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The impact of ventilator-associated pneumonia among prehospital intubated patients.

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The Impact of Ventilator-Associated Pneumonia among Prehospital Intubated Patients

by

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Abstract

The objective of this study was to determine if all-cause mortality and hospital length of stay among patients who develop ventilator-associated pneumonia (VAP) differs for patients intubated in the Prehospital setting compared to those intubated in the Emergency Department.

A retrospective cohort design was employed and secondary data was retrieved from the local VAP Surveillance database and manual chart reviews. Intubated patients entered the cohort upon VAP diagnosis and exited upon death or hospital discharge.

This study used data from three large inner-city adult hospitals within Calgary, Alberta Canada. The sample (n=193) consisted of all adult (>18 years old) patients that developed VAP in an Intensive Care Unit who were intubated either in the Prehospital or Emergency Department setting during the study period (January 01, 2005 and December 31, 2009).

Patients in this study intubated in the Prehospital setting were very similar to patients intubated in the Emergency Department with regards to basic demographic and admission characteristics.

This study provides several novel results about the association between endotracheal intubation (ETI) location and morbidity and mortality among patients who acquire VAP in the ICU. Patients who suffer severe illness or injury (APACHE II score >25) are more likely to die if they are intubated in the Prehospital setting compared to the Emergency Department (p=<0.001). Furthermore, Prehospital ETI patients who die, do so sooner than Emergency Department ETI patients; whereas Prehospital ETI patients who survive, have longer hospitalizations than their Emergency Department counterparts (p=<0.001).

Perhaps preventing ETI in the Prehospital setting or postponing ETI until Emergency Department would result in decreased hospital mortality. Further research is required before this information should be used in a clinical setting.

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To Alyssa,

I love everything you are, and all that you will be.

Table of Contents

List of Tables

List of Figures and Illustrations

List of Abbreviations

Abbreviation	Definition
APACHE	Acute Physiology and Chronic Health Evaluation
CI	Confidence Interval
ED	Emergency Department
EMS	Emergency Medical Services
ETI	Endotracheal Intubation
GCS	Glasgow Coma Scale
GNB	Gram Negative Bacteria
ICU	Intensive Care Unit
LOS	Length of Stay
MH	Mantel-Haenszel
OR	Odds Ratio
PH	Prehospital
RR	Risk Ratio
RSI	Rapid Sequence Induction
SD	Standard Deviation
SOFA	Sequential Organ Failure Assessment
TBI	Traumatic Brain Injury
VAP	Ventilator-Associated Pneumonia

CHAPTER ONE: INTRODUCTION

Prehospital[1] endotracheal intubations (ETI) are performed in less than ideal settings. The circumstances are often difficult, little preparation is possible and the environment is uncontrolled and contaminated. Current evidence about the efficacy and effectiveness of Prehospital ETI is inconsistent. (1-5) Urgent intubations are also performed in the emergency department. However, patients intubated in the Prehospital setting have lower survival rates than patients intubated in the emergency department, even though the first-attempt success rates and frequency of complications are similar for both settings. (2,6-11) Studies suggest that patients who are properly intubated in the Prehospital setting often survive the initial life threatening event but they do not survive the subsequent hospital stay. (2,12) Presently, the only long-term outcomes that have been extensively studied for patients intubated in the Prehospital setting are death and neurological status. (2,9,12,13)

In-hospital respiratory infections, specifically pneumonias, are quantifiable intermediate outcomes that are clinically important for intubated patients, regardless of initial setting of intubation. (14-19) Ventilator-associated pneumonia (VAP) is a serious nosocomial infection that has considerable attributable morbidity and mortality.

This thesis will describe and compare the mortality, length of stay and disease burden of ventilator-associated pneumonia among patients who are intubated in the Prehospital and Emergency Department settings. The results of this project are intended to provide findings to direct practice guidelines and further studies for both Prehospital and in-hospital management of intubated patients.

Purpose

The purpose of this retrospective cohort study was to describe patient outcomes and disease burden of VAP among adult patients, regardless of illness or injury type, who

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[1] Prehospital Setting- the time and space in which medical care is provided before and during transport to hospital, also known as “Out-of-Hospital”.

have an ETI initiated in the Prehospital setting in comparison to those who have an ETI initiated in the Emergency Department within a large urban city.

Objectives

Primary

The primary objective of this study is to determine if all-cause mortality and hospital length of stay differs for patients who develop ventilator-associated pneumonia for those patients intubated in the Prehospital setting compared to those intubated in the Emergency Department.

Secondary

The secondary objective is to describe the differences in ventilator-associated pneumonia etiology and microbiology between patients intubated in the Prehospital setting and patients intubated in the Emergency Department.

Rationale and Relevance

There is substantial controversy about the efficacy of Prehospital intubations and a sufficient gap in knowledge regarding intermediate sequelae that may affect long term outcomes. Ventilator-associated pneumonia is a nosocomial infection that is associated with prolonged mechanical ventilation of intubated patients. This disease is associated with increased morbidity, increased length of stay and increased mortality. (16,17,20-24) Not only does this disease cause poorer patient outcomes, it also puts considerable financial pressure on the healthcare system. Annually, the Canadian healthcare system pays an additional $46 million dollars for the costs associated with VAP. (25) Understanding the differences in outcomes for these groups of patients may enable targeted treatments, which are more efficient and ultimately cost less.

This work is interesting and timely because it rides the crest of the wave of integrative healthcare. More and more healthcare delivery systems are realizing the benefits of having one complete health record - from cradle to grave. This work mirrors

the notion that events which happen in the Prehospital setting likely impact those in the hospital and future outcomes.

Summary of Thesis Format

This thesis begins with a description of endotracheal intubations and the necessity of this procedure in emergency situations. Chapter two continues with a review of the literature regarding the controversies of endotracheal intubation in the Prehospital setting. Furthermore it compares the success and complication rates and outcomes to intubations in the Emergency Department. The literature review introduces the need to account for intermediate outcomes and discuss the risk factors, pathophysiology and microbiology of ventilator-associated pneumonia. A detailed description of the methodology used in the design and procedure of this retrospective cohort study is presented in Chapter three. The characteristics of the study sample and results of the statistical analysis are presented and discussed for the primary objective in Chapter four. The results of the secondary objective are presented in Chapter five. Finally, this thesis concludes with a discussion of the strengths and limitations of this research, a summary of the findings and their implications and recommendations for clinical practice and future research in Chapter six.

CHAPTER TWO: LITERATURE REVIEW

This chapter begins with an introduction to endotracheal intubation and its use in both the Emergency Department and Prehospital setting. The next section discusses and compares the success rates and immediate and long term complications associated with intubation within these two locations. The account of current literature identifies a paucity of research that addresses the impact of intermediate outcomes, such as ventilator-associated pneumonia, among patients who are intubated in the Emergency Department and Prehospital Setting. Therefore, the next section introduces the reader to the diagnosis, risk factors, pathophysiology and microbiology of ventilator-associated pneumonia. The review then describes the outcomes, covariates and data sources used in this study. Finally, the chapter ends with a summary and brings to light the significance of studying this topic.

Endotracheal Intubation

Intubation, the insertion of a soft-plastic lumen (tube) into the trachea, is used to maintain airway patency and deliver adequate ventilation to a patient who is unable to perform this essential function. It is the definitive procedure to ensure airway control during resuscitation. Successful tracheal intubation can be attained by inserting the tube via the nasal cavity (naso-tracheal intubation), the oral cavity (oral-tracheal intubation), or through a surgical incision in the cricoid cartilage (cricothyrotomy). The tube then passes the epiglottis, through the larynx and into the distal trachea just above the carina.

Proper tube insertion and placement is essential to maintaining adequate oxygenation and avoiding complications. Intubation is an advanced life saving skill that is performed on critically ill patients by qualified practitioners. It requires extensive training and regular practice. (6,26,27) Failure to perform this task properly or in a timely manner has been demonstrated to be harmful to patients. (3,4,8,9,28,29)

Various methods are used to ensure appropriate placement of the tube, such as: capnography; bag compliance; oxygen saturation; chest and gastric auscultation; abdominal distension; and chest radiograph. Methods used to ensure proper ETI

placement in the Prehospital setting are not as numerous as those in the hospital, and vary between Emergency Medical Services. Patient transport may also contribute to the added difficulty in maintaining proper tube placement.

Intubations are performed in various patient care settings throughout the hospital. Many patients in the Operating Room require intubation prior to surgery, however these intubations are non-emergent. Other more emergent intubations, occur in the Intensive Care Unit, on wards and of course, in the Emergency Department

Intubation in the Emergency Department

Karch et al. (1996) demonstrated that ETIs performed in the Emergency Department are most comparable to ETIs performed in the Prehospital setting because of ETI settings the Emergency Department environment most simulates the Prehospital environment. (12) Endotracheal intubations executed in the Emergency Department are typically done by physicians.

Intubation in the Prehospital Setting

Approximately 5.1 percent of all PH encounters[2] result in an attempted ETI. (30) Prehospital ETIs have additional complexities in comparison to intubations done in the Emergency Department setting. Paramedics perform ETI in uncontrolled situations with multiple distractions and without the assistance of nurses or intubation specialists, such as anesthetists.

Several researchers have evaluated the effectiveness of ETI in the Prehospital setting. Thus far, the results have been inconsistent. Four studies conclude that ETI in the Prehospital setting is no more effective than other less invasive methods of airway control, such as bag-valve mask, and sometimes can be harmful. (31-33) However, other research suggests that intubations done in this setting are beneficial as cardiac arrest survival rates are lower in communities where paramedics are not trained to intubate. (3,5,34)

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[2] In this study the term encounter is defined as: the time at which a patient first seeks emergent medical attention from a care provider (either in the Prehospital setting or Emergency Department) .

Success Rates

The expertise of the intubating practitioner has been shown to be highly correlated with first attempt successes and lower complications. Garza et al. (2003) demonstrated that paramedics who have the highest number of previous opportunities for intubation attempts also have the highest percentage of first attempt successes. (6)

Research that compares success rates in in the Prehospital setting to those in the Emergency Department shows that intubations done in the Prehospital setting are typically less successful. (4,11) First attempt success rates for the Emergency Department range from 80% to 90%. (7,9) In contrast, success rates for paramedics have been reported as low as 24% and as high as 80%. (6,8,10) Although reported paramedic success rates are variable, more recent studies indicate that Prehospital success rates are approaching the Emergency Department rates. (35)

Complications and Outcomes

Immediate Outcomes

Although emergency ETI is a lifesaving procedure, it may result in serious consequences when performed on inappropriate patients or administered incorrectly. As many as 60% of all ETI patients experience at least one complication, regardless of setting. (36) Several studies have outlined complications related to ETI, which include: hypoxia/desaturation; mucosal lacerations; esophageal intubation; hypotension; cardio-respiratory arrest; vomit/regurgitation; new on-set cardiac dysrthymia; bradycardia; aspiration; elevated arterial carbon dioxide; self-extubation; excessive cuff pressure; main-stem bronchus intubation; and inability to seal the airway. (9,13,26,27,29,36) Failure to recognize and address any of these problems can result in poor patient outcomes and death. (3,4,8,9,28,29)

Occasionally, one or more of these complications will result in failure to intubate and subsequent attempts are needed. Common causes of intubation failure include: gagging/combative patient (32-38%); blood/vomitus in the airway (16-23%); and difficult anatomy (39%). (4,12,30) Re-intubation may be required as a result of one or

more of these complications and occurs in approximately 13% of cases. (7) However the re-intubation rate is even higher in situations where paralytic agents are used to subdue patient reflexes, such as rapid sequence induction intubations. (7) There is a direct relationship between the number of intubation attempts and the frequency of complications; as the number of intubation attempts rises, so does the frequency of complications. (26)

Long term Outcomes

In addition to the immediate complications, listed above, patients who survive the initial critical event and are hospitalized are at risk of developing long term sequelae. The two long-term outcomes that have been studied for Prehospital patients are mortality and changes in neurological status.

A review, by Wang and Yearly in 2004, summarized the results of several studies that compared Prehospital ETI with groups that varied by airway interventions and location, including Prehospital bag valve mask, Emergency Department ETI, and no ETI (Table 2.1). (37) The table was amended to only include studies that compare ETI done in the Prehospital and Emergency Department settings. Three out of four studies indicate that the odds of mortality are higher for ETI performed in the Prehospital setting compared to those done in the Emergency Department. All of these studies include only severe traumatic brain injury (TBI) patients. Consequently, these results are likely not indicative of the odds of mortality or poorer neurological status for non-TBI patients.

There is no published research that describes the long term outcomes for all types of Prehospital ETI patients (i.e. including medical/non-traumatic, all types of trauma, and neurological) compared to Emergency Department ETI.

A recent study by Wang et al. (2009) that evaluated the impact of immediate complications, suggested that ETI performed in the Prehospital setting are not associated with deaths that occur up to and including the time until hospital admission. (41). On the other hand, Prehospital ETI patients have poorer long term neurological success and higher mortality than their Emergency Department counter parts. There is a paucity of

research regarding intermediate outcomes that may account for the divergence of long term patient success between these two settings.

Table 2.1: Summary of Studies Evaluating Mortality or Neurological Outcome after Endotracheal Intubations Performed in the Prehospital Setting compared to those Performed in the Emergency Department for Severe Traumatic Brain Injury Patients.

Study	Design	Size	Mortality (OR; 95%CI)	Neurological Status (OR; 95%CI)
Bochicchio et al. 2003 (38)	Prospective	PH n=78 ED n=113	Higher for PH group (2.1; 0.9-5.0)	Not Evaluated
Wang et al. 2004 (2)	Retrospective	PH n=1797 ED n=2301	Higher for PH group (4.0; 3.2-4.9)	Poorer for PH group (1.9; 1.3-2.5)
Davis et al. 2005 (39)	Retrospective	PH n=2,665 ED n=2,220	Higher for PH group (2.1; 1.8-2.5)	Not Evaluated
Sloane et al. 2005 (40)	Retrospective (RSI patients only)	PH n=47 ED n=267	No difference (0.6; 0.1-2.6)	No difference (1.1; 0.3-3.8)

Note: This is a modified version from Wang and Yealy's "Table-Studies evaluating survival or neurological outcome after out-of-hospital endotracheal intubation". (37) CI= Confidence Interval; ED=Emergency Department; OR= Odds Ratio; PH=Prehospital; RSI= Rapid Sequence Induction.

In-hospital respiratory infections, specifically pneumonias, are a quantifiable intermediate outcome that is important for all intubated patients. (14-19,42) In all settings, ETI is associated with the development of severe respiratory infections. The endotracheal tube prevents normal host defense mechanisms, such as, cough and mucocilary clearance. Davis et al (2006) describes the ETI as an "anatomical barrier and a direct conduit that allows for rapid access of pathogens into the lower respiratory tract." (17)

Ventilator-Associated Pneumonia

Infections that develop after a patient has been in the hospital longer than 48 hours are called nosocomial or "hospital-acquired" infections. One of the most serious infections for intubated patients is nosocomial pneumonia. Nosocomial pneumonia is a lung infection that was neither present nor incubating at the time of admission to a

healthcare facility. Intubated patients have longer hospitalization and nearly twice the risk of mortality from nosocomial pneumonia than patients who are not intubated. (14,19,20,43)

Ventilator-associated pneumonia (VAP) is a pneumonia that is associated with invasive mechanical ventilation following intubation. (19) The Institute for Healthcare Improvement (2009) defines VAP as a pneumonia occurring in patients requiring a device intermittently or continuously to assist respiration through a tracheotomy or endotracheal tube, which must have been placed within 48 hours of infection and for at least two consecutive days. (44)

Surveillance is often performed to measure the nosocomial pneumonia rates among Intensive Care Unit patients. The patients admitted to the ICU are a unique surveillance group because they have a high index of severity and many require invasive medical procedures, such as endotracheal tubes, which are often necessary for survival. VAP surveillance is performed in the ICU because it is a common, preventable disease with important consequences.

Incidence

Ventilator-associated pneumonia in ICU patients has been studied extensively. One measure of the burden of VAP is the incidence rate, which is the number of new cases over a certain period of time.

A study by Muscedere, Martin and Heyland published in 2008, describes the burden of VAP within the Canadian healthcare system. They estimated that the incidence of VAP was 10.6 cases per 1000 ventilator days (95% CI -2.4-14). (25) However, a study by Garrard and many others suggest that the incidence can range from 5-15 cases per 1000 ventilator days. (45)

Diagnosis

Quantitating and describing the disease burden of VAP depends on the criteria and definitions use to confirm a diagnosis. Most hospitals and regulatory bodies have relatively similar diagnostic criteria. However these differ in practical application due to varying patient populations, laboratory techniques, and equipment availability. The VAP

"gold standard" diagnostic criterion is unclear, though some have suggested a post-mortem histological exam is definitive. (16) In absence of an autopsy, most healthcare facilities focus on information from two sources to confirm a diagnosis: patient presentation and chest radiograph (x-ray).

Signs and symptoms of pneumonia include: fever; purulent secretions; leukocytosis or leucopenia; and alterations in lung mechanics and gas exchange. X-rays are reviewed for new or progressive pulmonary infiltrates shown on serial chest radiographs.

