis cases included 173 participants for 2008-2012 dataset. Diagnosis two of ICD-9 coded for necrotizing fasciitis included the remain of 420 cases for 2008-2012 dataset. The G*power analysis ran in chapter 3 illustrated that there was a total of 396 cases needed for 80% power. The final number of cases was 593 which is more than enough for the effect size and power needed in this study. After the inclusion criteria were met, missing

value analysis was conducted on the final participants. For the eight variables included in this study, there is less than 1% of missing data for seven of the eight variables. The only variable that had a higher percentage of missing data was region at 40%. The region variable was re-coded for the missing values, as 0, and all analysis of the missing data was excluded from analysis. Table 3 gives the percentage of missing variables.

TABLE 2

UNWEIGHTED PERCENTAGE OF MISSING VALUES BY VARIABLE (N = 593)

VARIABLE	Missing n (%)
AGE	0.3%
LENGTH OF STAY	0.2%
INSURANCE STATE	0.5%
OBESITY	0.2%
REGION	40.0%
RENAL FAILURE	0.2%
DIABETES	0.2%
GENDER	0.2%

Results

Descriptive Statistics

The target population for this study was all participants from the NIS dataset for the years of 2008-2012 that were diagnosed with necrotizing fasciitis and died while in the hospital. Descriptive statistics were ran on the target population. Table 3 shows the frequency counts for the selected variables. The population was split with almost half being men 50% (n=299) and half being woman 50% (n=294). The most prevalent race

was white at 56% (n=332), black at 13% (n=75), and Hispanic at 10% (n=57). Those aged 55 to 64 years old accounted for 27% (n=159) of the study population followed by age group 45 to 54 years old at 19% (n=115). Approximately 52% (n=307) used Medicare as their health insurance, while private insurance represented 20% (n=118) of the health care payee among the study population. The most predominant median household income of 38,999 or less with 34% of the cases (n=200), followed by medium income of 49,000 to 63,999 at 25% (n=148) and median household income of 39,000 to 48,999 at 24% (n=141). The most common region cases were from was the South at 24% (n=145), then Midwest 13% (n=76), West 11% (n=68), and Northeast 11% (n=64). The percentage of diabetes was 13% (n=77), chronic renal failure 4% (n=25), and obesity 3% (n=17) in the population (Table 3).

Table 3

One-Way Frequency Table for Selected Variable in Necrotizing Fasciitis Cases

Variable		Frequency Count	Percentage
Gender	Male	299	50
	Female	294	50
Race	White	332	56
	Black	75	13
	Hispanic	57	10
	Other Race	22	4
	Asian or Pacific	12	2
	Islander	7	1
	Native American		
Age	24 or younger	6	1
	25-34	16	3
	35-44	30	5

	45-54	115	19
	55-64	159	27
	65-74	111	19
	75-84	98	17
	85 and older	57	10
Insurance Payer	Medicare	307	52
	Medicaid	85	14
	Private Insurance	118	20
	Self-pay	59	10
	No charge	3	1
	Other	19	3
Median Household Income	38,999 or less	200	34
	39,000 to 48,999	141	24
	49,000 to 63,999	148	25
	64,000 or more	84	14
Region	South	145	24
	Midwest	76	13
	West	68	11
	Northeast	64	11
Diabetes Status	0	516	87
	1	77	13
Obesity Status	0	576	97
	1	17	3
Chronic Renal Failure	0	568	96
	1	25	4

Statistical Assumptions

There are several statistical assumptions for the use of Kaplan-Meier analysis. The first assumption is having two mutually exclusion states and exhaustive states (Goel et al., 2010). For this study, the event was death of necrotizing fasciitis cases. The second assumption for Kaplan-Meier analysis is the measurement of the "event" must be precise (Goel et al., 2010). This study event was the length of stay prior to death in the hospital. The third assumption is left-censoring should be minimized (Goel et al., 2010). This

study used the first and second out of the fifteen-diagnosis provided to minimize left-censoring cases. The fourth assumption in Kaplan-Meier analysis is the independence of censoring of event (Goel et al., 2010). Since all cases died in this study, this assumption is void. The fifth assumption secular changes (Goel et al., 2010). The study collected data over a five-year period for cases that had been diagnosed with and died from necrotizing fasciitis. There has not been an improvement in treatment over the five-year study period to influence a secular change in this study. Lastly, the log-rank was ran to ensure censoring between groups were similar for the two groups being analyzed (male or female).

Cox proportional hazards was used for research question two and three of this study. There are a couple of assumptions that need to be met using cox proportional hazards, which include: non-informative censoring and hazard function must be proportional over a specific period of time (Bender, Augustin, & Blettner, 2006). Non-informative censoring was not an issue for this study due to the underlying nature of the variables in the study (Bender et al., 2006). Stated differently, this study focused on mean survival time for necrotizing fasciitis patients who had died in the hospital therefore there was not a follow-up period nor was there dependency on the necrotizing fasciitis patients having a follow-up since the research questions were only the cases that had died. Log-log plots were ran for research question two (Figure 2) and research question three (Figure 3) to ensure that there was an absence of indication to oppose the proportionality assumption in the second assumption of cox proportional hazards. For the absence of proportionality, log-log plots should be approximately parallel (Bender et al., 2006).