Quantitative or qualitative microbiological cultures from the respiratory system are commonly captured for surveillance purposes, and can also be used to further classify the VAP diagnosis. Culture specimens from the lower respiratory tract can be obtained by a variety of methods such as: endotracheal aspirate; protected brush; and bronchoalveolar lavage. The significance of quantitative results from cultures depends on the specimen collection technique utilized. In general, bronchoalveolar lavage results that report microbial counts of $\geq 10^4$ cfu/ml (colony forming unites per millilitre) are considered very supportive of a VAP diagnosis when combined with other signs and symptoms. (20,46)

This study used the definitions and diagnostic criteria set forth by the Department of Critical Care Medicine from Alberta Health Services. The guidelines stipulate that each patient must have met all of the following conditions to be classified as having VAP:

1. Admitted to the ICU for at least 48 hours
2. Received invasive mechanical ventilation continuously (>18 hours/day) via an endotracheal-tube or tracheostomy for at least 48 hours. (This does not include non-invasive ventilation such as continuous positive airway pressure or bi-level positive airway pressure.)
3. Onset of VAP is either while receiving or within 48 hours of having received invasive mechanical ventilation

4. Persistent new or progressive infiltrates, consolidation or cavitation on a chest x-ray.
5. At least one of either fever (>38.0˚C) or hypothermia (<35 ˚C), altered white blood count (>12,000 or <4,000 cells per cubic millimetre), or a change in the purulence, character or amount of sputum over 24 hours. (47,48)

These criteria is based on the National Nosocomial Infection Surveillance system definitions and remained unchanged over the study period to ensure a consistent definition was used.

The VAP diagnosis classification is a categorical value from one to six that represents the level of evidence supporting the VAP diagnosis. This score is assigned by the Infection Control practitioner based on time-dependent physiological, radiological and microbiological data. The diagnosis of VAP algorithm can be found in Figure 2.1.

The VAP diagnosis classification will be captured and described for the study sample. This variable is necessary to explain the similarities and differences of diagnostic criteria used to confirm VAP for the two exposure groups. Additionally, there are several methods of VAP diagnosis throughout the literature and including this information will ensure the results are generalizable.

Time to Diagnosis

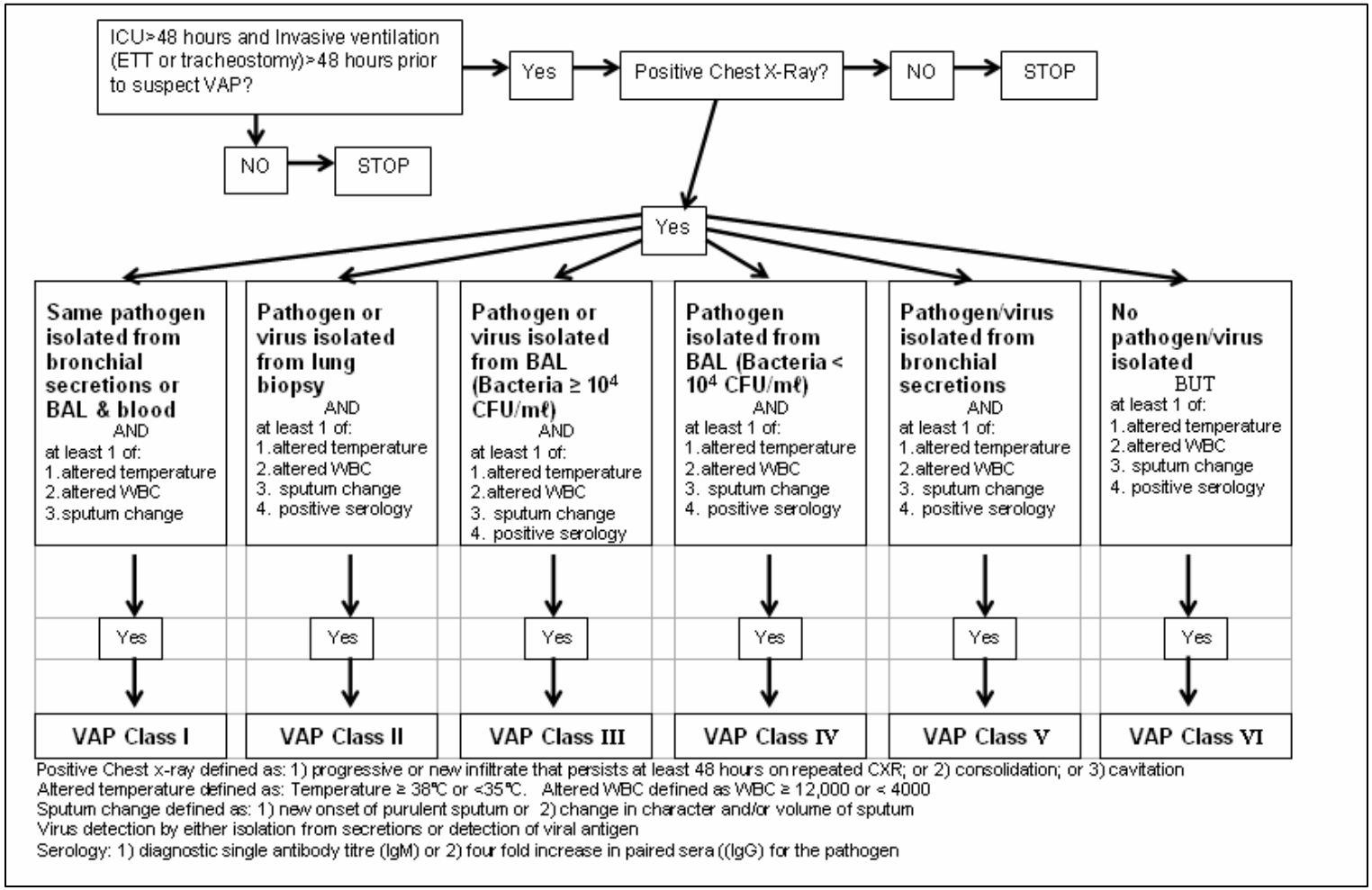
Another key piece of information regarding the diagnosis of VAP, is when it occurs. Although a VAP diagnosis can occur at any time during the hospitalization, in the Intensive Care Unit VAP is often categorized as early-onset versus late-onset. A patient is classified as having early-onset VAP when the signs, symptoms, radiological and microbial evidence culminate in a diagnosis in the first 4 days of hospitalization. Conversely, late-onset VAP occurs when the diagnosis is made greater than or equal to 5 days post admission. This dichotomization is based on the definition provided by Kollef et. al (1995) and commonly used throughout the VAP literature. (49)

This is an important covariate to include as studies suggest that the etiology and outcome of VAP may differ based on time to VAP diagnosis. (49) Patients who develop

VAP early in their hospital stay have a better prognosis than those who develop VAP later. (50) Patients who develop late-onset VAP are often infected with multi-drug resistant pathogens which are associated with a higher mortality rate. (46,50)

Currently, there is no literature indicating whether patients intubated in the Prehospital setting tend to develop early or late-onset VAP. In addition, there is no literature on whether patients intubated in the Prehospital setting have the same or different timing of onset in comparison to those intubated in the Emergency Department.

Figure 2.1: Diagnosis of Ventilator-Associated Pneumonia Algorithm



Note: This chart is an excerpt from the Infection Prevention and Control and Department of Critical Care Medicine, Alberta Health Services Calgary Zone VAP Surveillance Program Manual May 2010. (48)

Risk Factors

There are several conditions that increase the risk of developing VAP. A meta-analysis performed by Chastre and Fagon (2002) summarize several important host related risk factors: age ≥60; comorbidities such as pulmonary disease; impaired consciousness; organ failure; severity of illness; gastric aspiration; and gastric or upper respiratory tract colonization. (51)

Various admitting diagnoses have been shown to alter the risk of acquiring VAP as well. Cook and the Canadian Clinical Trail Group (1998) calculated risk ratios (RR) for developing VAP based on admitting diagnosis and found that patients with burns (RR=5.09, 95% CI: 1.52-17.03) have the highest risk. (52) The risk for patients with trauma (RR=5.00, 95% CI: 1.91-13.11), central nervous system disease (RR=3.40, 95% CI: 1.31-8.81), respiratory disease (RR=2.79, 95% CI: 1.04-7.51), and cardiac disease (RR=2.72, 95%CI: 1.05-7.01) follow in decreasing increments, respectfully. (52) These results were replicated by Rello et al just a few years later in 2002. (53)

Pathophysiology

Respiratory infections are acquired via three primary routes: aspiration; inhalation; and hematogenous spread (from another site in the body). Normally, without intubation, the lower respiratory tract is protected by extensive defense mechanisms. (19) Intubation results in an anatomical bypass route for invading microorganisms, and supports aspiration of oropharyngeal secretions and/or gastric contents colonized with microbial pathogens. (14,19) This is believed to be the most common mechanism for patients developing VAP.

Microbiology

Ventilator-associated pneumonia can be caused by a vast array of bacteria, viruses and fungi. However, bacteria are the most common causative isolate. (51) The microbiology of VAP differs significantly by reporting center and country.

In much of Europe and many centers in the United States, aerobic gram negative bacteria are the most common pathogens associated with VAP. (20) The reasons that gram negative bacteria are so successful in causing this disease are: their inherent

antibiotic resistance; they are adaptable for survival in harsh environments; and their ability to produce antimicrobial substances that inhibit competing microbes. (54) The five most common bacteria associated with VAP include: *Pseudomonas aeruginosa* (24.4%); *Staphylococcus* spp. (20.4%); Enterobacteriaceae (14.1%); *Haemophilus* spp.(9.8%); and *Streptococcus* spp. (8.0%) (according to a literature review from 1980-2001). (51) It is important to note, however, that up to 40% of all VAP are polymicrobial infections. (43)

The VAP surveillance program analyzing adult critical care units in Calgary identifies the most common pathogens associated with VAP to be: *Staphlyococcus* spp.; *Haemophilus influenzae;* and *Pseudomonas* spp. (47) This list is very similar to that noted in the meta-analysis above.

Although non-bacterial pathogens account for a small number of infections, their contribution is significant as these infections are not typically diagnosed until later in the progression of the disease and they are often difficult to treat.

The type of pathogens associated with VAP diagnosis has been shown to differ with regards to admission category. For example, patients with a history of chronic obstructive pulmonary disease are at increased risk for *Haemophilus influenzae*; whereas patients who experience a trauma are at an increased risk for developing VAP due to *Staphylococcus aureus*. (51)

Mortality

Most patients who require intubation are quite ill. There is limited data about the survival of patients who are intubated in the Prehospital setting. One study, by Egly et al. (2011) suggests that of all patients who suffer a Prehospital cardiac arrest only 20% survive long enough to be admitted to hospital, and only 7% survive until hospital discharge. (55) A similar study suggests that the survival rate for patients who are resuscitated within the hospital, including the Emergency Department, is 33%. (56)

Patients who suffer severe illness or injury, regardless of setting, most often end up in the Intensive Care Unit. The estimated mortality rate from 42 ICUs ranges from

6.4% to 40%. The patients in this study, though, have an additional infection to contend with and mortality rates for VAP are quite a bit higher than the general ICU population

The estimated all-cause mortality rate for patients diagnosed with VAP is reported to be between 20-74%. (14,17,42,43,49,52,57). Chastre and Fagon conclude that "ICU ventilated patients appear to have a 2- to 10- fold higher risk of death compared to patients without pneumonia." (51)

In the past, the attributable mortality for VAP was estimated to be between 25 to 43%. (20) Recent systematic reviews of the observational studies that assessed VAP-attributable mortality suggest that these estimates are variable due to differences in methodology and analysis. The actual attributable mortality is likely lower than originally thought. (22)

In 1990, Torres et al. set forth to explore which covariates were risk factors for death among VAP patients. Respiratory failure, fatal underlying condition, presence of shock and inappropriate microbial therapy were all associated with poor prognosis. (14) Other studies have suggested that bloodstream infection, severity of illness, and organ dysfunction be added to this list. (57)

There is no published research that describes the mortality rates for VAP patients who were intubated in the Prehospital setting compared to Emergency Department.

Length of Stay

Critically ill patients who survive to hospital discharge often have long hospitalizations. An increased length of stay results in higher healthcare utilization and cost. The financial impact of increased length of stay was quantitated by Davis et. al in 2006. That study reported that a single case of VAP in an ICU resulted in additional healthcare costs of $40,000 USD. Similarly in Canada, the estimated annual cost of all cases of VAP is $46 million dollars CND (for approximately 4000 cases). (25)

There are several ways to quantify length of stay; some studies measure days admitted to ICU while others use total days hospitalized. Several studies conclude that VAP causes a prolonged ICU and hospital length of stay.(58-61) One study in particular,

by Baker et al. (1996) suggested that VAP resulted in an additional 4.5 days in the ICU and a total of 9 extra days in the hospital. (62) More recently, Muscedere, Martin & Heyland (2008) mirrored those results for Canadian hospitals estimating an increased ICU length of stay of 4.3 days (95% CI 1.5-7.0) for each episode of VAP. (25)

Heyland et al. (1999) identified that medical admission diagnosis and certain pathogen types are risk factors associated with a prolonged length of stay among VAP patients.(63) Another study that discusses risk factors indicates that severity of disease (acute physiologic derangements) is the highest relative contributor to increased length of stay among all types of ICU patients. (64)

There is no published research that describes changes in length of stay for VAP patients who were intubated in the Prehospital setting compared to Emergency Department.

Covariates

A list of clinically relevant covariates was decided upon prior to commencing the study. These covariates were chosen because they are or have been identified as risk factors of the primary outcomes and are readily available. The inclusion of these variables will aid in the accurate description of the results in this study.

Acute Physiology and Chronic Health Evaluation II score

The Acute Physiology and Chronic Health Evaluation II (APACHE II) score was developed by Knaus et al. in 1985 as a disease severity classification system (65). It is a 71 point score calculated by a combination of age, previous health status and physiologic measurements. Higher scores correspond to more severe disease and higher risk of death. Several studies have identified APACHE II score as an independent predictor of mortality among VAP patients. (66)

Since this variable can change over the course of the VAP episode it is important to specify which APACHE II scores to use. Gursel & Demitras (2006) concluded that an APACHE II score taken at the time of VAP diagnosis was the best predictor of mortality. (67) This time-dependent variable was not available. Instead, APACHE II score taken at

the time of admission to the ICU was used. Since this variable is closer in time to the intubation it will serve as a better surrogate for initial severity. This is important to capture as a difference in initial illness or injury severity may explain the difference between Prehospital and Emergency Department intubated patients and their outcomes.

Admission Category

It is reasonable to propose that admission category may confound the exposure-outcome relationship. For example, a patient who suffers a stroke, which causes progressive neurological deterioration, may not require ETI in the Prehospital setting but as time passes, may require it later on in the Emergency Department. In contrast, the necessity for ETI may not change over time for a patient who suffers a significant trauma. Several studies suggest there is a difference in mortality for trauma patients who are intubated in the Prehospital setting compared to the Emergency Department setting. (37,68) There is also evidence to supporting results that indicate a difference in mortality among VAP patients based on admission category. (51)

Age

Aging alters pathophysiology and disease progression and elderly people are at a greater risk of death, therefore age is a necessary variable to include in the analysis as it may act as a confounder.

Gender

Gender is a confounder of many disease-mortality relationships. It is plausible to suggest that VAP etiology and mortality differs between men and women. Gender may also be related to other covariates. For example, the primary diagnosis (captured as admission category) may differ for men and women. Men are more likely to participate in high risk activities, leading to a higher proportion of traumatic admissions, in turn affecting the intubation location and patient mortality as well.

Sequential Organ Failure Assessment score

The Sequential Organ Failure Assessment score was designed to determine the extent of a patient's organ function and failure among critically ill patients. (69). This is a 24 point scoring system, where higher scores correspond to more severe disease and a

higher risk of death. SOFA score has also been identified as a predictor of mortality among VAP patients. (24) SOFA scores are time-dependent variables and, like APACHE II, SOFA scores were collected at the time of ICU admission.

Data Sources

Ventilator-Associated Pneumonia Surveillance Database

The VAP Surveillance program was started in 1998 to collect, track and report epidemiological data about VAP throughout the adult ICUs in Calgary. This program is run by Infection Prevention and Control within Alberta Health Services Calgary Zone and the Department of Critical Care Medicine at the University of Calgary. An Infection Control practitioner is assigned to actively capture suspicious cases from diagnostic triggers. Since Infection Control practitioners review all results from respiratory cultures sent from the ICU, the most common trigger is microbiology. Automated microbial surveillance has been shown to capture just as many or more cases in comparison to comprehensive surveillance. (70-72)

The key assumption in using microbiology as a trigger is that the performance of a respiratory culture indicates some suspicion for respiratory infection, as routine cultures are not done upon admission to the ICU. In the ICUs included in this study, it is not routine to perform an endotracheal aspirate culture unless there is clinical suspicion of infection.

Secondary methods of case identification are either radiology or clinical suspicion. The practitioner follows a strict set of guidelines based on time, physiological measurements, treatments and diagnostic tests to determine if a suspicious case meets the VAP criteria and definition. Using the algorithm posted in Figure 2.1, each case is then assigned a class based on the level of evidence provided. (48)

The database which supports this program is comprised of several sources of patient information. The ICU uses a bedside charting system (Quantitative Sentinel 6.6.9 Clinical Information System- GE Marquette Medical Systems Inc., Milwaukee, WI). This system integrates information from electronic patient monitors as well as other measures

captured by care providers. All patient information is stored in a local database, called ICU Tracer. The ICU Tracer database provides the basis of the dataset used by the VAP Surveillance program.

Once a trigger for VAP is identified, pertinent information is uploaded to the VAP Surveillance database. Other information such as pharmacy records, diagnostic images and microbiology data are also pulled into the VAP Surveillance database. A full data review is conducted for each suspected VAP episode by a trained Infection Control Practitioner. The Infection Control Practitioner decides if the criterion for diagnosis is met and assigns a classification based on the available evidence. Cases in which a conclusion cannot be made, are further reviewed by a multidisciplinary group.

Use of Secondary Data

The use of the data from the VAP Surveillance program for the purpose of research was not the original intent of the database. In using secondary data researchers are often limited to the number and quality of potential confounders and have no influence over definition or categorization of variables. This database was chosen as its design and content was extremely relevant to this project. During the design of this study a list of necessary variables was developed. Since this database includes a combination of information from several sources all of the variables discussed *a priori* were able to be included in the final dataset. The issue of defining variables is also sidestepped because the VAP Surveillance program was built to use standardized definitions based on the National Nosocomial Infection Surveillance system. (73) The use of this data had several advantages: inexpensive, quick and complete.

Collecting this data prospectively would be very labour intensive and take several years. Using retrospective data saved both time and money. Since this data is pulled directly from electronic charting systems, the physiologic and diagnostic information is deemed reliable and accurate as it is the same information used to treat the patient at the bedside. This database has also been used in the past for other projects. (74)

Summary and Significance

Studies suggest that patients who are properly intubated in the Prehospital setting often survive the initial life threatening event but may not survive their subsequent hospital stay. Though many factors likely contribute to hospital mortality over and above the presenting illness, the acquisition of nosocomial complications has been identified as one key influence to outcome. Ventilator-associated pneumonia is the most important nosocomial infection for intubated patients in terms of associated attributable morbidity and mortality.

Research is needed to follow patients from Prehospital intubation through to discharge and describe in-hospital events and sequelae that affect the risk of poor outcomes and death. This type of research would be important for evaluating and modifying practice guidelines for Prehospital and in-hospital management of intubated patients and it would provide necessary feedback about patient outcomes to paramedic services.

CHAPTER THREE: METHODOLOGY

This chapter provides a detailed description of the methodology used in this study. The research design is declared followed by a description of the setting and sampling procedures. A brief listing of operation definitions is then provided for the reader. Finally, a thorough explanation of the data acquisition process, preparation and analysis techniques is presented.

Research Design

This study was conducted using a retrospective cohort design. This is an observational design based on secondary data from the local ventilator-associated pneumonia (VAP) surveillance database and chart reviews. This design provides maximal congruency with the research objectives as it is an efficient way to study rare exposures, capture incident events, and explore multiple covariates.

The timeline theory associated with the design of the study can be seen in Figure 3.1. A patient must endure a critical event, such as cardiac arrest or sufficient trauma to necessitate intubation either in the Prehospital or Emergency Department setting. These patients are then cared for in the Emergency Department and then move to the Intensive Care Unit (ICU). The patients enter the cohort once a diagnosis of VAP is made. The inherent assumption with this design is that the patient is severely ill enough to require prolonged intubation and must remain alive long enough to make it to the ICU and develop VAP. Each patient was then followed through time to determine the length of stay and discharge status.

Figure 3.1: Study Design

Note: ED=Emergency Department; ICU=Intensive Care Unit; VAP=Ventilator-Associated Pneumonia.

Setting

This study was conducted within the City of Calgary, Alberta Canada. In 2009, the estimated population was 1,065,455. It is the largest municipality in Alberta and the third largest in Canada. (75) There are three large inner-city adult hospitals: Peter Lougheed Center; Rockyview General Hospital; and Foothills Medical Center. Each of the hospitals has an Emergency Department and a multidisciplinary ICU. Peter Lougheed Center and Rockyview General Hospital ICUs usually handle single-system trauma patients, while Foothills Medical Centre handles multi-system (polytrauma) trauma patients as it is a level 1 trauma center. Foothills Medical Centre also has a cardiovascular ICU.

In 2005, the total ICU bed count was 46 (Peter Lougheed Center=12; Rockyview General Hospital=10; Foothills Medical Center=24). By the end of the study, in 2009, the number of ICU beds has risen to 51 (Peter Lougheed Center=16; Rockyview General Hospital=10; Foothills Medical Center=25). In total, the four ICUs admit over 3,000 patients annually. The inner-city hospitals admit patients from Calgary, as well as all over southern Alberta, southeastern British Columbia, southwestern Saskatchewan and, in a few instances, the United States.

There are two main Emergency Medical Services (EMS) that provide care and deliver patients to these hospitals. The City of Calgary is currently served by a collective EMS administered by Alberta Health Services. However, the EMS Calgary Zone service was operated by the City of Calgary until April 2009. In 2009, the Calgary Zone EMS operated 45 ambulances with a call volume of approximately 112,464 per year. (76) Although administration changed, the call volume, the number of ambulances and operations did not change during the study period. In 2009, the department provided 100% Advanced Life Support (ALS) service, meaning each unit had a trained paramedic that can administer additional medications and perform advanced procedures (such as intubation).

The Shock Trauma Air Rescue Society is the second service that provides care to this population. It operated a 100% ALS helicopter service that responded to 1,368 calls

in 2009. (77) This service often works in conjunction with local services to transport critically ill patient quickly over long distances. This is the main method of transport for patients outside the City of Calgary limits. However, a small number of patients also arrived via ground transport from other services.

Study Population and Sample

Sampling Frame

The population that was investigated in this study consisted of all adult patients who developed VAP in a City of Calgary ICU that were intubated either in the Prehospital or Emergency Department setting during the study period. A consecutive sampling technique was used to identify all adult patients that were admitted to a City of Calgary ICU between January 01, 2005 and December 31, 2009. The sampling frame consisted of all patients who were identified as have VAP and entered into the VAP Surveillance database. The sample is comprised of all patients who met the following inclusion criteria.

Inclusion Criteria

To be included in this study each patient met the following inclusion criteria:

- ≥ 18 years of age at time of ICU admission
- Successful ETI initiated in the Prehospital or Emergency Department setting
- Admission to City of Calgary ICU between January 1, 2005 and December 31, 2009
- First confirmed VAP episode (≥ 48 consecutive hours of ETI and invasive mechanical ventilation) as per the VAP Surveillance Database

Exclusion Criteria

Any patient that did not meet <u>all</u> inclusion requirements was excluded from the study. Additionally, a contingency plan was developed for multiple admissions to the ICU. It was decided that only the first ICU admission would be captured per hospital admission. Similarly, patients may also develop a second case of VAP after recovery

from the primary case during their first admission to ICU. Once again, only the first case of VAP was captured per hospital admission.

Patients were excluded from the analysis if the intubation location, length of hospitalization or discharge status could not be determined. Basic characteristics were described for all patients excluded for this reason.

Sample Size Calculation

The *a priori* sample size calculation was performed based on the number of ICU admissions, VAP incidence and clinical judgement. In 2007, Calgary area ICUs treated 2524 patients, 1972 (78%) which were ventilated. (47) There is no published data that describes the percentage of ventilated ICU patients who are intubated in the Prehospital or Emergency Department setting. In this absence, we estimate that approximately 18% of the ICU population was intubated in the Prehospital setting. (78) Therefore, approximately 355 ventilated ICU patients have Prehospital ETI annually.

The incidence of suspected VAP among ICU patients in Calgary area hospitals in 2007 was approximately 14%. (47) Assuming the proportion of patients that will develop VAP is the same for both Prehospital and Emergency Department patients (i.e. no difference between groups); we calculated that there are approximately 49 Prehospital ETI patients who develop VAP annually.

The crude mortality rates for patients who develop VAP ranges from 24-50%. (51) For the following calculation we assume that the crude mortality is, on average, 37%. A 50% difference in mortality was established as a clinically significant value. (78)

Using a two-sided sample size calculation, at the 5% significance level with 90% power to detect a 50% difference in mortality, a total of n=324 patients would be required for this study (n=162 for each group). The sample size was increased by an additional 15% to account for missing data. This raised the total sample size to n=374 patients (n=187 for each group).

According to this calculation, approximately five years of data was needed to attain a sufficient sample. Five years was a sufficient amount of time to account for

seasonal fluctuations of VAP, but not enough time to introduce biases due to protocol changes. This calculation balances both clinical significance and practicality.

Operational Definitions

The definitions, listed alphabetically, in this section are those used for this study.

Acute Physiology and Chronic Health Evaluation Score

In this study Acute Physiology and Chronic Health Evaluation (APACHE) II score, taken at the time of ICU admission, is recorded as a continuous variable. It can have a value between zero and 71. It is intended that this variable serves as a surrogate for severity taken at the same point in time for both patient groups (Emergency Department and Prehospital ETI).

APACHE II score was dichotomized at the 25 point mark. Patients who had an APACHE II score (upon ICU admission) of less than 25 represented were less severe than patients who had an APACHE II (upon ICU admission) score of greater than or equal to 25. This cut-point is commonly used in ICU literature and was first established by Bernard et al in 2001. (79)

Admission Category

Each patient was assigned an admission category based on the primary diagnosis assigned by an ICU physician. This category was confirmed by the admission diagnosis recorded in the chart review. There are four distinct admission categories: neurological; trauma; surgical; and medical.

A patient would fall into the neurological category if their admitting diagnosis relates to the central nervous system. Examples of this would include stroke syndrome, subarachnoid hemorrhage, status epilepticus, etc. The second category includes patients who have traumatic injuries (with and without a head injury). The third category includes all patients who were admitted for a surgical procedure. This does not include patients that had surgery for a traumatic injury. The final category, medical, captures all patients who do not fall under another heading.

Age

The patient's exact age, in years, as of the date of the initial encounter was recorded as captured as a continuous variable. Age was calculated as follows:

Age= Date of Initial Encounter – Date of Birth

During the analysis age was shifted left by 18 years to ensure regression results had a meaningful intercept (y=age-18). Age was also dichotomized at 65 years of age. This cut-point was chosen because it has been used previously in VAP literature and it allowed for adequate cells sizes during stratification.

Gender

In this study, gender is synonymous with sex and is dichotomized into either male or female.

Intubation Location

The exposure of interest for this study is location of the first successful endotracheal intubation (ETI). This means that the attempt to insert the tube into the trachea was confirmed by an external measure as mentioned in the literature review and charted as successful.

This exposure was dichotomized in to two groups of interest: (1) patients who are intubated in the Prehospital setting; and (2) patients who are intubated in the Emergency Department setting. Patients are considered 'exposed' if they were intubated in the Prehospital setting and 'unexposed' if they were intubated in the Emergency Department setting. The exposure classification was determined during the manual chart review. Since this is a fixed cohort study, exposure status could not change during the study period.

A patient who was intubated in the Prehospital setting, extubated in the Emergency Department and then re-intubated in the Emergency Department will be classified as an exposed patient, because the Prehospital setting is the location of the first

successful ETI. Patients who have a failed ETI in the Prehospital setting, and then a successful ETI in the Emergency Department will be classified as an unexposed patient.

Hospital Length of Stay

Length of stay (LOS) was a primary outcome in this study. It was captured as a continuous variable that describes the number of days from the initial patient encounter (critical event) to discharge from the hospital or transfer to a hospital outside the City of Calgary. The time prior to arrival at the study hospital is included as this information was available in the chart, whereas post-transfer information was not. This calculation represents the most accurate description of time and resources utilized. Length of stay was calculated as follows:

Hospital Length of Stay = Date of Hospital Discharge– Date of Initial Encounter

To further describe the relationship between LOS and covariates, the median of the entire dataset (40 days) was used as a cut-point for dichotomization.

Hospital Mortality

All-cause hospital mortality was a primary outcome in this study. It was captured as a dichotomous variable that describes the outcome of the patient upon discharge from the hospital or transfer to another hospital outside of the City of Calgary. All-cause mortality was described as either “alive” or “deceased”. This data element was captured by both the VAP Surveillance dataset and through the chart review to ensure accuracy.

Primary Microbiological Pathogen

The primary microbiological pathogen represents the causative organisms associated with the diagnosis of VAP. This assignment is based on results from respiratory specimens taken within 48 hours of the date of diagnosis (based on the date and time of the sentinel chest x-ray) as determined by survillance protocol.

This variable was categorized based on microbial properties. The three most common pathogens, *Staphylococcus aureus*, *Haemophilus influenzae*, and *Streptococcus* species, were kept separate. However, the remainder of the pathogens were classified as

either gram-negative bacteria or yeast species. Additionally there were separate categories for oropharyngeal flora and specimens in which no growth was detected.

Sequential Organ Failure Assessment Score

The Sequential Organ Failure Assessment (SOFA) score, taken upon ICU admission, was recorded as a continuous variable. It can have a value between zero (0) and 24.

SOFA was also dichotomized at the median score of the dataset, seven. Patients who had a SOFA score less than seven, had less organ dysfunction; whereas patients who had a SOFA score greater than or equal to seven, had a higher degree of organ dysfunction.

Time to Ventilator-Associated Pneumonia Diagnosis

The date of VAP diagnosis is based on the date of the chest x-ray that indicated a persistent new or progressive infiltrate, consolidation or cavitation. (48) The time to VAP diagnosis is the number of days from intubation until the date of sentinel chest x-ray, it is calculated as follows:

Time to VAP Diagnosis= Date of VAP Diagnosis-Date of Intubation

For descriptive purposes, time to VAP diagnosis was also dichotomized into two categories, less than 5 days and greater than or equal to 5 days. These two categories represent early-onset and late-onset VAP respectively. This dichotomization was chosen based on the definition provided by Kollef et. Al (1995) and commonly used throughout the VAP literature. (49)

Ventilator-Associated Pneumonia

All patients in this study were diagnosed with ventilator-associated pneumonia (VAP). The definition of VAP used in this study is a pneumonia occurring in ICU intubated patients requiring mechanical ventilation which must have been placed within 48 hours of infection and for at least two consecutive days. The diagnostic criteria used to classify VAP cases are listed in Figure 2.1 (above).

Data Management

The data collection procedure for this study began by getting a one-time data extraction from the VAP surveillance database of ICU patients admitted during January 1, 2005 to December 31, 2009. Using the inclusion criteria, a list of all the patients who developed VAP was generated. A manual chart review was performed on this sample to identify the location of the first successful ETI. The chart review information was transcribed into a spreadsheet program and synthesized into one dataset for analysis.

Data Sources

Ventilator-Associated Pneumonia Surveillance Database

The data elements extracted from the VAP Surveillance database are listed in Table 3.1. First name, last name, gender, and date of birth, Personal Health Number and Regional Health Record Number were collected to facilitate data linkages with paper charts. Gender and date of birth (used to calculate age) were also used as covariates for the analysis along with primary diagnosis, admission category, APACHE II score, SOFA score, and date of VAP diagnosis. Date of admission, date of discharge, and discharge status were used to calculate outcomes for the primary research objectives; whereas VAP diagnosis category and isolated pathogen were used to address the secondary research objectives.

The credibility and validity of this data was evaluated by cross-referencing specific data elements gleaned from the chart review. The quality and completeness of the data is discussed further in the data preparation section.

Table 3.1: Ventilator-Associated Pneumonia Surveillance Database Extraction Requirements

Symbol	Meaning
🔑	Item is used to facilitate accurate data linkage
➕	Item is used to calculate a variable for final analysis
1°	Item is used to address the primary research question
2°	Item is used to address the secondary research question
C	Item is an important covariate to be considered in final analysis

Note: This legend applies to Table 3.1 and Table 3.2.

Field	Data Type	Options	Purpose
First Name	Text	Free Text	🔑
Last Name	Text	Free Text	🔑
Gender	Dichotomous	M/F	🔑
Date of Birth	Date	MM-DD-YYYY	🔑
Personal Health Number	Numerical	#####-####	🔑
Regional Health Record Number	Numerical	########	🔑
Date of Admission	Date	MM-DD-YYYY	**1° (➕)**
Primary Diagnosis	Text	Free Text	**C**
Admission Category	Pick list	Medical/Trauma/ Surgical/ Neurological	**C**
APACHE II Score (on ICU admission)	Measured	###	**C**
SOFA Score (on admission)	Measured	###	**C**
VAP	Dichotomous	Yes/No	**1°**
VAP Diagnosis Category	Pick list	I/II/III/IV/V/VI	**2°**
Date of VAP Diagnosis	Date	MM-DD-YYYY	**C(➕)**
Isolated Pathogen	Text	Free Text	**2°**
Date of Discharge	Date	MM-DD-YYYY	**1° (➕)**
Discharge Status	Dichotomous	Alive/Deceased	**1°**

Note: APACHE=Acute Physiology and Chronic Health Evaluation II; DD= Day; F=Female; ICU=Intensive Care Unit; M=Male; MM=Month; SOFA=Sepsis-relate Organ Failure Assessment; VAP=Ventilator-Associated Pneumonia; YYYY=Year.