Research Question 1 and Hypothesis 1

Research Question 1: "For the people who have been diagnosed with and died from necrotizing fasciitis, is there a significant difference in mean survival time between the genders while in the hospital?"

Ho1: There is no significant difference in mean survival time between the genders while in the hospital for the people who have been diagnosed with and died from necrotizing fasciitis.

Ha1: There is a significant difference in mean survival time between the genders while in the hospital for the people who have been diagnosed with and died from necrotizing fasciitis.

Kaplan-Meier Analysis

As shown in Table 4, I calculated the Kaplan-Meier analysis necrotizing fasciitis cases that had died to compare the length of stay between genders. The mean survival time for men was 11.7 days (95% CI of 9.4 to 14.0) and the mean survival time woman was 13.9 days (95% CI of 11.0 to 16.8). A log-rank test was performed to determine if there was statistical significant difference in mean survival time between the two genders. The mean survival time for the two genders was not statistically significantly different, $\chi^2(2) = 1.186$, $p < .276$ (Figure 1).

Table 4

Mean days until death from initial diagnosis and confidence intervals for Between Genders

	Mean days	95% Confidence Interval

Male	11.7	9.4	14.0
Female	13.9	11.0	16.8

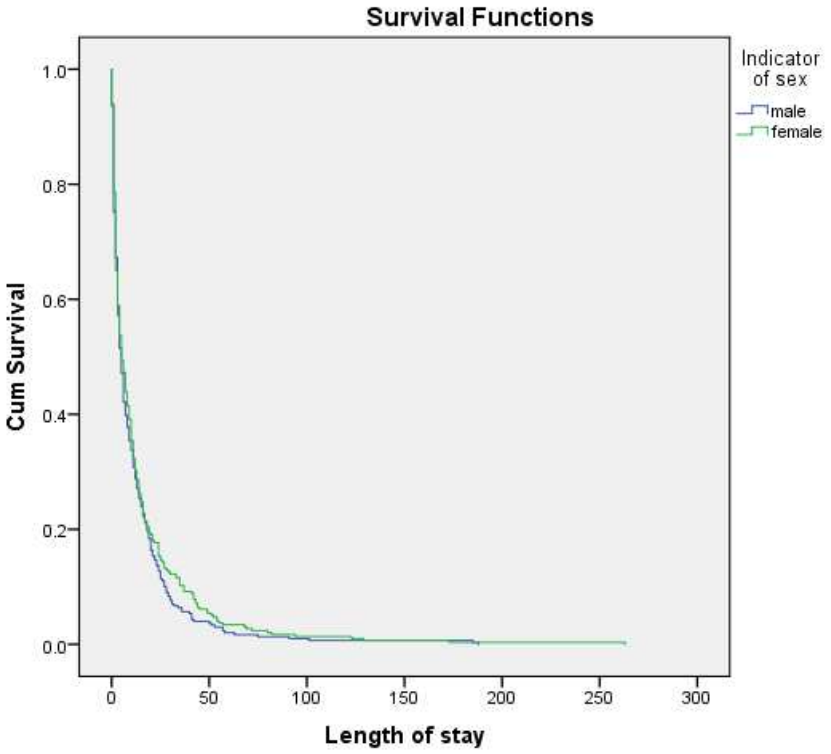


Figure 1: Survival Function between Genders for Necrotizing Fasciitis Cases

Research Question 2 and Hypothesis 2

Research Question 2: "For the people who have been diagnosed with and died from necrotizing fasciitis, is any difference in mean survival time between genders while in the hospital modified by sociodemographic risk factors which is defined as age,

insurance state, and region?" The null and alterative hypotheses associated with Research Question 2 are as follows:

$H2_{o1}$: The difference in mean survival time between genders while in the hospital will not be modified by age.

$H2_{a1}$: The different in mean survival time between genders while in the hospital will be modified by age.

$H2_{o2}$: The difference in mean survival time between genders while in the hospital will not be modified by insurance state.

$H2_{a2}$: The different in mean survival time between genders while in the hospital will be modified by insurance state.

$H2_{o3}$: The difference in mean survival time between genders while in the hospital will not be modified by region.

$H2_{a3}$: The different in mean survival time between genders while in the hospital will be modified by region.

For research question 2 and shown in Table 5, I used bivariate analysis to assess three covariates: age, insurance state, and region, for the 597 cases of necrotizing fasciitis who died to see if there was a difference of survival time through the genders modified by the covariates. The covariate age was separated into seven ranges, which include: range 1) 24 or younger, range 2) 25 to 34 years, range 3) 35 to 44 years, range 4) 45 to 54 years, range 5) 65 to 74 years, range 6) 75 to 84 years, and range 7) 85 and older. Since age group 55 years to 64 years was the most common, that range was used for the baseline comparison for all the remaining groups. Insurance state was separated into five

categories: 1) Medicaid, 2) Private insurance, 3) Self-pay, 4) No charge, and 5) Other. Medicare was the most common insurance for the cases and was used as a baseline for comparison in the analysis. The covariate region was separated into three regions: 1) Northeast, 2) Midwest, and 3) West. The South region was the most common region for the cases and was used for comparison for the other regions in the analysis.

Table 5

Bivariate analysis using cox proportional hazard analysis examining covariates that are associated with time to death among men and women diagnosed with necrotizing fasciitis, 2008-2012

Covariates	Parameter Estimate	SE	95% CI
Age			
24 years and younger	-0.09	0.63	0.27-3.11
25 to 34 years	-0.71	0.38	0.23-1.03
35 to 44 years	-0.13	0.31	0.47-1.62
45 to 54 years	-0.72	0.24	0.31-0.77
65 to 74 years	-0.62	0.23	0.35-0.83
75 to 84 years	-0.46	0.22	0.41-0.98
85 and older	-0.29	0.23	0.48-1.17
Region			
Northeast	-0.30	0.19	0.52-1.07
Midwest	-0.16	0.17	0.61-1.20
West	-0.27	0.16	0.56-1.03
Insurance			
Medicaid	-0.50	0.29	0.34-1.08
Private insurance	-0.59	0.32	0.30-1.03
Self-pay	-0.18	0.30	0.46-1.50

No charge	-0.25	0.32	0.42-1.47

Note. CI=95% Confidence intervals

The results indicate the significant values and hazard ratios (Exp (B)) of the covariates that included all the predictor variables with a significant p-value from the univariate analysis. A hazard ratio that is <1.0 means that the variable of interest is less likely to have a shorter time to event compared with the reference group and a hazard ratio >1.0 is more likely to have poorer survival with the reference group. Statistically significant differences for survival were observed in age (p=0.04). There was not a statistical significance in region or insurance type.

The hazard ratio for age 45 to 54 years was 0.49, 95% CI [0.31-0.77] indicating that there was a 46% increase in mean survival time compared to the reference group (55 to 64 years). The hazard ratio for age 65 to 74 years was 0.54, 95% CI [0.35-0.83] indicating that there was a 48% increase in mean survival time compared to the reference group while the hazard ratio for those 75 to 84 years was 0.63, 95% CI [0.41-0.98] indicating that there was a 57% increase in mean survival time compared to the reference group.

Next, cox regression was ran by splitting the groups to analyze the genders for mean survival difference for necrotizing fasciitis cases that could be modified by age, region, and insurance type (Table 6). The results indicate that there is not statistical significance with female cases of necrotizing fasciitis who died modified by age, region, or insurance state. The results also indicate that male cases of necrotizing fasciitis who died where not modified by region or insurance state. The analysis does illustrate that age

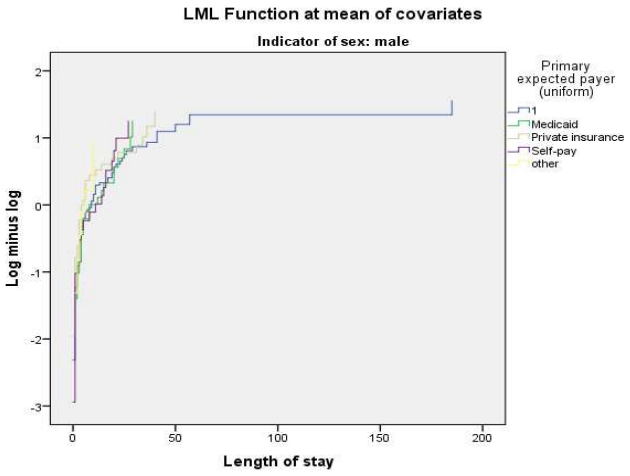
is statistically significant for male necrotizing fasciitis cases and therefore modified the mean survival time for male necrotizing fasciitis case who died while in the hospital. The hazard ratio for age in male cases was 1.17, 95% CI 1.03-1.32, which indicates that mean survival time was less than female cases.