Chart Review

A manual chart review was performed on all confirmed VAP cases to identify details about the first successful ETI. Medical records were requested from the Health Information & Records Management department based on patient name, regional health record number and admission date. All chart reviews were completed using a standardized data collection form (Appendix A).

The data collection tool was created using guidelines described in "Case Record Form Design" by G. Lawrence and "Designing Case Report Forms" by Spriet. (80,81) Key data elements were internally validated by means of collecting several details about one item. For example, when assessing a case for the occurrence of intubation, a simple yes or no was not sufficient or valid. Other items, such as time of procedure and type of intubation, were recorded to support the statement of intubation.

The chart reviews were completed between August and October 2011 by a single reviewer. The data items extracted from the chart review are listed in Table 3.2. The data elements collected in the chart review were very similar to those extracted from the VAP surveillance database. The patient identifiers and primary outcome measures were recorded as previously explained. Additional covariates included were: patient treatment location (captured throughout entire encounter); severity measures upon admission; date of intubation; time of intubation; location of intubation; number of attempts; complications and rapid sequence induction status.

Data Preparation and Cleaning

The VAP Surveillance database extraction was received and managed using Microsoft Excel 2010 (Microsoft Corp, Redmond, WA). The data from the chart reviews was transcribed from paper to digital format. The chart review information was added to the VAP Surveillance excel dataset. As soon as the two data sources were assembled, all identifying information was stripped permanently from the dataset.

The data was evaluated for nonsensical, missing or duplicate data. All errors found were corrected using the original medical record. If a discrepancy was found between the two data sources, the chart review was used as the correct source.

Table 3.2: Chart Review Extraction Requirements

Field	Data Type	Options	Purpose
First Name	Text	Free Text	
Last Name	Text	Free Text	
Gender	Dichotomous	M/F	
Date of Birth	Date	MM-DD-YYYY	
Personal Health Number	Numerical	#####-####	
Regional Health Record Number	Numerical	#########	
Date of Admission	Date	MM-DD-YYYY	**1^{o} ( )**
Patient Flow (Several Fields)	Text	Admission Location, Method of Arrival, Facility Transfer	**C**
Primary Diagnosis	Text	Free Text	**C**
Admission Category	Pick list	Medical/Trauma no Brain Injury/ Trauma with Brain Injury/ Surgical/Neurological	**C**
Severity upon admission (Several Fields)	Text	Heart Rate, Blood pressure, GCS, Level of Consciousness	**C**
Date of Intubation	Date	MM-DD-YYYY	**1^{o}**
Time of Intubation	Time	##:##	**1^{o}**
Location of Intubation	Pick list	PH/ED/OR/ICU/Other	**C**
Number of Attempts	Measured	##	**C**
Complications	Dichotomous	Yes/No	**C**
Rapid Sequence Induction Status	Dichotomous	Yes/No	**E**
Date of Discharge	Date	MM-DD-YYYY	**1^{o} ( )**
Discharge Status	Dichotomous	Alive/Deceased	**1^{o}**

Note: APACHE=Acute Physiology and Chronic Health Evaluation II; DD= Day; F=Female; ED=Emergency Department; GCS=Glasgow Coma Scale; ICU=Intensive Care Unit; M=Male; MM=Month; OR=Operation Room; PH=Prehospital; SOFA=Sepsis-relate Organ Failure Assessment; VAP=Ventilator-Associated Pneumonia; YYYY=Year.

All data cleaning procedures were applied consistently to all records and documented in an electronic research log. The amount of unattainable or unusable data is described in Chapter four.

Data Analysis

The following section outlines the descriptive and statistical analysis performed on the dataset to answer each of the objectives of the study. The alpha level used in this study was 0.05. An alpha level is a fixed probability cut-off used to judge statistical significance. At this level, an observation that has a p-value of >0.05 is deemed "statistically non-significant"; whereas, an observation that has a p-value of <0.05 is deemed "statistically significant".

Several comparisons are made in the following chapter. It is important to consider that at least 5% of the statistical tests shown will be significant by chance alone. Additionally, several of the comparisons are made with very small cell sizes making the results less meaningful (especially in the secondary analysis).

These calculations were completed using Stata statistical software version 11.0 (StataCorp, College Station, TX). (82) Clinical significance was also considered during the interpretation of the analyses and is discussed further in chapter six.

Descriptive Statistics

The demographic and covariate characteristics of the study population, the study sample and then each exposure group is described and compared. Continuous variables are described using means and standard deviations. Dichotomous and categorical variables were described using proportions.

Comparative Analysis

The descriptive statistics of the two study groups were compared to determine if the measures were significantly different. Continuous variables were compared using two-sample student t-tests under the chi-squared distribution. The use of t-tests is justified as the observations are statistically independent (e.g. the age of one subject does not influence the age of another subject). Variables that have a right skewed distribution,

such as age, time to VAP diagnosis and hospital length of stay will also be described using means and standard deviations on the assumption that the data follows the central limit theorem because the sample size is greater than 30.[3] Dichotomous and categorical variables were compared using a two-sample test of proportions (Fisher's Exact, z-test) under the binomial distribution.

Stratified Analysis (Univariate)

A classic stratified analysis was performed to explore the potential effects of covariates on the relationship between intubation location and outcome. Stratified analysis is used to assess the effect of a risk factor on an outcome while holding another variable constant. Stratification, using criteria to separate a sample into homogenous groups, is an important technique that allows for the recognition of patterns, with regards to changes in the measure of association, across different levels of a variable. The stratified analysis was used to determine which variables should be included in the multivariate regression analysis.

Odds ratios were employed to quantify the measure of association. The odds ratio was calculated as the odds of the outcome for those intubated in the Prehospital setting over the odds of the outcome for those intubated in the Emergency Department. Two-sided confidence intervals, at the 95% confidence level, calculated using exact methods are used to demonstrate point estimate precision of each odds ratio. Confidence intervals represent the range in which there is 95% certainty that the true value of the parameter is encompassed.

Effect measure modification is defined as variation in the magnitude of a measure of association across levels of another variable. Effect measure modification was identified in the comparison of stratum specific estimates that differed 15% in magnitude from each other and had non-overlapping confidence intervals. In this study the Mantel-Haenszel test for homogeneity is also used to assess whether stratum-specific estimates

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[3] The central limit theorem states that even if the distribution of the individual observations is not normal, the distribution of the sample means will be normally distributed if the sample size is equal to or greater than 30. (UCLA Academic Technology Services, Statistical Consulting Group)

significantly differed from each other. The null hypothesis was that the two stratum specific estimates are equal. In contrast, the alternative hypothesis was that the two stratum specific estimates are not equal. A significant p-value indicated that there was effect measure modification across stratum. In addition to statistical significance, judgment of effect measure modification was also based on clinical significance. Covariates that did not vary by strata were further assessed for confounding.

Assessment of confounding was the next necessary step. Uncontrolled or unrecognized confounding causes a type of systematic error in which the measure of association is distorted due to the presence of an extraneous variable that is associated with both the exposure and the outcome. (83) The Mantel-Haenszel odds ratio is a weighted average of stratum specific odds ratio. This method of summarization is used to control for confounding. Confounding of the intubation location-hospital mortality association by an extraneous variable was identified by comparing the crude odds ratio with the Mantel-Haenszel odds ratio. This was captured as either a 15% difference in magnitude and non-overlapping confidence intervals. The Mantel-Haenszel test of homogeneity and Mantel-Haenszel adjusted odds ratio estimates are considered valid even in the presence of multiple stratifications (low cell sizes). (84)

Several of the continuous variables were dichotomized to facilitate this stratified analysis which may misrepresent the dataset. To evaluate the effect of each strata, dichotomized variables were created for variables that were categorized, such as admission category and pathogen. For example, trauma admission category was removed from the other admission categories. The new variable compared was trauma admission versus non-trauma admission.

The results of the descriptive statistics and comparative and stratified analyses were used to inform the model formation process of the regression analyses.

Regression Analysis (Multivariate)

Model Construction

Regression techniques provide odds ratio estimates while adjusting for several important covariates simultaneously. Models were constructed using variables from the

stratified analysis in which the Mantel-Haenszel test of significance p-value was less than 0.20 as well as any variable where a clinically significant difference was found between the Emergency Department ETI and Prehospital ETI groups.

Clinical significance, effect measure modification, confounding and plausible interactions were all considered while constructing the models. Forward stepwise regression procedures were used to develop hierarchically well formulated multivariable models. This means that all covariates (admission category, age, APACHE II score, gender, pathogen, SOFA score and time to VAP diagnosis) and the applicable interaction terms were added to the crude model one at a time. If an interaction term changed the crude estimate by more than 15% (effect measure modification), it was retained along with the original covariate term. Each covariate was also assessed for confounding through appropriate model ratio tests.

Covariates and interaction terms were added until no more changes in the estimate were observed or until the model was saturated. The assumptions for the various regression techniques were evaluated and each of the final models presented were assessed for specification errors and goodness of fit.

Primary Objective

Hospital Mortality

Logistic regression techniques were employed to calculate the odds ratio for being deceased upon hospital discharge for patients intubated in the Prehospital setting compared to those intubated in the Emergency Department. Coefficients for variables that indicated effect measure modification (i.e. exposure*covariate) or interaction (i.e. covariate*covariate) that have a significant p-value resulting from Wald z-test (based on the chi^2 distribution) were considered significant and kept in the model. Log likelihood ratio tests were used to compare nested models to assess for the presence of confounding.

Length of Stay

Linear regression techniques were used to describe the difference in the mean length of stay for patients intubated in the Prehospital setting compared to those intubated in the Emergency Department. The same evaluation for effect measure modification and

interaction were employed, however the student t-tests were used (which is based on the f-distribution) instead of Wald z-tests.

Time to Death

Cox-proportional hazard regression techniques were used to calculate the instantaneous risk[4] of death for patients intubated in the Prehospital setting compared to those intubated in the ED. Covariates that were significant in either the mortality or length of stay analyses were considered for inclusion in the model. Effect modification and interaction were evaluated in the same manner as logistic regression. As well, log likelihood ratio tests were used to compare nested models and to assess for the presence of confounding.

Secondary Objective

Two separate outcomes were evaluated to describe the etiology of VAP among patients intubated in the Prehospital and Emergency Department settings. The time to VAP diagnosis was evaluated using both stratified analysis and linear regression techniques as previously described. The primary pathogen associated with VAP was described in detail and a stratified analysis was performed to assess the impact of various covariates.

Ethical Considerations

Ethical review and approval was granted by Conjoint Health Research Ethics Board at the University of Calgary. Data from this study was extracted from Emergency Medical Service, Emergency Department and Intensive Care Unit records. Signatures approving this project from the appropriate Department Heads were obtained. Upon ethical approval by the Conjoint Health Research Ethics Board, access to patient care charts was granted and facilitated by Health Information and Records Management.

[4] Instantaneous risk is a term used to describe the conditional probability that death will occur in a defined period of time, given that it has not occurred before that interval.

Data from both electronic and paper charts were synthesised and matched using a unique identifier (Personal Health Number).

Consent

This study did not require patient contact or intervention and did not seek consent from the individual patients. A waiver of consent was granted by the Conjoint Health Research Ethics Board. Due to the retrospective nature of this study it was not feasible to obtain consent given many patients would have been deceased and many of the survivors would have been inaccessible. A study by Lizana et al. (2003) described the difficulty in longitudinally following ICU patients. A total of 51.8% of patients could not be reached 18-months post discharge (16.8% ICU non-survivors, 11.3% hospital non-survivors, 13.3% 18-months post discharge non-survivors, and 10.4% were lost to follow-up). (85)

This project was also conducted under the direction of the Infection Prevention and Control department as a quality assurance activity and clinical audit of the VAP surveillance database.

Privacy Protection

The management and protection of all data followed the Freedom of Information and Protection of Privacy Act, Health Information Act and ethical guidelines. Patient information was kept strictly secure throughout the study and all identifying information (i.e. first name, last name, Personal Health Number) was permanently removed from the dataset once the VAP Surveillance database and chart review information were synthesized. All published data will be presented in aggregate form, such that individual identification will not be possible.

CHAPTER FOUR: PRIMARY RESULTS

This chapter begins with an overview of the study population and sampling procedures. The characteristics of included and excluded patients are described, followed by an inventory of omitted data.

The focus of the chapter then turns to the results of the primary objective. The descriptive and comparative statistics, stratified and regression analyses are presented for all-cause hospital mortality and hospital length of stay. Then finally, a brief time to event analysis is presented.

Overview of Study Population

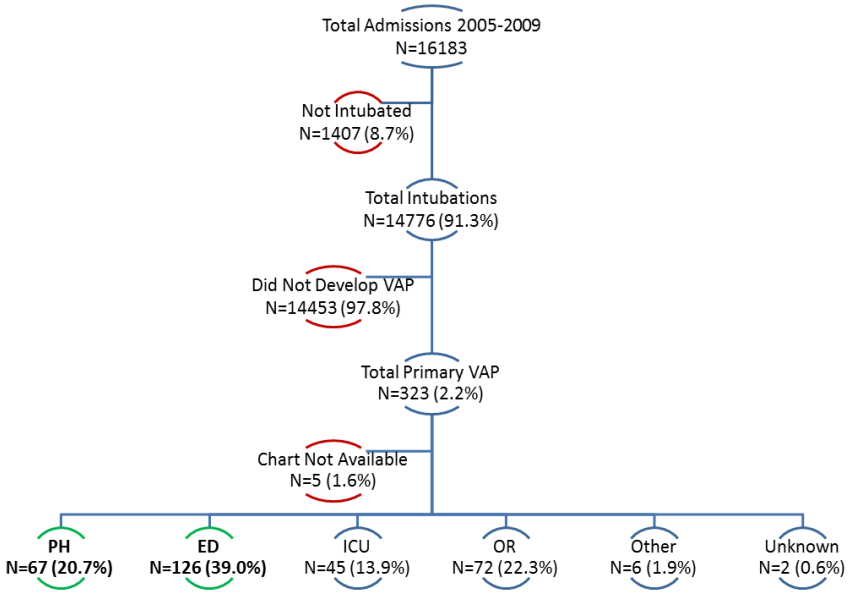
From the period of January 1, 2005 to December 31, 2009 there were a total of 16,183 admissions into the four Calgary Intensive Care Units (ICU). Although the majority of these admissions required intubation (91%, n=14776), there were only 323 (2%) primary episodes[5] of VAP. All of these patients were unique and at least 18 years old upon ICU admission.

A chart review was completed for all patients diagnosed with a primary ventilator-associated pneumonia (VAP). It was found that 20% (n=67) of VAP patients were initially intubated in the Prehospital setting and 39% (n=126) of VAP patients were initially intubated in the Emergency Department. The intubation location could not be determined for 7 patients (chart not available: n=5, unknown: n=2). A diagrammatic representation of the sampling frame can be seen in Figure 4.1.

Table 4.1 shows a comparison of the means and proportions for basic characteristics of patients who did not develop VAP and patients who did develop VAP. A higher proportion of patients who developed VAP during their ICU admission were male (no-VAP=63% vs. VAP=74%, $p<0.001$) and an average of 10 years younger (no-VAP=59.41±SD16.80 vs. VAP=49±SD19.79, $p<0.001$) than their non-VAP counterparts.

[5] Recall that this study is only examining the first VAP episode per hospital admission.

Figure 4.1: Overview of Study Sample



Note: ED= Emergency Department; ICU= Intensive Care Unit; OR=Operating Room; PH=Prehospital; VAP=Ventilator-Associated Pneumonia.

Although, the Acute Physiology and Chronic Health Evaluation (APACHE) II score upon admission, which serves as a proxy for disease severity, was not statistically or clinically different between the two groups (no-VAP=24.35±SD8.30 vs. VAP=25.21±SD7.61, p=0.06), the VAP patients did have poorer outcomes. The VAP group stayed an average of 36 days longer in the hospital (no-VAP=22.35±SD34.19 vs. VAP=58.74±SD66.46, p<0.001) and suffered a higher proportion of deaths than patients without VAP (no-VAP=18% vs. VAP=28%, p<0.001).

Table 4.1: Means and Proportions of Basic Characteristics for Intensive Care Unit Patients who did not develop Ventilator-Associated Pneumonia compared to those who did develop Ventilator-Associated Pneumonia

	No VAP n=15,860	VAP n=323	*P*
Age (years), mean±sd	59.41±16.80 (6 missing values)	49.19±19.79	<0.001†
Gender			
Female	5,937(37%)	85(26%)	-
Male	9,917(63%)	238(74%)	<0.001†
APACHE II score*, mean±sd	24.32±8.30 (48 values missing)	25.21±7.61 (3 values missing)	0.06
Hospital Length of Stay (days), mean±sd	22.35±34.19 (343 values missing)	58.74±66.46	<0.001†
Hospital Mortality			
Alive	12,929(82%)	232(72%)	-
Deceased	2,931(18%)	91 (28%)	<0.001†

Note: All results are represented as "n (%)", unless otherwise stated; * indicates the measure was taken upon ICU admission; † indicates p-value <0.05; APACHE= Acute Physiology and Chronic Health Evaluation; ICU= Intensive Care Unit; sd= Standard Deviation; VAP= Ventilator-Associated Pneumonia.