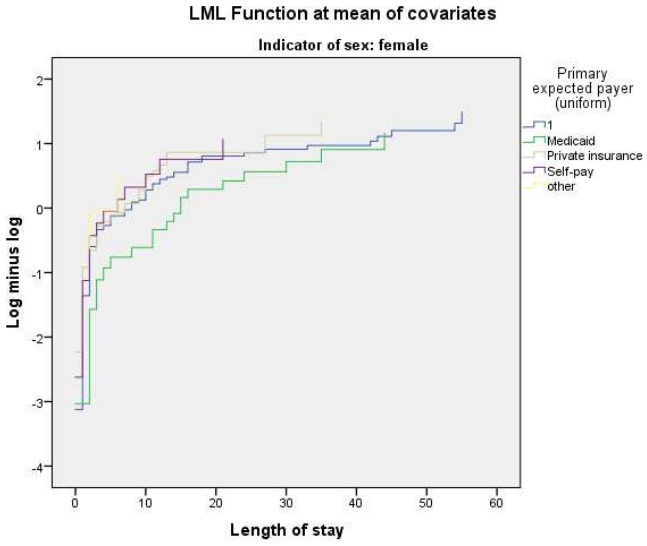
Table 6

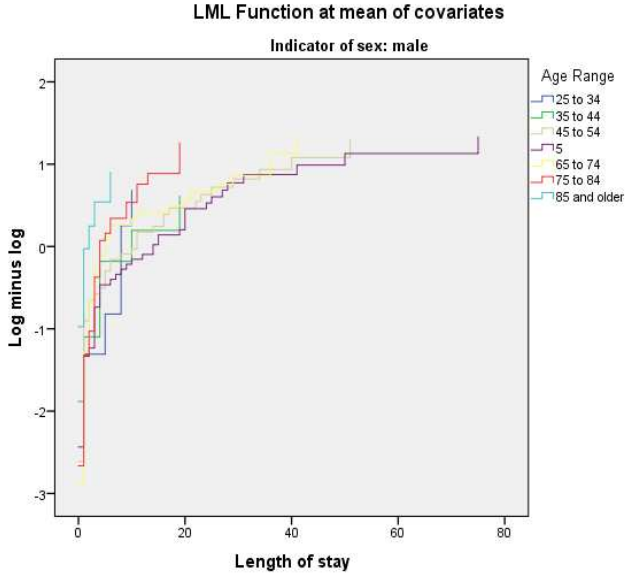
Cox proportional hazards, to examine whether differences in survival time between males and females diagnosed with necrotizing fasciitis, is modified by region, age, and insurance, 2008-2012

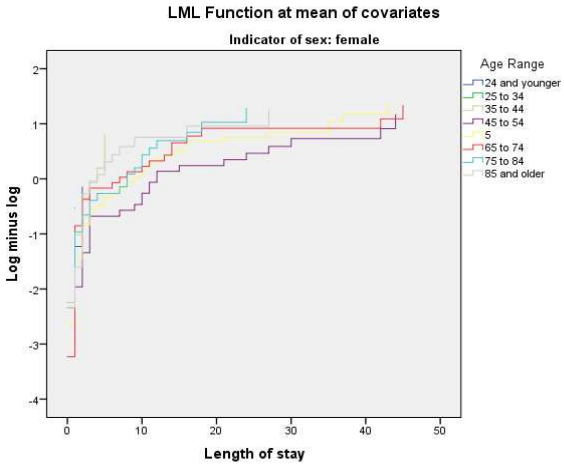
	Covariate	B	SE	p-value	Exp(B)	95%CI
Male						
	Region	0.04	0.08	0.62	1.04	0.89-1.21
	Age	0.16	0.06	0.01	1.17	1.03-1.32
	Insurance	0.08	0.06	0.17	1.08	0.97-1.21
Female						
	Region	0.05	0.08	0.58	1.05	0.89-1.23
	Age	0.08	0.06	0.18	1.08	0.96-1.21
	Insurance	0.13	0.07	0.07	1.14	0.99-1.31

Note. CI=confidence interval; LCI=lower confidence interval; UCL=upper confidence interval.


LML Function at mean of covariates
Indicator of sex: male
Log minus log
Length of stay
Primary expected payer (uniform)
1
Medicaid
Private insurance
Self-pay
other


LML Function at mean of covariates
Indicator of sex: female
Log minus log
Length of stay
Primary expected payer (uniform)
1
Medicaid
Private insurance
Self-pay
other


LML Function at mean of covariates
Indicator of sex: male
Log minus log
Length of stay
Age Range
25 to 34
35 to 44
45 to 54
5
65 to 74
75 to 84
85 and older


LML Function at mean of covariates
Indicator of sex: female
Log minus log
Length of stay
Age Range
24 and younger
25 to 34
35 to 44
45 to 54
5
65 to 74
75 to 84
85 and older

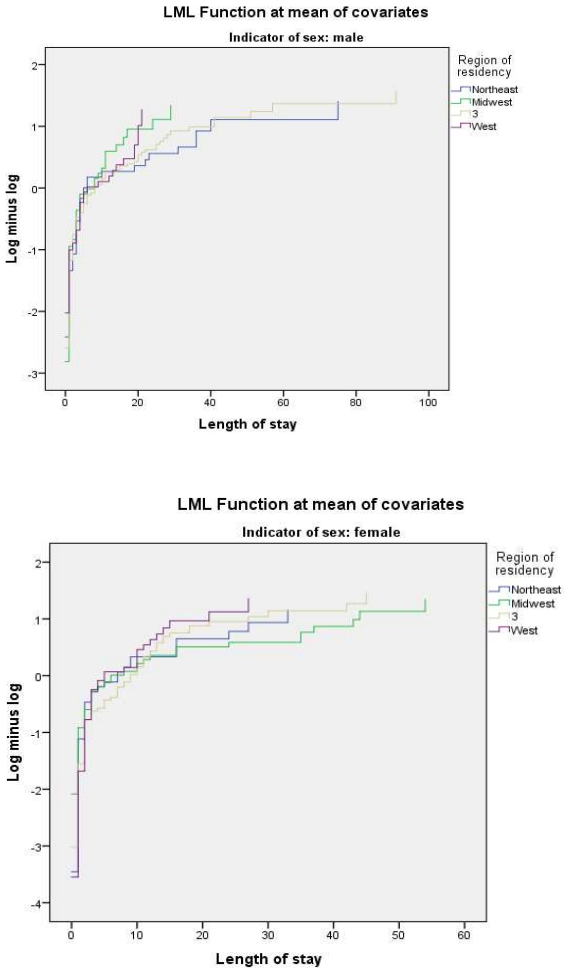


Figure 2. Log-Log plot of covariates: age, region, and insurance for male and female necrotizing fasciitis cases.