Characteristics of Study Sample

The final study sample included 193 unique patients. Over the five year study period, there were 126 (39%) patients intubated in the Emergency Department and 67 (20.7%) patients who were intubated in the Prehospital setting. The means and proportion for the characteristics between the two exposure groups are shown in Table 4.2.

The average age of patients intubated in the Emergency Department is not significantly different from the average age of patients intubated in the Prehospital setting (ED=44.50±SD19.91 vs. PH=40.85±SD17.28, p=0.20). The proportion of males intubated in the Emergency Department is slightly higher than the proportion of males intubated in the Prehospital setting (ED=73% vs. PH=85%, p=0.06).

Table 4.2: Means and Proportions of Characteristics for Patients who were Intubated in the Emergency Department compared to those were Intubated in the Prehospital Setting

	Emergency Dept. n=126	Prehospital n=67	*P*
DEMOGRAPHICS & DISEASE STATE			
Age (years), mean±sd	44.50±19.91	40.85±17.28	0.20
<65	97(77%)	58(87%)	-
≥65	29(23%)	9(13%)	0.11
Gender			
Female	34(27%)	10(15%)	-
Male	92(73%)	57(85%)	0.06
APACHE II score*, mean±sd (3 missing values)	23.35±6.74	25.01±7.32	0.12
<25	82(65%)	32(48%)	-
≥25	44(35%)	35(52%)	0.02†
SOFA score*, mean±sd	7.88±3.26	8.55±3.14	0.17
<7	50(40%)	19(29%)	-
≥7	76(60%)	48(71%)	0.12
Admission category by primary diagnosis			
Medical	31(25%)	13(19%)	0.41
Trauma	80(63%)	48(72%)	0.25
Surgical	0(0%)	0(0%)	-
Neurological	15(12%)	6(9%)	0.53
VAP Etiology			
Diagnostic Criteria			
Class I	7(6%)	2(3%)	0.41
Class II	0(0%)	0(0%)	-
Class III	35(28%)	19(28%)	0.93

	Emergency Dept. n=126	Prehospital n=67	*P*
Class IV	12(10%)	7(10%)	0.84
Class V	58(46%)	35(52%)	0.41
Class VI	14(11%)	4(6%)	0.25
Pathogen (2 missing values)			
Gram Negative Bacteria (not specified)	31(25%)	19(28%)	0.65
Haemophilus influenzae	24(19%)	13(19%)	1.00
Staphlyococcus aureus	38(30%)	24(36%)	0.40
Streptococcus spp.	15(12%)	5(8%)	0.32
Yeast spp.	3(2%)	0(0%)	0.20
Oropharyngeal Flora	10(8%)	6(9%)	0.83
No Growth	3(2%)	0(0%)	0.20
Time to VAP diagnosis (days), mean±sd (1 missing value)	7.62±9.12	6.83±4.83	0.51
Early (<5 days)	42(34%)	27(40%)	-
Late (≥5 days)	83(66%)	40(60%)	0.36
OUTCOME			
Hospital length of stay (days), mean±sd	60.65±66.32	65.58±69.68	0.63
Hospital Mortality			
Alive	93(74%)	50(75%)	-
Deceased	33(26%)	17(25%)	0.90

Note: All results are represented as "n (%)", unless otherwise stated; * indicates the measure was taken upon ICU admission; † indicates p-value <0.05; APACHE= Acute Physiology and Chronic Health Evaluation; sd= Standard Deviation; SOFA= Sequential Organ Failure Assessment; VAP= Ventilator-Associated Pneumonia.

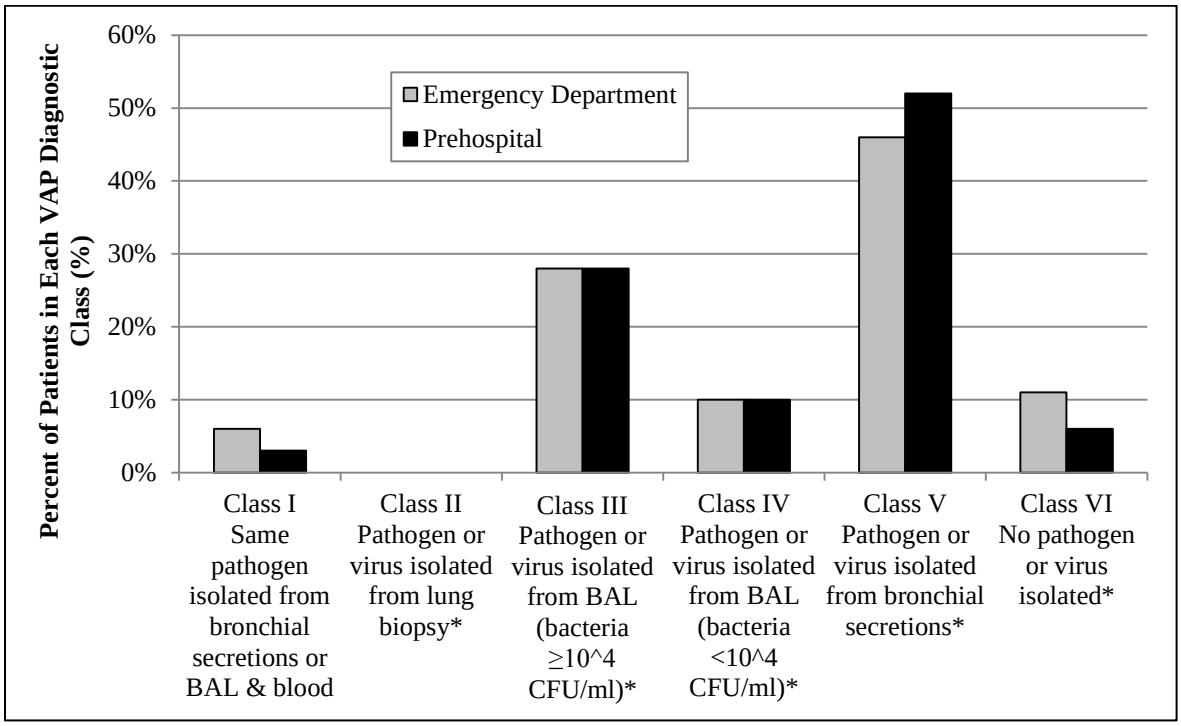
The mean APACHE II score, taken upon ICU admission, did not significantly differ between the two groups (ED=23.35±SD6.74 vs. PH=25.01±SD7.32, p=0.12). However, a higher proportion patients intubated in the Prehospital setting had an APACHE II score greater than 25 (ED=35% vs. PH=52%, p=0.02). Neither the mean SOFA score upon admission, nor the proportion of SOFA scores greater than seven, differed between patients intubated in the Emergency Department and Prehospital setting (ED=7.88±SD3.26 vs. PH=8.55±SD3.14, p=0.17). Trauma was the most common admission category for both groups (ED=63% vs. PH=72%, p=0.25), followed by medical (ED=25% vs. PH=19%, p=0.41) and finally neurological (ED=12% vs. PH=9%, p=0.53). There were no patients whose admission category was surgical. The proportion of patients in each admission category was not significantly different between Emergency Department and Prehospital intubated patients.

Figure 4.2 shows the percent of patients in each VAP diagnostic class by intubation location. The most common method of VAP diagnosis for both groups was a positive microbial presence from bronchial secretions (Class V, ED=46% vs. PH=52%, p=0.41) followed by bronchoalveolar lavage (Class III, ED=28% vs. PH=28%, p=0.93). There was no significant difference in the way VAP was diagnosed between the two groups.

The three most common pathogens for both groups were: *Staphlyococcus aureus* (ED=28% vs. PH=36%, p=0.28), *Haemophilus influenzae* (ED=19% vs. PH=19%, p=1.00); and *Streptococcus* species (ED=12% vs. PH=8%, p=0.32). Overall the pathogens associated with VAP among the two groups were not different.

Neither the mean time to VAP diagnosis, nor the proportion of patients who were diagnosed at equal to or greater than five days post-intubation were significantly different between the Emergency Department and Prehospital ETI patients (ED=7.62±SD9.12 vs. PH=6.83±SD4.83, p=0.51; ED=66% vs. PH=60%, p=0.36).

Figure 4.2: Percent of Patients in Each Ventilator-Associated Pneumonia Diagnostic Class by Intubation Location



Note: *Each case of VAP must also meet symptomatic criteria and show signs of at least one of the following: altered temperature; altered white blood cell count; sputum change; or positive serology (except Class I); BAL=Bronchoalveolar lavage; CFU=Colony Forming Units; ml=Milliliter; VAP=Ventilator-Associated Pneumonia.

The two groups also did not differ by hospital length of stay or mortality. The mean hospital length of stay for patients who were intubated in the Emergency Department was 60.65±SD66.32 days; whereas the mean hospital length of stay for patients who were intubated in the Prehospital setting was 65.58±SD69.68 (p=0.63). The proportion of patients who were deceased upon hospital discharge was similar between the two groups (ED=26% vs. PH=25%, p=0.90)

The purpose of the comparative analysis was to examine the similarities and differences of the Emergency Department ETI and Prehospital ETI groups. Patients who were intubated in the Prehospital setting had a slightly higher severity of disease than the patients who were intubated in the Emergency Department, which is to be expected. Other than that these two groups do not differ in any clinically or statistically significant way.

Omissions

Characteristics of Excluded Subjects

There were 7 VAP patients for which the intubation location could not be determined (chart not available: n=5, unknown exposure: n=2). Five charts could not be located. The two remaining charts were reviewed. Both patients were transferred, already intubated, from another facility into a Calgary area ICU. The records from the previous facility were not available and therefore the primary intubation location could not be determined. All 7 patients had complete datasets from the VAP Surveillance Database and Table 4.3 describes their basic characteristics. These patients were excluded from the description, stratified and regression analysis for both the primary and secondary objectives.

Table 4.3: Means and Proportions of Basic Characteristics for Patients who were Excluded from the Study due to Insufficient Intubation Information

	Excluded n=7
Age (years), mean±sd	46.28±20.67
Gender	
Female	3 (43%)
Male	4 (57%)
APACHE II score*, mean±sd	22.14±7.60
Hospital Length of Stay (days), mean±sd	55.71±69.19
Hospital Mortality	
Alive	4 (57%)
Deceased	3 (43%)

Note: All results are represented as "n (%)", unless otherwise stated; * indicates the measure was taken upon ICU admission; APACHE= Acute Physiology and Chronic Health Evaluation; sd= Standard Deviation.

Missing Data

Detailed comparisons and statistical analysis was not performed for several variables that describe the circumstances of the primary intubation. The three variables are: the number of attempts made by the provider to place and confirm the first successful ETI (continuous); whether or not there were complications during the procedure (dichotomous) ; and whether or not a rapid sequence induction (RSI) technique was used (dichotomous). These data should have been available from the chart review. However, a sufficient amount of data was not available and there is a high proportion of blank cells.

Table 4.4 provides a brief description of the number of attempts and proportion of intubations with complications for patients who were intubated in the Emergency Department compared to those were intubated in the Prehospital setting. Of the 193 eligible cases (ED=126, PH=67), 125 had missing data for the number of intubation attempts. Among patients who were intubated in the Prehospital setting the number of intubation attempts was not recorded for 25% of cases (n=17). Data regarding the number of intubation attempts could not be determined for 85% (n=108) of patients who were intubated in the Emergency Department. There was a total of 129 missing values for presence or absence of complications during the intubation. This data item was missing for 52% (n=35) of patients intubated in the Prehospital setting and 74% (n=94) of patients intubated in the Emergency Department.

As previously mentioned in the literature review, rapid sequence induction (RSI) techniques have a different risk profile for immediate complications than non-RSI intubations. It was this studies intent to capture data regarding whether or not an RSI intubation was performed. There is a specific location for this data in both the Prehospital (Patient Care Report) and Emergency Department record. However, this item was not captured because the availability was inconsistent and the information could not be validated. For example, a patient chart may indicate that certain RSI drugs, such as Etomidate (anesthetic) or Succinylcholine (paralytic), were given but the dosage and time of administration were not definite. This omission is discussed further in Chapter six.

Table 4.4: Means and Proportions of Omitted Variables for Patients who were Intubated in the Emergency Department compared to those were Intubated in the Prehospital Setting

	Emergency Dept. n=126	Prehospital n=67
Number of Attempts, mean±sd (125 missing values)	2.33±1.08	1.56±0.67
=1	5(28%)	27(54%)
>1	13(72%)	23(46%)
Complications (129 missing values)		
No	5(16%)	3(9%)
Yes	27(84%)	29(91%)

Note: All results are represented as "n (%)", unless otherwise stated; sd=Standard Deviation.

The remaining variables in the dataset had a high degree of completeness and contained no obvious errors. There were three missing values for APACHE II score, two missing values for pathogen and one missing value for time to VAP diagnosis. All of the missing values were from patients who were intubated in the Prehospital setting. None of the patients had more than one omission.

Hospital Mortality

Descriptive and Comparative Statistics

Characteristics of Patients Intubated in the Emergency Department

During this study, there were a total of 126 patients who developed VAP and whose primary successful intubation took place in the Emergency Department. Seventy-four percent (n=93) of these patients survived until hospital discharge; whereas 26% (n=33) of patients died. To assess the impact of key covariates, the means and proportions for patients who survived were compared to those who did not survive (Table 4.5). The patients who survived until hospital discharge differed in several ways compared to those who died.

The mean age of patients who lived were significantly younger than those who died (Alive=41.92±SD18.92 vs. Died= 51.78±SD21.12, p=0.01). Likewise, the proportion of patients over 65 who lived was significantly less than those who died (Alive=18% vs. Died=36%, p=0.03). The proportion of patients that lived who were admitted for a medical problem was also significantly lower than those who died (Alive=18% vs. Died=42%, p=<0.01). The opposite is true for patients admitted with trauma (Alive=70% vs. Died=42%, p=<0.01).

All patients whose primary pathogen was yeast died (Alive=0% vs. Died=9%, p=0.003); however, these are very small cell sizes. The number of days from intubation until diagnosis was significantly less for patients who lived compared to those who died (Alive=6.36±SD6.90 vs. Died=11.15±SD13.15, p=0.01).

Finally, patients who lived until hospital discharge had a much longer hospital length of stay than those who died (Alive=70.20±SD71.91 vs. Died=33.72±36.07, p=<0.01). These two groups of patients did not significantly differ by gender, APACHE II score, or SOFA score.

Characteristics of Patients Intubated in the Prehospital Setting

During this study there were a total of 67 patients who developed VAP and whose primary successful intubation took place in the Prehospital setting. Seventy-five percent (n=50) of these patients survived until hospital discharge; whereas 25% (n=17) patients died. To assess the impact of key covariates among patients intubated in the Prehospital setting relative to hospital mortality, the means and proportions for patients who survived were compared to those who did not survive (Table 4.6). The patients who survived until hospital discharge differed in several ways compared to those who died.

Although the mean age of patients who lived was not different than those who died, the proportion of patients equal to or greater than 65 years old was higher in the deceased group (Alive=8% vs. Died=29%, p=0.02). There were a higher proportion of male patients who lived than the proportion of male patients who died. (Male: Alive=90% vs. Died=71%, Female: Alive=10% vs. Died=29%, p=0.05). The mean APACHE II score and proportion of patients whose severity score was ≥25 was

significantly higher among deceased patients (Score <25: Alive= 23.14±SD 6.36 vs. Deceased=30.51±SD7.32 ,p=<0.001; Score ≥25: Alive=44% vs. Deceased =76%, p=0.02) The proportion of patients that lived who were admitted for a medical or neurological problem was significantly lower than those who died (Medical: Alive=12% vs. Died=41%, p=<0.01; Neuro: Alive=4% vs. Died=23%, p=0.01). The opposite is true for patients admitted with trauma (Alive=84% vs. Died=35%, p=0.003).

Finally, patients who lived until hospital discharge had a much longer hospital length of stay than those who died (Alive=82.36±SD72.60 vs. Died=16.23±20.54, p=<0.001). These two groups of patients did not significantly differ by SOFA score, pathogen or time to VAP diagnosis.

The Emergency Department ETI patients who were deceased upon hospital discharge were significantly older, had higher admittance for a medical problem and had lengthier time to VAP diagnosis and shorter hospital stays than their alive counterparts. Patients that remained alive had a higher admittance for a traumatic problem than those who died.

The Prehospital ETI patients who were deceased upon hospital discharge had the same profile as Emergency Department ETI patients who were deceased and also significantly more severe, admitted for a neurological problem and consisted of a higher proportion of males than their alive counterparts.

Table 4.5: Means and Proportions of Characteristics for Patients who were Intubated in the Emergency Department and were Alive Upon Hospital Discharge compared to those who were Deceased Upon Hospital Discharge

	Alive n=93	Deceased n=33	*P*
DEMOGRAPHICS & DISEASE STATE			
Age (years), mean±sd	41.92±18.92	51.78±21.12	0.01†
<65	76(82%)	21(64%)	-
≥65	17(18%)	12(36%)	0.03†
Gender			
Female	24(26%)	10(31%)	-
Male	69(74%)	23(69%)	0.62
APACHE II score*, mean±sd (3 missing values)	23.03±6.45	24.32±7.59	0.36
<25	63(68%)	19(58%)	-
≥25	30(32%)	14(42%)	0.29
SOFA score*, mean±sd	7.72±3.25	8.33±3.32	0.36
<7	38(41%)	12(37%)	-
≥7	55(59%)	21(63%)	0.65
Admission category by primary diagnosis			
Medical	17(18%)	14(42%)	<0.01†
Trauma	66(70%)	14(42%)	<0.01†
Neurological	10(11%)	5(15%)	0.50
INTUBATION			
Unsuccessful in Prehospital	13(14%)	3(9%)	0.46
VAP ETIOLOGY			
Pathogen (2 missing values)			
Gram Negative Bacteria (not specified)	24(26%)	7(22%)	0.65

	Alive n=93	Deceased n=33	*P*
Haemophilus influenzae	19(21%)	5(16%)	0.53
Staphlyococcus aureus	30(33%)	8(25%)	0.40
Streptococcus spp.	11(12%)	4(25%)	0.08
Yeast spp.	0(0%)	3(9%)	<0.01†
Oropharyngeal Flora	6(7%)	4(13%)	0.28
No Growth	2(2%)	1(3%)	0.78
Time to VAP diagnosis (days), mean±sd (1 missing value)	6.36±6.90	11.15±13.15	0.01†
Early (<5 days)	33(36%)	9(28%)	-
Late (≥5 days)	59(64%)	24(72%)	0.37
OUTCOME			
Hospital length of stay (days), mean±sd	70.20±71.91	33.72±36.07	<0.01†

Note: All results are represented as "n (%)", unless otherwise stated; ***** indicates the measure was taken upon ICU admission; † indicates p-value <0.05; ; APACHE= Acute Physiology and Chronic Health Evaluation; sd= Standard Deviation; SOFA= Sequential Organ Failure Assessment; VAP= Ventilator-Associated Pneumonia.

Table 4.6: Means and Proportions of Characteristics for Patients who were Intubated in the Prehospital Setting and were Alive Upon Hospital Discharge compared to those who were Deceased Upon Hospital Discharge

	Alive n=50	Deceased n=17	*P*
DEMOGRAPHICS & DISEASE STATE			
Age (years), mean±sd	38.68±16.05	47.23±19.60	0.08
<65	46(92%)	12(71%)	-
≥65	4(8%)	5(29%)	0.02†
Gender			
Female	5(10%)	5(29%)	-
Male	45(90%)	12(71%)	0.05†
APACHE II score*, mean±sd	23.14±6.36	30.51±7.32	<0.001†
<25	28(56%)	4(24%)	-
≥25	22(44%)	13(76%)	0.02
SOFA score*, mean±sd	8.16±2.94	9.70±3.53	0.08
<7	17(34%)	2(12%)	-
≥7	33(66%)	15(88%)	0.08
Admission category by primary diagnosis			
Medical	6(12%)	7(41%)	<0.01†
Trauma	42(84%)	6(35%)	<0.001†
Neurological	2(4%)	4(23%)	0.01†
VAP ETIOLOGY			
Pathogen			
Gram Negative Bacteria (not specified)	18(36%)	1(6%)	0.02†
Haemophilus influenzae	9(18%)	4(24%)	0.62
Staphlyococcus aureus	17(34%)	7(41%)	0.60
Streptococcus spp.	3(6%)	2(12%)	0.43

	Alive n=50	Deceased n=17	*P*
Yeast spp.	0(0%)	0(0%)	-
Oropharyngeal Flora	3(6%)	3(18%)	0.14
No Growth	0(0%)	0(0%)	-
Time to VAP diagnosis (days), mean±sd	7.00±5.11	6.35±4.01	0.64
Early (<5 days)	22(44%)	5(29%)	-
Late (≥5 days)	28(56%)	12(71%)	0.29
OUTCOME			
Hospital length of stay (days), mean±sd	82.36±72.60	16.23±20.54	<0.001†

Note: All results are represented as "n (%)", unless otherwise stated; * indicates the measure was taken upon ICU admission; † indicates p-value <0.05; ; APACHE= Acute Physiology and Chronic Health Evaluation; sd= Standard Deviation; SOFA= Sequential Organ Failure Assessment; VAP= Ventilator-Associated Pneumonia.

Stratified Analysis

A classic stratified analysis was performed to analyze the potential effects of covariates on the relationship between intubation location and hospital mortality. Odds ratios were employed to quantify the measure of association. The odds ratio was calculated as the odds of mortality for those intubated in the Prehospital setting over the odds of mortality for those intubated in the Emergency Department. The outcome of the stratified analysis was used to determine which variables should be included in the logistic regression analysis.

The estimated crude odds ratio for hospital mortality is 0.96 (95% CI 0.45-1.98). This means that the odds of hospital mortality are 4% lower among Prehospital intubated patients than the odds of hospital mortality for Emergency Department intubated patients. However, the precision of this estimate is quite poor as the 95% confidence interval is wide and crosses the null value. Therefore, the null hypothesis, that the risk of mortality for these two groups is not different, cannot be rejected (p=0.90). This crude estimate does not account for the influence of confounding and modifying factors. To further

evaluate the odds ratio of mortality based on intubation location, a classic stratified analysis was performed on key covariates (Table 4.7).

There were several variables in which the stratum specific estimates varied greatly. Using the designated alpha level of 0.20, effect measure modification was identified for gender (p=0.19), APACHE II score (p=0.20), SOFA score (p=0.20) trauma (p=0.16) and neurological admission category (p=0.14), and gram negative bacteria (excluding *Haemophilus influenzae*) (p=0.10).

For all of the group-sets in which effect modification was identified, one of the strata illustrated a protective effect (OR<1) and the other was harmful (OR>1). For example, the odds ratio for female gender was 2.40 (95%CI 0.44-12.85). This means that for females the odds of hospital mortality are 240% (or 2.4 times) higher among Prehospital intubation patients than the odds of hospital mortality for Emergency Department intubated patients. The opposite is true among males. The odds of hospital mortality among males who are intubated in the Prehospital setting is 20% lower than the odds of hospital mortality among males who are intubated in the Emergency Department (OR=0.80, 95%CI 0.33-1.88). Ergo, when interpreting the intubation location-mortality relationship being a female is harmful (when exposed) and being a male is protective (when exposed).

The odds ratio of mortality were much higher among female (2.40, 95%CI 0.44-12.85) than among males (0.80, 95CI 0.33-1.88). The odds ratio for mortality were also higher for patients whose severity was higher (APACHE II <25=0.27, 95% CI 0.11-1.62; APACHE II ≥25=1.29, 95% CI 0.45-3.57). Similarly, patients who experienced higher organ dysfunction upon ICU admission also had higher odds ratio for mortality (SOFA <7=0.37, 95% CI0.04-1.99; SOFA≥7=1.19, 95% CI 0.50-2.81). Patients who were admitted with a neurological problem as their primary diagnosis had a higher odds ratio for mortality than patients admitted for any other reason (Yes=4.00, 95% CI 0.38-55.03; No=0.80, 95% CI 0.35-1.79). This result is mirrored by the fact that patients who did not experience trauma, which include the neurological group, also had a higher odds ratio than those who did experience a trauma (No=1.95, 95% CI 0.58-6.71; Yes=0.67, 95% CI

0.20-2.05). Finally, any patient in which a gram negative bacteria was isolated as their pathogen (other than *Haemophilus influenzae*) had a lower odds ratio of mortality than those who did not (Yes=0.19, 95% CI 0.004-1.75; No=1.36, 95% CI 0.59-3.07). None of the Mantel-Haenszel combined estimates differed significantly from the crude OR, therefore confounding was not identified as a concern for any of the other covariates.

In summary, the descriptive and comparative statistics show that severity of illness was different for patient intubated in the Prehospital and Emergency Department settings. This observation was also found in the stratified analysis. The APACHE II and SOFA scores, as well as gender, trauma and neurological admission category, and gram negative bacteria were identified as effect modifiers.

No conclusions can be drawn from the univariate analysis because the confidence intervals of all the comparative estimates overlap and crossed the null value. The results of the stratified analysis indicate that a multivariate analysis is necessary as the relationship is not clearly explained by a univariate analysis. These results were used strictly to inform the model formation process for the multivariate regression analysis.

Table 4.7: Stratified Analysis of Covariates Effect on the Relationship Between Intubation Location and Odds Ratio for Hospital Mortality

		Odds Ratio (95% CI)	MH Combined (95% CI)	*P*
Crude Estimate		0.98 (0.45-1.98)	-	0.90
DEMOGRAPHICS & DISEASE STATE				
Age (years)				
<65		0.94 (0.39-2.24)	1.08 (0.53-2.18)	0.47
≥65		1.77 (0.30-10.80)		
Gender				
Female		2.40 (0.44-12.85)	1.02 (0.52-2.03)	0.19‡
Male		0.80 (0.33-1.88)		
APACHE II score*				
<25		0.27 (0.11-1.62)	0.83 (0.41-1.69)	0.20‡
≥25		1.29 (0.45-3.57)		
SOFA score*				
<7		0.37 (0.04-1.99)	0.91 (0.45-1.81)	0.20‡
≥7		1.19 (0.50-2.81)		
Admission category by primary diagnosis				
Medical	No	0.91 (0.35-2.28)	1.04 (0.51-2.11)	0.57
	Yes	1.41 (0.32-6.40)		
Trauma	No	1.95 (0.58-6.71)	1.10 (0.54 -2.28)	0.16‡
	Yes	0.67 (0.20-2.05)		
Neurological	No	0.80 (0.35-1.79)	0.99 (0.50-1.95)	0.14‡
	Yes	4.00 (0.38-55.03)		
VAP ETIOLOGY				
Pathogen				
Gram Negative Bacteria (unspecified, not *H.influenzae*)	No	1.36 (0.59-3.07)	1.00 (0.50-1.98)	0.09‡
	Yes	0.19 (0.004-1.75)		

		Odds Ratio (95% CI)	MH Combined (95% CI)	*P*
Haemophilus influenzae	No	0.86 (0.36-1.95)	0.98 (0.49-1.93)	0.44
	Yes	1.69 (0.26-10.04)		
Staphlyococcus aureus	No	0.78 (0.30-1.95)	0.98 (0.50-1.95)	0.36
	Yes	1.54 (0.40-5.84)		
Streptococcus spp.	No	0.92 (0.41-2.00)	0.99 (0.50-1.96)	0.55
	Yes	1.83 (0.11-22.88)		
Yeast spp.	No	1.08 (0.50-2.26)	1.08 (0.50-2.26)	-
	Yes	----- (----------)		
Oropharyngeal Flora	No	0.91 (0.40-2.00)	0.97 (0.49-1.93)	0.65
	Yes	1.50 (0.12-17.72)		
No Growth	No	0.99 (0.46-2.06)	0.99 (0.46-2.06)	-
	Yes	----- (----------)		
Time to VAP diagnosis (days), mean±sd				
Early (<5 days)		0.83 (0.20-3.23)	0.98 (0.49-1.94)	0.75
Late (≥5 days)		1.05 (0.42-2.57)		

Note: All results are represented as "n (%)", unless otherwise stated; * indicates the measure was taken upon ICU admission; ‡ indicates p-value <0.20; APACHE= Acute Physiology and Chronic Health Evaluation; MH=Mantel Haenszel; sd= Standard Deviation; SOFA= Sequential Organ Failure Assessment; VAP= Ventilator-Associated Pneumonia.

Regression Analysis

Logistic regression techniques were used to evaluate the odds of death for patients intubated in the Prehospital setting compared to the odds of death for patients intubated in the Emergency Department while adjusting for multiple covariates. The crude model included only the effect of the exposure (intubation location). The baseline model was:

$$log\left(\frac{p}{1-p}\right) = \beta_0 + \beta_{exposure}$$

Since no other information is included in this model, the results are the same as the stratified analysis. The odds ratio of mortality is 0.98 (95% CI 0.45-1.98). This model

was insufficient in explaining the relationship of intubation location and hospital mortality (p=0.90).

Further models were constructed based on the information obtained from the descriptive and stratified analyses. Age, APACHE II and SOFA scores were used as continuous variables in the regression analysis even though they were used dichotomously in the stratified analysis. The other four variables evaluated, gender, gram negative bacteria, trauma and neurological admission category, remained dichotomous.

A forward stepwise selection process was used to determine which of these variables influenced the association in a multivariate model. The entire modelling process is outlined in Appendix B (Table B.2). Gram negative bacteria, SOFA score and neurological admission category did not influence the model and were removed.

The proposed final model was:

$$log\left(\frac{p}{1-p}\right) = \beta_0 + \beta_{exposure} + \beta_{(age-18)} + \beta_{gender} + \beta_{apache} + \beta_{exposure*apache} + \beta_{trauma}$$

This model was constructed based on the assessment of effect measure modification, confounding and clinical significance of the above stated variables. This equation states that the log odds ratio of mortality is the summation of some baseline effect (β_0) plus the exposure effect ($\beta_{exposure}$) and several other patient characteristics ($\beta_{(age-18)} + \beta_{gender} + \beta_{apache} + \beta_{exposure*apache} + \beta_{trauma}$). Acute Physiology and Chronic Health Evaluation II score was identified as an effect modifier; hence the inclusion of the interaction term ($\beta_{exposure*apache}$). Both age (shifted by -18) and trauma admission category confounded the intubation location-mortality relationship; while, gender was kept in the model on the basis of clinical significance. There was no interaction identified between variables.

This model was further assessed to ensure that the assumptions for logistic regression were not violated and that the model was constructed properly. Firstly, the observations of each patient were independent of one another. For example, the age of

one patient, did not influence the age of another patient. This was accounted for in the study design.

Second, all variables were independent of one another (i.e. gender does not influence age). This was assessed by testing the collinearity of the variables. In fact, none of the variable pairings had a correlation value (r) of greater than 0.55 or less than -0.55 (Appendix B: Table B.3). The variance inflation factor measures how much of the inflation of the standard error is caused by collinearity. Typically, a variance inflation factor of 10 or greater is a cause for concern. (86) Although there was concern of collinearity between age and APACHE II score, since age is used in the APACHE II calculation, the test for collinearity refuted that issue. The variance inflation factor was tested for each unique variable (i.e. not interaction terms). All tests resulted in a variance inflation factor of less than 10 (exposure=1.05; age=1.12; gender=1.22; APACHE II=1.12; trauma admission=1.37).

Thirdly, the use of logistic regression assumes linearity of independent variables and log odds of mortality. Each continuous variable was assessed using the Box-Tidwell test, which test the null hypothesis that each of the variables is a linear term (i.e. do not need to be transformed). Both age and APACHE II were non-significant (age p=0.18; APACHE II p=0.27).

The final assumption for logistic regression requires that the sample size have at least 10 deceased patients per independent variable. The total number of deceased patients in this study was 50 and therefore, five unique variables would be the maximum for this regression. The final model did not exceed this number. Assessments were also made to ensure there were no specification errors and to quantify the Goodness of Fit.

A specification error results when a model has included a variable that should have been omitted or when a model has omitted a variable that should have been included. The Linktest indicates that the model is specified correctly. The null hypothesis that the variables in the model are not meaningful can be rejected (p=0.001) and the null hypothesis that there are no missing variables cannot be rejected (p=0.63).

Finally the Goodness of Fit is assessed using the log likelihood chi^2 test, which indicates whether or not the whole model is statistically significant. The above stated model achieved statistical significance (X^2=34.09, p=<0.001).

In all accounts this model proved to be constructed properly and in accordance with the logistic regression assumptions. A summary of the model performance results are in shown in Table 4.8

Table 4.8: Summary of Model Performance Indicators for Hospital Mortality Logistic Regression

Final Proposed Model: $log\left(\frac{p}{1-p}\right) = \beta_0 + \beta_{exposure} + \beta_{(age-18)} + \beta_{gender} + \beta_{apache} + \beta_{exposure*apache} + \beta_{trauma}$

Assumption	Test	Measurement	Significance Threshold	Result	
Independence of subjects	None	--	--	No concern. Inherent in study design.	
Independence of Variables (Collinearity)	Correlation	Measure of independence of variables	0.55>r<-0.55	No concern. See Appendix B (Table B.3).	
	Variance Inflation Factor	Measure of how much of the inflation of the standard error is caused by collinearity	>10	Exposure	1.05
				Age	1.12
				Gender	1.22
				APACHE II	1.12
				Trauma	1.37
Linearity of Independent Variables	Box-Tidwell	Ho: Each continuous variable is a linear term (does not need to be transformed)	p<0.05	Age	p=0.18
				APACHE II	p=0.27
				Exp*APACHE II	p=0.24
Specification Errors	Linktest	Ho: The model is not specified correctly	p<0.05	p<0.001	
		Ho: There are no missing variables	p<0.05	p=0.63	
Goodness of Fit	Log Likelihood chi^2	Ho: The whole model is not statistically significant	p<0.05	p<0.001 (X^2=34.09)	

Note: APACHE=Acute Physiology and Chronic Health Evaluation; Exp=Exposure (Intubation Location); Ho=Null Hypothesis.