Research Question 3 and Hypothesis 3

Research Question 3: "Is there any difference in mean survival time between genders while in the hospital mediated by pre-existing medical conditions, which is defined as diabetes, obesity, and chronic renal disease?" The null and alterative hypotheses associated with Research Question 3 are as follows:

$H3_{o1}$: The difference in mean survival time between genders while in the hospital will not be mediated by diabetes.

$H3_{a1}$: The difference in mean survival time between genders while in the hospital will be mediated by diabetes.

$H3_{o2}$: The difference in mean survival time between genders while in the hospital will not be mediated by obesity.

$H3_{a2}$: The difference in mean survival time between genders while in the hospital will be mediated by obesity.

$H3_{o3}$: The difference in mean survival time between genders while in the hospital will not be mediated by chronic renal disease.

$H3_{a3}$: The difference in mean survival time between genders while in the hospital will be mediated by chronic renal disease.

For research question 3 and shown in Table 6, cox proportional hazard was used to assess mediation. The three covariates examined to assess mediation included diabetes, obesity, and chronic renal disease, I first examined the bivariate association between time to death and having been diagnosed with diabetes, obesity or chronic renal failure among the 597 cases of necrotizing fasciitis who died between 2008 and 2012 (Table 6). The data provided evidence that those who had a previous diabetes diagnosis had statistically significant decreased survival times compared to those not diagnosed with diabetes (Table 6). No other statistically significant associations were found.

Table 6

Cox Proportional Hazard of Covariates: Diabetes, Obesity, and Chronic Renal Failure, for Necrotizing Fasciitis Cases, 2008-2012

Covariate	Beta	SE	95% CI
Diabetes	-0.46	0.13	0.49-0.81
Obesity	-0.43	0.25	0.40-1.06
Chronic Renal Failure	-0.28	0.21	0.50-1.14

Note. 95% CI=95% confidence interval

The next analysis, Table 7, examined if the proportion of males and females diagnosed with diabetes, obesity and chronic renal failure differed. There was a statistical significant difference in in the hazard ratio of male and female necrotizing fasciitis cases diagnosed with diabetes. Male necrotizing fasciitis cases had a hazard ratio of 0.69, 95% CI 0.49-0.97, which indicates that there is an increased rate of death among males who are diagnosed with diabetes compared to those not diagnosed with diabetes. We found similar results among females diagnosed with diabetes who experience an increased time to death compared to those not diagnosed with diabetes, hazard ratio of 0.55, 95% CI 0.38-0.89, which indicates a 51% decrease in mean survival time for female necrotizing fasciitis cases.

TABLE 7

COX PROPORTIONAL HAZARDS, EXAMINING DIFFERENCE IN SURVIVAL TIMES BY PREVIOUS DIAGNOSIS WITH DIABETES, OBESITY AND CHRONIC RENAL FAILURE, BETWEEN MALE AND FEMALE NECROTIZING FASCIITIS CASES, 2008-2012

Covariate	B	SE	95% CI

MALE				
	Diabetes Status	-0.36	0.17	0.49-0.97*
	Obesity Status	-0.40	0.34	0.34-1.31
	Chronic Renal Failure	-0.21	0.28	0.47-1.40
FEMALE				
	Diabetes Status	-0.59	0.19	0.38-0.80*
	Obesity Status	-0.44	0.36	0.32-1.31
	Chronic Renal Failure	-0.48	0.33	0.33-1.18

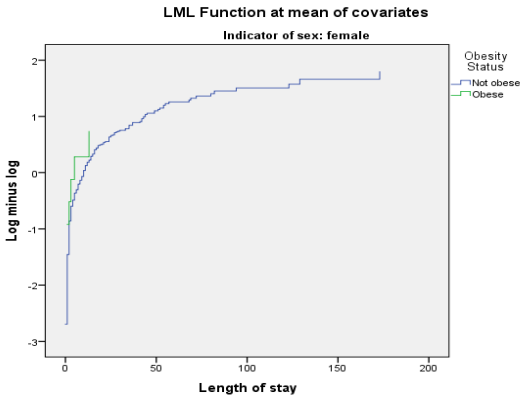
Note. CI=confidence interval; Coded diabetes diagnosis=1, no previous diabetes diagnosis=0; previous obesity diagnosis=1, no previous obesity diagnosis=0; previous chronic renal failure=1, no previous renal failure=0; *P<0.05 statistically significant.

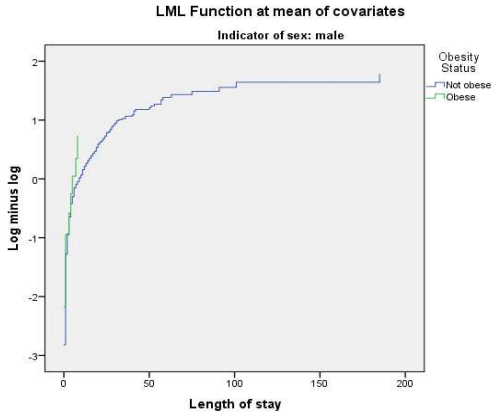
Lastly, I ran cox regression to analyze the association between survival time of necrotizing fasciitis cases and gender controlling for diabetes. Table 8 illustrates that diabetic male and female cases of necrotizing fasciitis cases is statistically significant for mean survival time. Male cases had a p-value of 0.01 while female cases had a p-value of 0.00.