The results of this model are summarized in Table 4.9. Each odds ratio listed is interpreted as the changes in the odds of death for Prehospital intubated patients compared to Emergency Department intubated patients for every one unit change in the variable, while holding all other variables constant. This model indicates that there is a significant association between intubation location and mortality in the presence of multiple variables (exposure coefficient p=0.05).

Acute Physiology and Chronic Health Evaluation II score was an effect modifier (p=0.03). Although gender was not identified as either an effect modifier or a confounder, it was forced into the model based on clinical significance. Interaction, where two components either synergistically or antagonistically act together to alter the exposure-outcome relationship, was not identified during the modelling process.

Table 4.9: Odds Ratio of Hospital Mortality for the Final Multivariate Logistic Regression Model

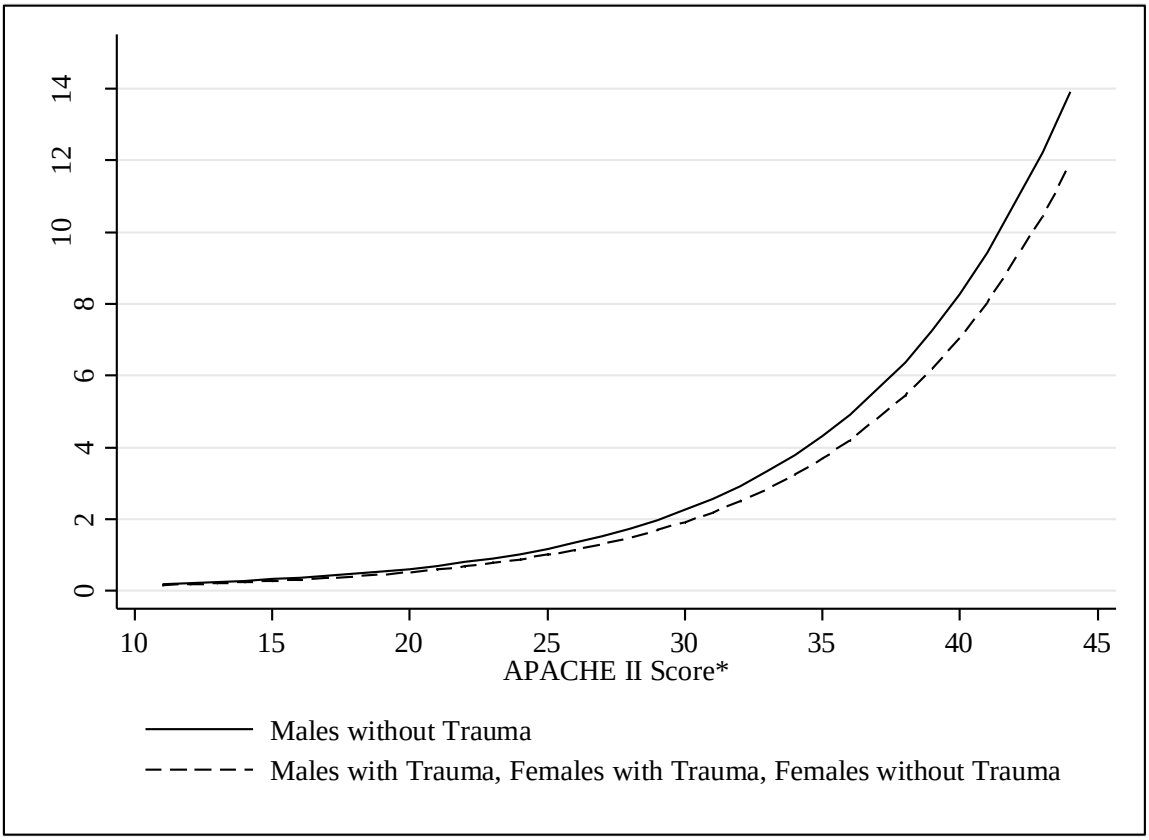
Variable	Data Type	OR	95% CI	*P*
Exposure	ED=0, PH=1	0.039	(0.001-0.955)	0.05†
Age	Continuous (shifted left by 18)	1.017	(0.998-1.037)	0.09
Gender	F=0, M=1	1.171	(0.490-2.801)	0.72
APACHE II score*	Continuous	0.995	(0.933-1.060)	0.87
Exposure*APACHE II*	ED=0, PH=continuous	1.139	(1.011-1.283)	0.03†
Trauma admission	No=0, Yes=1	0.241	(0.105-0.552)	0.001†

Note: * indicates the measure was taken upon ICU admission; † indicates Wald test p-value <0.05; APACHE=Acute Physiology and Chronic Health Evaluation; ED=Emergency Department; F=Female; M=Male; OR=Odds Ratio; PH=Prehospital.

As previously mentioned age and admission due to trauma were both found to confound the intubation location-mortality relationship. This was determined via the comparison of nested models using likelihood ratio tests. The p-value and chi square statistics were significant when both of the variables were removed (Age: p=<0.01, X^2=9.07; Trauma: p=<0.001, X^2=11.59; Appendix B: Table B.2)

Figure 4.3 demonstrates the association between intubation location and hospital mortality, while considering the above variables for patients who were18 years old. The variable that had the highest influence on the model, APACHE II score, was chosen to be represented continuously.

Figure 4.3: Mortality Odds Ratio of Intubation Location by Acute Physiology and Chronic Health Evaluation II Score for Gender and Trauma Admission Category Groups
(18 years old)



Note:* indicates the measure was taken upon ICU admission; APACHE= Acute Physiology and Chronic Health Evaluation.

The difference in the mortality odds ratio between male patients who do not experience trauma and all other patients (males with trauma, females with trauma, and females without trauma) is relatively small and ranges from 0.02-2.03. This difference is

arguably not clinically significant. To present a clinically relevant estimated an adjusted odds ratio will be considered for all gender and admission categories group types (all patients will be grouped together regardless of gender or trauma admission).

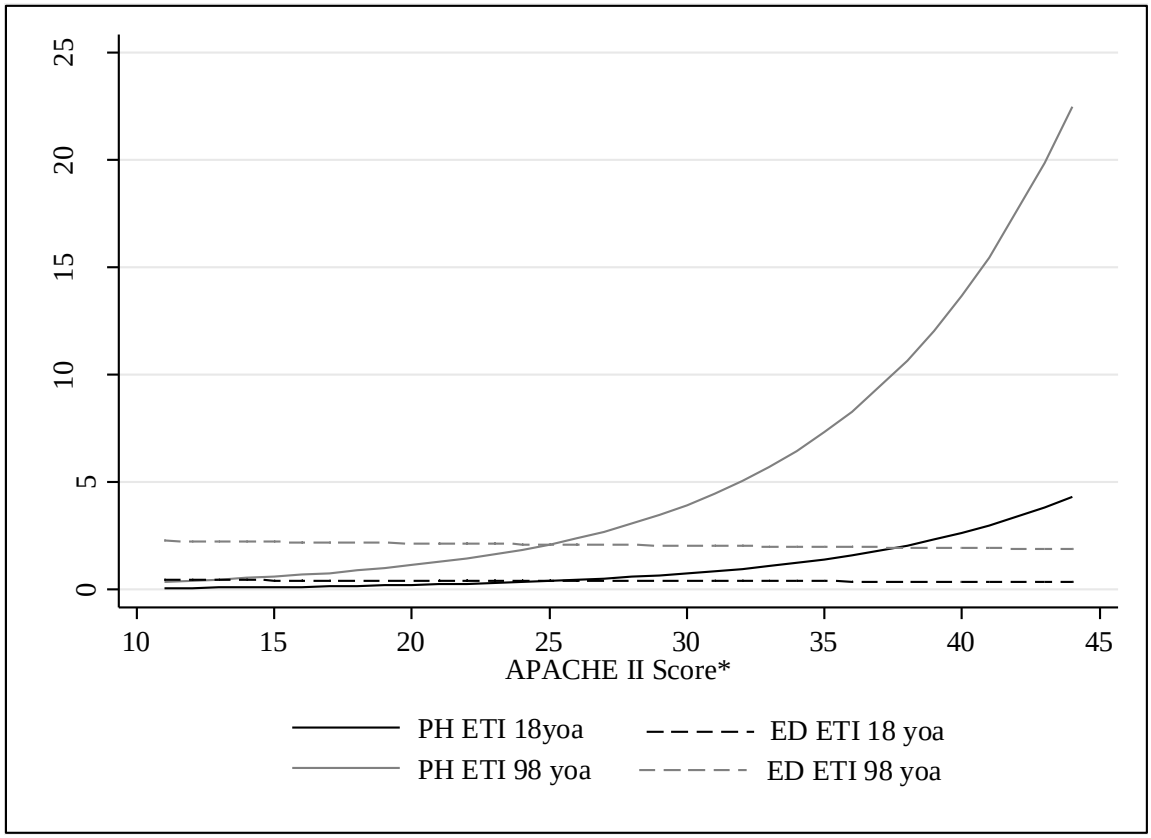
The odds of death for the Emergency ETI and Prehospital ETI groups are displayed for two separate age groups in Figure 4.4. The black lines represent the 18 year old age group, while the grey lines represent the 98 year old age group.

This graph also demonstrates that the odds of death increase as severity (APACHE II score) increases for patients intubated in the Prehospital setting; whereas the odds of death remain relatively the same as severity increases for patients intubated in the Emergency Department. This finding is counterintuitive to what is known and accepted in current ICU literature, and is discussed further in chapter 6.

Although the odds of death increases substantially by age (difference between black and grey lines), the ratio between the groups remains constant, meaning that the odds ratio is the same.

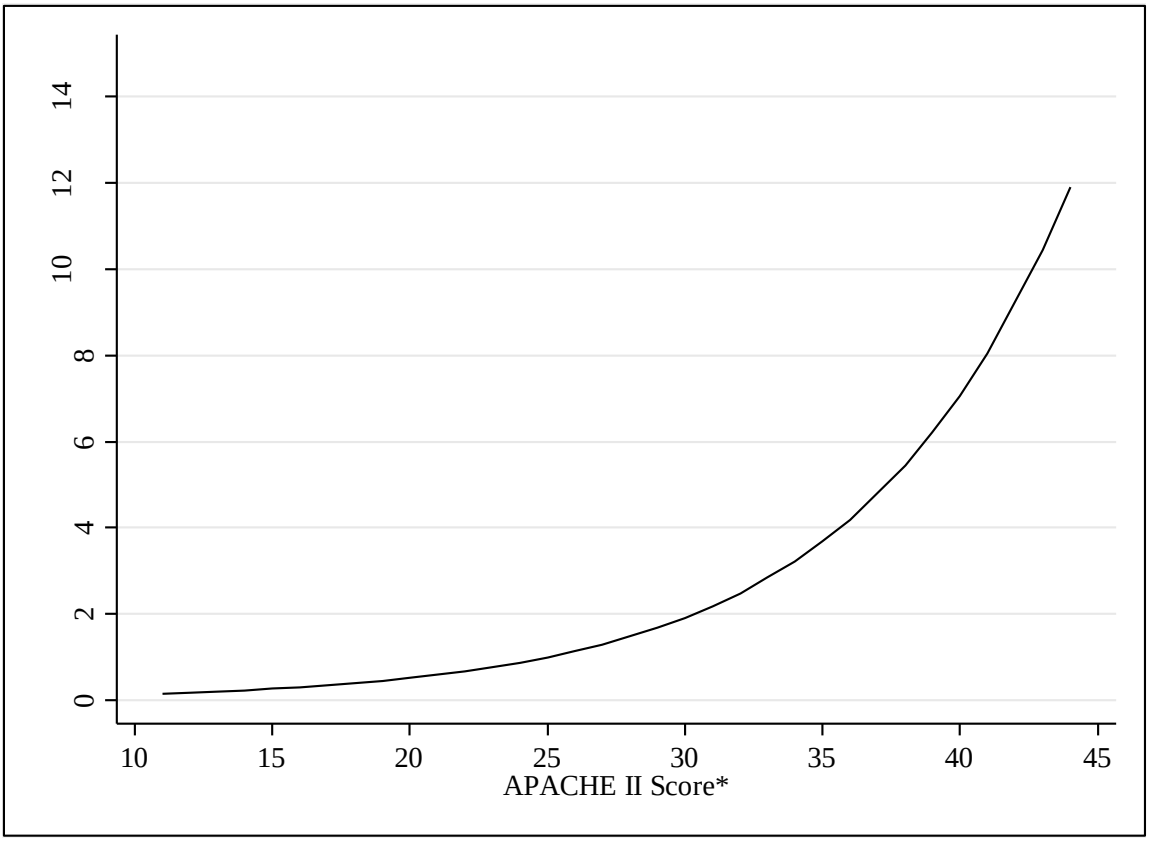
In summary, varied levels of gender, trauma, and age do not alter the mortality odds ratio enough to be represented separately. Therefore, the adjusted mortality odds ratio is shown for all groups (Figure 4.5). This graph indicates that among patients with VAP the odds of mortality for patients intubated in the Prehospital setting are lower than the odds of mortality for patients intubated in the Emergency Department when the APACHE II score is lower than 25 (mortality odds ratio <1). However, once the APACHE II score is greater than 25 the odds of mortality for patients intubated in the Prehospital setting are significantly higher than the odds of mortality for patients intubated in the ED (mortality odds ratio >1).

Figure 4.4: Odds of Mortality for Prehospital Endotracheal Intubation and Emergency Department Endotracheal Intubation Patients (18 years old vs. 98 years old - adjusted for gender and trauma admission category)



Note:* indicates the measure was taken upon; APACHE=Acute Physiology and Chronic Health Evaluation; ICU admission; ED=Emergency Department; ETI=Endotracheal Intubation; PH=Prehospital; yoa=years of age.

Figure 4.5: Mortality Odds Ratio by Acute Physiology and Chronic Health Evaluation II Score (adjusted for age, gender, and trauma admission category)



Note:* indicates the measure was taken upon ICU admission; APACHE= Acute Physiology and Chronic Health Evaluation; CI= Confidence Interval; OR= Odds Ratio.

The calculated odd ratios for several APACHE II scores are represented in Table 4.10. This table is included to show the numerical values of the odds ratio of mortality, as calculated by this model, for several different scenarios. For example, when the APACHE II score upon admission is 15, the odds of mortality is 73% lower among Prehospital ETI patients, than Emergency Department ETI patients (OR 0.27, 95% CI -0.02-4.13). The odds of mortality are equal when 10 points are added and the APACHE II score is now 25 (OR 1.00, 95% CI 0.07-15.20). With an additional 10 points, an APACHE II score of 35, the odds ratio of mortality climb sharply; Patients who are

intubated in the Prehospital setting are 368 times more likely to die than their Emergency Department counterparts (OR 3.68, 95% CI 0.24-55.91).

The confidence intervals seen in this regression model get wider as APACHE II score increases. There is an increase in variability because there are few patients who have an APACHE II score at the high end of the scale. Although the confidence intervals are wide and cross the null value, the results presented here are novel and evoke careful clinical consideration.

Table 4.10: Mortality Odds Ratio by Acute Physiology and Chronic Health Evaluation II Score (adjusted for age, gender, and trauma admission category)

APACHE II Score*	Odds Ratio	95% CI	Odds of Mortality Given PH ETI (compared to ED ETI)
10	0.14	(0.01-2.16)	86% less likely
15	0.27	(0.02-4.13)	73% less likely
20	0.52	(0.03-7.93)	48% less likely
25	1.00	(0.07-15.20)	Equal
30	1.92	(0.13-29.15)	92% more likely
35	3.68	(0.24-55.91)	368% more likely
40	7.06	(0.47-107.21)	706% more likely

Note:* indicates the measure was taken upon ICU admission; APACHE= Acute Physiology and Chronic Health Evaluation; CI=Confidence Interval; ED=Emergency Department; ETI=Endotracheal Intubation; PH=Prehospital.

Hospital Length of Stay

Descriptive and Comparative Statistics

To evaluate which variables influence the relationship between intubation location and hospital length of stay (LOS) a second set of descriptive and stratified analyses were performed. To facilitate this task, hospital length of stay was dichotomized at the median (40 days).

The means and proportions of the characteristics for patients intubated in the Emergency Department are described with regards to their hospital length of stay in Table 4.11. Patients who incurred a longer length of stay also had a longer time to VAP diagnosis (LOS<40=5.69±SD3.02 vs. LOS≥40=9.52±SD 12.32, p=0.02) and were less frequently discharged deceased (LOS<40=37% vs. LOS≥40=16%, p=<0.01) than their shorter length of stay counterparts. Patients intubated in the Emergency Department who had a shorter length of stay did not differ substantially to those who had a longer length of stay for any other characteristics.