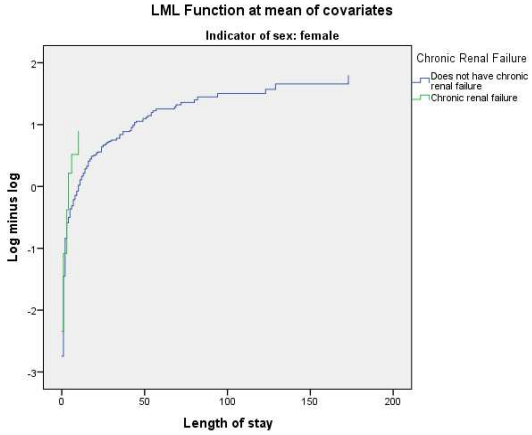
Table 8

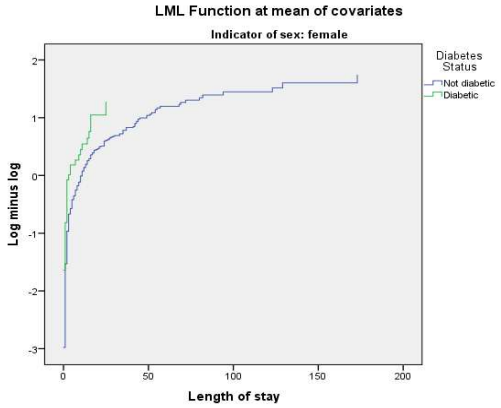
Cox Proportional Hazard for Survival time for Genders in Necrotizing Fasciitis Cases Controlling for Diabetes,2008-2012

Indicator of Sex	Beta	SE	p-value	Exp (B)
Male Diabetic Status	0.42	0.17	0.01	1.52
Female Diabetic Status	0.60	0.19	0.00	1.80




LML Function at mean of covariates
Indicator of sex: male
Obesity Status
Not obese
Obese
Log minus log
Length of stay


LML Function at mean of covariates
Indicator of sex: female
Chronic Renal Failure
Does not have chronic renal failure
Chronic renal failure
Log minus log
Length of stay


LML Function at mean of covariates
Indicator of sex: female
Diabetes Status
Not diabetic
Diabetic
Log minus log
Length of stay

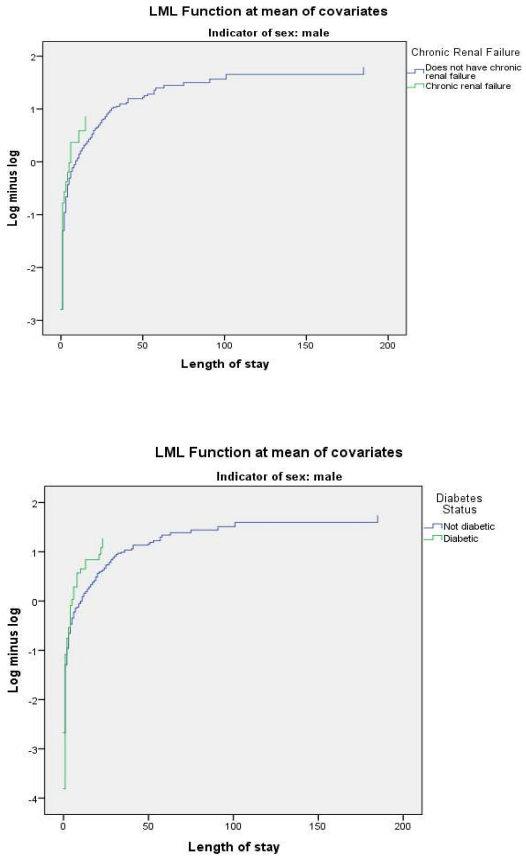


Figure 3. Log-Log plot of covariates: diabetes, obesity, and chronic renal failure for male and female necrotizing fasciitis cases.

Summary

The results of this study indicated that there is not a statistical difference in mean survival time between genders for those who have been diagnosed with and died from necrotizing fasciitis. Therefore, the null hypotheses of no significant difference in survival time between the genders while in the hospital for the people who have been diagnosed with and died from necrotizing fasciitis was not rejected. The researcher also determined that there was not an association mediated for mean survival time between

genders from obesity and chronic renal failure. The null hypothesis difference in mean survival time between genders while in the hospital will not be mediated by obesity or chronic renal failure is not rejected. Additionally, the null hypotheses of difference in mean survival time between genders while in the hospital will not be modified by region or insurance state was not rejected. This researcher did determine that there was an association modified for mean survival time between genders for age for the male cases of necrotizing fasciitis which illustrates that 54 years and younger of male cases had a better chance of mean survival compared to male necrotizing fasciitis cases with an older age. Furthermore, this researcher found that there was an association mediated from diabetes for mean survival time for both genders for those who have been diagnosed with and died from necrotizing fasciitis which illustrates that both genders with diabetes had a shorter length of mean survival time compared to cases without diabetes.

Chapter 4 illustrated the study results to answer the overarching research questions. Chapter 5 will discuss an overview of the results, interpretation of the findings of this study, limitation in this study, give recommendations for further research, and illustrate the social change in this study.

Chapter 5: Discussion, Conclusions, and Recommendations

The purpose of this cross-sectional, quantitative study was to examine survival time between genders for people who had been diagnosed with and died from necrotizing fasciitis during their time in the hospital. In this chapter, I will give an introduction, interpretation of the findings, limitations of the study, recommendations for future studies, illustrate the positive social change in the study, and implications.

Mortality for people who have been diagnosed with necrotizing fasciitis ranges 15% to 40% (Shimizu & Tokuda, 2010). In spite of the copious amount of research in diagnostic and treatment of necrotizing fasciitis, there is limited knowledge and research of survival analysis for short and long-term outcomes of necrotizing fasciitis patients who have been diagnosed with necrotizing fasciitis, particularly in the United States. This study sought to narrow the gap in a small way. This study used secondary data from the NIS for the years of 2008-2012 to answer the three main research questions, which were: 1) For the people who have been diagnosed with and died from necrotizing fasciitis, is there a significant difference in mean survival time between the genders while in the hospital? 2) For the people who have been diagnosed with and died from necrotizing fasciitis, is any difference in survival time between genders while in the hospital modified by sociodemographic risk factors which is defined as age, insurance state, and region? 3) Is there any difference in mean survival time between genders while in the hospital mediated by pre-existing medical conditions, which is defined as diabetes, obesity, and chronic renal disease?

A sequence of analysis was conducted through bivariate and univariate statistical techniques. Kaplan-Meier was used to analyze the first research question while cox proportional hazards was used to analyze the second and third research questions. The results of the study were mixed. There was not a statistical significance in the mean survival time between genders for those diagnosed with and died from necrotizing fasciitis. However, there was a statistical significance for male necrotizing fasciitis patients that was modified by age for mean survival time. Additionally, there was a statistical significance that was mediated from diabetic status in both male and female necrotizing fasciitis patient's mean survival time.

Interpretation of Findings

Survival Analysis, Gender, and Necrotizing Fasciitis

Necrotizing fasciitis research has not focused noticeably on mean survival times and factors that influence mean survival times in short and long-term outcomes for patients in the United States (Light et al., 2010, Oud & Watkins, 2015). The few studies in the literature that have examined gender differences for mean survival time in necrotizing fasciitis patients chiefly found that women had a lower chance of survival than men (Khamnuan et al. 2015; Oud & Watkins, 2015; Wang & Lim, 2013). However, in this study, there was not a statistical significance for mean survival time between genders for necrotizing fasciitis patients; with the mean survival time for men at 11.7 days and the mean survival time for woman at 13.9 days. The results of this study may have been different than previous literature due to the sample size being relatively small while the overall incidence of necrotizing fasciitis also remains small. Though, this study

does suggest that there is an equal probability of mortality for woman and men than what was previous suggested through the literature.

Survival Analysis, Age, Insurance, Region, and Necrotizing Fasciitis

The association of age, insurance type, and region was examined in this study. Consistent with Krieg et al. (2014), Khamnuan et al. (2014), and Oud and Watkins (2015) this study found a statistical significance in age and mortality in necrotizing fasciitis patients. Oud and Watkins (2015) found that age great than 65 was associated with mortality among both genders in necrotizing fasciitis patients. Most studies have not examined the association of mean survival time between genders and necrotizing fasciitis patients. This study found that male, 45 years and older, necrotizing fasciitis patients had a lower chance of mean survival compared to younger, 44 and younger, male necrotizing fasciitis patients while there was not a statistical difference in female necrotizing fasciitis cases. This was different than the studies presented in the research due to examining age as a modifying factor for mortality outcomes between genders in necrotizing fasciitis patients.

There were not many studies that looked at association between insurance and region. Similar to Oud and Watkins (2015), this study found no association between region and mortality among necrotizing fasciitis patients. Many studies had not examined this region in mortality and outcomes for necrotizing fasciitis patients. Additionally, none of the studies presented in the research examined insurance type and mortality outcomes for necrotizing fasciitis patients. Even though, there was not a statistical difference in the

findings in this study, it does open a door for more understanding in necrotizing fasciitis and survival analysis for this type of research.

Survival Analysis, Diabetes, Obesity, Chronic Renal Disease, and Necrotizing Fasciitis

Survival analysis was ran on diabetes, obesity, and chronic renal failure for mortality in necrotizing fasciitis patients. There were mixed results in the literature over diabetic status increasing mortality among necrotizing fasciitis patients. Though, Oud and Watkins (2015) did find a high correlation to diabetic status and increased mortality in necrotizing fasciitis patients. This was correspondingly to the results shown in this study which illustrated that being diabetic had a higher mortality compared to those who are not diabetic for mortality in necrotizing fasciitis patients in both genders (Khamnuan et al, 2015; Oud & Watkins, 2015). These results did go against Lee et al. (2011) and Wang and Lim (2013) study that found no statistical in diabetic status for morality outcomes in necrotizing fasciitis patients.

Going against Oud and Watkins (2015), this study did not find a statistical significance in mortality for necrotizing fasciitis patients mediated by obesity or chronic renal failure. The results of this study may have not shown statistical insignificant due to the smaller sample size compared to Oud and Watkins study. This study was aligned with the findings from Wang & Lim (2013) who found no statistical significance obesity or chronic renal failure for necrotizing fasciitis mortality outcomes.

Limitations of the Study

There are a few noted limitations in this study. The major limitation is the use of secondary data, which falls under the umbrella of misclassification. Misclassification can occur in secondary data when there are errors in data entry or diagnosis (Frankfort-Nachmias & Nachmias, 2008). Due to the threat of external validity by misclassification of secondary data than this study recognizes that temporal relationships cannot be recognized (Frankfort-Nachmias & Nachmias, 2008). Additionally, since this study is cross-sectional in nature, there cannot be a cause-and-effect relationship assumed for the population and study variables for other researchers (Frankfort-Nachmias & Nachmias, 2008). Though, the use of a large population that covers 97% of the of all U.S. community hospital discharges aids in the external generalizability of people and place in the United States with necrotizing fasciitis during the study period. Lastly, internal validity is the extent the results of the study are true ((Frankfort-Nachmias & Nachmias, 2008). Purposive sampling is a limitation in internal validity. However, and as mentioned previously, necrotizing fasciitis is a rare disease and purposive sampling is the best method to focus on specific characteristics of the population and have a robust population under study (Frankfort-Nachmias & Nachmias, 2008).

Recommendations for Future Research

Future research should focus on longer term outcomes of mean survival analysis of necrotizing fasciitis patients between genders. This research solely examined patients who had died while in the hospital. It would be beneficial to examine mean survival difference between genders of those who survive the initial stay in the hospital and see if

there is a statistical difference in mean survival time between the genders. Other studies could extent the years examined, since this study included a five year period, it would be beneficial to examine mean survival time in a ten year period for those who had been diagnosed with and died from necrotizing fasciitis and see if there is a difference between gender for mean survival time.

Another area that should be examined is the length of mean survival time for both genders in necrotizing fasciitis patients after leaving the hospital for those who have diabetes and those who do not have diabetes. Moreover, examining other demographic variables, like income, education, and inter-hospital transfer, would be helpful for mean survival time analysis for necrotizing fasciitis patients between genders and for both genders. Lastly, examining the mean survival time for both genders for other pre-existing conditions would be beneficial for necrotizing fasciitis research in the United States.

Implications

Positive Social Change

Increasing the knowledge of necrotizing fasciitis survival is of utmost importance to not only educate health practitioners and patients but also implement better practices of care. This research added to social change in the several ways. First, at a community level, this study gave more overall knowledge of necrotizing fasciitis survival factors in the United Sates and give health practitioners and patients of necrotizing fasciitis a more comprehensive awareness of the infection. This research also added to the body of literature in necrotizing fasciitis research. This study is unique in the manner that it is one

of the initial endeavors in the United States to statistically measure necrotizing fasciitis regarding gender, sociodemographic factors, and risk factors that can be associated with the mean survival time. This study was also unique in the manner that it is the only study that looked specifically at how sociodemographic factors and risk factors were associated to mortality outcome between the genders of necrotizing fasciitis patients. The results of the study aided to a better understanding of mortality outcomes between genders for necrotizing fasciitis patients. The study results also illustrated that both genders have an equal probability of mean survival time which went against most research findings. The study results found that diabetic status and older age for men were contributing factors to higher mortality for necrotizing fasciitis patients in the United States which gives public health, health practitioners, researchers, and patients more knowledge of the mortality outcomes.

Recommendations for Practice

Mortality of people diagnosed with necrotizing fasciitis ranges from 15% to 35% which is high for any bacterial infection. This research aimed to increase the knowledge of mortality outcomes to aid in the information and potentially help in different areas that treatment could focus on for patients of the infection. Older age and diabetic status are two key factors that contribute to higher mortality of people diagnosed with necrotizing fasciitis. Public health practitioners and providers can help reduce factors that contribute to mortality in necrotizing fasciitis by a better understanding of what is causing it. This study narrowed that gap in a small way and illustrated that diabetic status is a major issue

in mean survival time for necrotizing fasciitis patients which should be taken into account while treating them in short-term and long-term settings.

Conclusion

Necrotizing fasciitis is an uncommon bacterial infection. Yet, mortality rates still remain high ranging from 32% to 65% and the cost for the United States runs from $50,000 to $100,000 per patients (Mukhopadhyay, et al., 2011; Widjaja, et al., 2005). Since necrotizing fasciitis is rare, diagnoses can be problematic because it can often be overlooked but extensive research has revealed best practices for diagnostics of necrotizing fasciitis to be surgical exploration and tissue biopsy (Davoudian & Flint, 2012). Research has also focused much attention on treatment of necrotizing fasciitis which illustrates that surgical debridement and antibiotic treatment to be the best course of action (Anaya & Dellinger, 2007; Meyers, 2012; Shimizu & Tokuda, 2010).

Management and survival analysis has limited research in necrotizing fasciitis outcomes. This leaves a gap in knowledge for health practitioners, public health, patients, and families of those diagnosed with necrotizing fasciitis. Along with a few other researchers, this research starts to close the hole in the unknown for survival analysis and outcomes for necrotizing fasciitis patients. The results illustrate that there is an equal chance of survival for both genders that had not been previously studied. Additionally, the results of this study, illustrated that older men have a lower chance of mean survival from necrotizing fasciitis than younger men. However, women's age was not statistically significant in mean survival outcomes. Lastly the results of this study, show that both

genders have a higher mortality when the patient is diabetic compared to those that are not diabetic.

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