A similar set of descriptive statistics were evaluated for patients who were intubated in the Prehospital setting (Table 4.12). Patients who had a shorter length of stay, suffered from a higher severity (LOS<40=27.06±SD7.88 vs. LOS≥40=22.91±SD6.12, p=0.02), were more frequently admitted for a medical problem (LOS<40=29% vs. LOS≥40=9%, p=0.03), and more frequently discharged deceased (LOS<40=47% vs. LOS≥40=13%p=<0.001). A higher proportion of patients who were admitted for a traumatic problem (LOS<40=56% vs. LOS≥40=88%, p=<0.01) experienced a longer length of stay. A significantly higher proportion of patients who experienced a shorter length of stay were diagnosed with oropharyngeal flora as their primary microbial VAP pathogen (LOS<40=18% vs. LOS≥40=0%, p=0.01). However, since this statistic has a zero cell, it is viewed with caution. These two patient groups did not differ in any other way.

Table 4.11: Means and Proportions of Characteristics for Patients who were Intubated in the Emergency Department and stayed in the Hospital for <40 days compared to those who stayed in the Hospital for ≥40 days

	LOS <40 n=62	LOS ≥40 n=65	*P*
DEMOGRAPHICS & DISEASE STATE			
Age (years), mean±sd	43.95±20.34	46.01±19.53	0.56
<65	50(81%)	47(73%)	-
≥65	12(19%)	17(27%)	0.29
Gender			
Female	18(29%)	16(25%)	-
Male	44(71%)	48(75%)	0.61
APACHE II score*, mean±sd (3 missing values)	22.97±6.48	23.73±7.03	0.52
<25	39(63%)	43(67%)	-
≥25	23(37%)	21(33%)	0.64
SOFA score*, mean±sd	7.61±2.98	8.14±3.53	0.37
<7	25(40%)	25(39%)	-
≥7	37(60%)	39(61%)	0.91
Admission category by primary diagnosis			
Medical	15(24%)	16(25%)	0.90
Trauma	41(66%)	39(61%)	0.56
Neurological	6(10%)	9(14%)	0.49
VAP ETIOLOGY			
Pathogen (2 missing values)			
Gram Negative Bacteria (not specified)	17(28%)	14(22%)	0.44
Haemophilus influenzae	11(18%)	13(21%)	0.67
Staphlyococcus aureus	19(31%)	19(30%)	0.90

	LOS <40 n=62	LOS ≥40 n=65	*P*
Streptococcus spp.	8(13%)	7(11%)	0.73
Yeast spp.	1(2%)	2(3%)	0.72
Oropharyngeal Flora	4(7%)	6(10%)	0.55
No Growth	1(2%)	2(3%)	0.72
Time to VAP diagnosis (days), mean±sd (1 missing value)	5.69±3.02	9.52±12.32	0.02†
Early (<5 days)	26(42%)	16(25%)	-
Late (≥5 days)	36(58%)	47(75%)	0.04†
OUTCOME			
Hospital Mortality			
Alive	39(63%)	54(84%)	-
Deceased	23(37%)	10(16%)	<0.01†

Note: All results are represented as "n (%)", unless otherwise stated; * indicates the measure was taken upon ICU admission; † indicates p-value <0.05; APACHE= Acute Physiology and Chronic Health Evaluation; LOS=Length of Stay; sd= Standard Deviation; SOFA= Sequential Organ Failure Assessment; VAP= Ventilator-Associated Pneumonia.

Table 4.12: Means and Proportions of Characteristics for Patients who were Intubated in the Prehospital and stayed in the Hospital for <40 days compared to those who stayed in the Hospital for ≥40 days

	LOS <40 n=34	LOS ≥40 n=33	*P*
DEMOGRAPHICS & DISEASE STATE			
Age (years), mean±sd	43.29±18.77	38.33±15.48	0.24
<65	27(79%)	31(94%)	-
≥65	7(21%)	2(6%)	0.07
Gender			
Female	7(21%)	3(9%)	-
Male	27(79%)	30(91%)	0.17
APACHE II score*, mean±sd (3 missing values)	27.06±7.88	22.91±6.12	0.02†
<25	14(41%)	18(55%)	-
≥25	20(59%)	15(45%)	0.25
SOFA score*, mean±sd	9.09±3.52	8.00±2.66	0.16
<7	8(24%)	11(33%)	-
≥7	26(76%)	22(67%)	0.41
Admission category by primary diagnosis			
Medical	10(29%)	3(9%)	0.03†
Trauma	19(56%)	29(88%)	<0.01†
Neurological	5(14%)	1(3%)	0.10
VAP ETIOLOGY			
Pathogen (2 missing values)			
Gram Negative Bacteria (not specified)	9(26%)	10(30%)	0.71
Haemophilus influenzae	5(15%)	8(24%)	0.35
Staphlyococcus aureus	11(32%)	13(39%)	0.55

	LOS <40 n=34	LOS ≥40 n=33	*P*
Streptococcus spp.	3(9%)	2(6%)	0.64
Yeast spp.	0(0%)	0(0%)	-
Oropharyngeal Flora	6(18%)	0(0%)	0.01†
No Growth	0(0%)	0(0%)	-
Time to VAP diagnosis (days), mean±sd (1 missing value)	6.20±3.52	7.48±5.87	0.28
Early (<5 days)	10(29%)	17(52%)	-
Late (≥5 days)	24(71%)	16(48%)	0.06
OUTCOME			
Hospital Mortality			
Alive	18(53%)	32(97%)	-
Deceased	16(47%)	1(3%)	<0.001†

Note: All results are represented as "n (%)", unless otherwise stated; * indicates the measure was taken upon ICU admission; † indicates p-value <0.05; ; APACHE= Acute Physiology and Chronic Health Evaluation; LOS=Length of Stay; sd= Standard Deviation; SOFA= Sequential Organ Failure Assessment; VAP= Ventilator-Associated Pneumonia.

Stratified Analysis

A classic stratified analysis was performed to analyze the potential effects of covariates on the relationship between intubation location and hospital length of stay. Odds ratios were employed to quantify the measure of association. The odds ratio was calculated as the odds of ≥40 day hospitalization for those intubated in the Prehospital setting over the odds of ≥40 day hospitalization for those intubated in the Emergency Department. The outcome of the stratified analysis was used to determine which variables should be included in the linear regression analysis.

The estimated crude odds ratio for length of stay equal to or greater than 40 days is 0.94 (95% CI 0.50-1.78). This means that the odds of staying ≥40 days is approximately 6% lower for Prehospital intubated patients than the odds of staying ≥40

days for Emergency Department intubated patients. However, the precision of this estimate is quite poor as the 95% confidence interval is wide and crosses the null value. Therefore, the null hypothesis, that the risk of mortality for these two groups is not different, cannot be rejected (p=0.83). This crude estimate does not account for the influence confounding and modifying factors. To further evaluate the odds ratio of longer length based on intubation location, a classic stratified analysis was performed on key covariates (Table 4.13).

There were several variables in which the stratum specific estimates varied greatly. Using the designated alpha level of 0.20, effect measure modification was identified for age (p=0.06), admission category (medical p=0.07, trauma p=<0.01, neurological p=0.09), time to VAP diagnosis (p=<0.01) and hospital mortality (p=0.05).

The odds ratio for length of stay ≥40 days was higher among younger patients than among older patients (Age<65=1.22, 95% CI 0.61-2.4; Age≥65=0.20, 95% CI 0.19-1.27). Patients who were admitted with a traumatic injury had a higher odds ratio of length of stay ≥40 days than those admitted for any other illness (Yes=1.60, 95% CI 0.73-3.54; No=0.22, 95% CI 0.05-0.86). This result was replicated in that, patients without either neurological or medical illness had a higher odds ratio of length of stay ≥40 days than those who did (Medical: No=1.22, 95% CI -.59-2.53; Yes=0.28, 95% 0.04-1.43; Neurological: No=1.12, 95% CI 0.57-2.20; Yes=0.13, 95% CI 0.01-1.78). Patients who experienced early onset VAP (time to VAP diagnosis <4 days) had a higher odds ratio for length of stay ≥40 days than patients who experienced late onset VAP (Early=2.76, 95% 0.91-8.50; Late=0.51, 95% CI 0.22-1.18). Finally, patients who were discharged alive had a higher odds ratio for length of stay ≥ 40 days than those who were discharge deceased (Alive=1.28, 95% CI 0.60-2.80; Dead=0.14, 95% CI 0.003-1.23). None of the Mantel-Haenszel combined odds ratio for length of stay ≥40 days estimates differed significantly from the crude odds ratio; therefore, confounding was not identified as a concern for any of the other covariates.

Table 4.13: Stratified Analysis of Covariates Effect on the Relationship between Intubation Location and Odds Ratio for Length of Stay ≥40 days

		Odds Ratio (95% CI)	MH Combined (95% CI)	*P*
Crude Estimate		0.94 (0.50-1.78)	-	0.83
DEMOGRAPHICS & DISEASE STATE				
Age (years)				
<65		1.22 (0.61-2.47)	0.94 (0.52-1.70)	0.06‡
≥65		0.20 (0.19-1.27)		
Gender				
Female		0.48 (0.07-2.62)	0.90 (0.49-1.64)	0.37
Male		1.02 (0.50-2.08)		
APACHE II score*				
<25		1.17 (0.47-2.90)	0.99 (0.54-1.82)	0.57
≥25		0.82 (0.31-2.20)		
SOFA score*				
<7		1.38 (0.42-4.65)	0.95 (0.52-1.73)	0.41
≥7		0.80 (0.27-1.76)		
Admission category by primary diagnosis				
Medical	No	1.22 (0.59-2.53)	0.92 (0.51-1.67)	0.07‡
	Yes	0.28 (0.04-1.42)		
Trauma	No	0.22 (0.05-0.86)	0.92 (0.51-1.65)	<0.01‡
	Yes	1.60 (0.73-3.54)		
Neurological	No	1.12 (0.57-2.20)	0.94 (0.52-1.69)	0.09‡
	Yes	0.13 (0.01-1.78)		
VAP ETIOLOGY				
Pathogen				
Gram Negative Bacteria (unspecified, not *H.influenzae*)	No	0.83 (0.39-1.76)	0.94 (0.52-1.71)	0.47
	Yes	1.35 (0.37-4.95)		

		Odds Ratio (95% CI)	MH Combined (95% CI)	*P*
Haemophilus influenzae	No	0.86 (0.43-1.76)	0.94 (0.52-1.70)	0.56
	Yes	1.35 (0.28-6.88)		
Staphlyococcus aureus	No	0.83 (0.37-1.84)	0.94 (0.52-1.70)	0.58
	Yes	1.18 (0.38-3.73)		
Streptococcus spp.	No	0.95 (0.48-1.85)	0.93 (0.51-1.69)	0.84
	Yes	0.76 (0.05-8.98)		
Yeast spp.	No	0.95 (0.50-1.81)	----- (----------)	-
	Yes	----- (----------)		
Oropharyngeal Flora	No	2.28 (0.60-2.31)	----- (----------)	-
	Yes	----- (----------)		
No Growth	No	0.95 (0.50-1.81)	----- (----------)	-
	Yes	----- (----------)		
Time to VAP diagnosis (days), mean±sd				
Early (<5 days)		2.76 (0.91-8.50)	0.97 (0.54-1.73)	<0.01‡
Late (≥5 days)		0.51 (0.22-1.18)		
OUTCOME				
Hospital Mortality				
Alive		1.28 (0.60-2.80)	0.92 (0.49-1.73)	0.05‡
Deceased		0.14 (0.003-1.23)		

Note: All results are represented as "n (%)", unless otherwise stated; * indicates the measure was taken upon ICU admission; ‡ indicates p-value <0.20; APACHE= Acute Physiology and Chronic Health Evaluation; MH=Mantel Haenszel; sd= Standard Deviation; SOFA= Sequential Organ Failure Assessment; VAP= Ventilator-Associated Pneumonia.

Although the odds ratios of length of stay ≥40 days from the stratified analysis are not comparable to the desired mean length of stay; the results provide valuable information that explains which factors effect length of stay. Differences in severity and admission category were seen for the Prehospital patients; whereas differences in time to VAP diagnosis were seen for the Emergency Department patients. Both groups displayed

difference in length of stay based on mortality. The stratified analysis also showed that age was an important factor to consider in explaining the relationship.

The precision of these estimates is quite poor as all of the confidence intervals of the comparative estimates overlap and cross the null value. There is a huge loss of information using the stratified analysis technique, because the outcome measure has been dichotomized. A more accurate evaluation of this relationship can be seen using a multivariate regression approach.

Regression Analysis

Linear regression was used to calculate the mean hospital length of stay with a multivariate model. The crude model included only the effect of the exposure (intubation location). The baseline model was:

$$Length\ of\ Stay = \beta_0 + \beta_{exposure}$$

The coefficients associated with the model were a baseline length of stay (β_0) and intubation location ($\beta_{exposure}$), were 60.65 days and 4.93 days respectively. This means that patients who are intubated in the Emergency Department (β_0) the mean length of stay is 60.65. For patients who are intubated in the Prehospital setting ($\beta_0 + \beta_{exposure}$), the length of stay is 65.58 days. Since there are no other variables in this model, these number are the same means as the original descriptive statistics (Table 4.2) However, this model was insufficient in explaining the relationship of intubation location and length of stay (p=0.63).

Further models were constructed based on the information obtained from the descriptive and stratified analyses. Age and APACHE II score were used as continuous variables in the regression analysis; while gender and mortality remained dichotomous. Admission category was considered categorically and then as three separate dichotomous variables. Time to VAP diagnosis was not considered in the model as it is a part of the total length of stay (LOS= time to VAP diagnosis + time after VAP diagnosis).

A forward stepwise selection process was used to determine which of these variables influenced the association in a multivariate model. The entire modelling process is outlined in Appendix B (Table B.4). Neither neurological, nor medical admission categories influenced the model and were removed.

The proposed final model was:

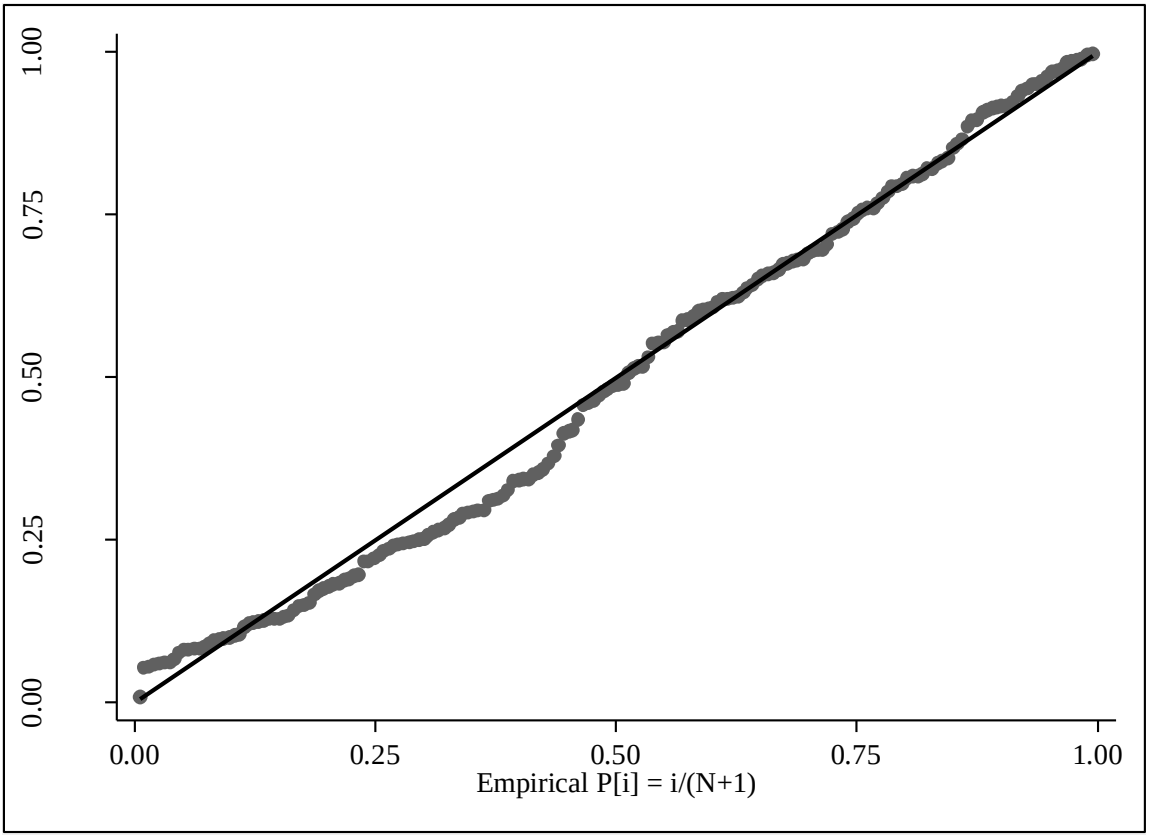
$$log(LOS) = \beta_0 + \beta_{exposure} + \beta_{dead} + \beta_{exposure*dead} + \beta_{(age-18)} + \beta_{(age-18)*dead} + \beta_{gender}$$

This model was constructed based on the assessment of effect measure modification, confounding and clinical significance of the above stated variables. This equation states that the log mean length of stay is the summation of some baseline effect (β_0) plus the exposure effect ($\beta_{exposure}$) and several other patient characteristic ($\beta_{dead} + \beta_{exposure*dead} + \beta_{(age-18)} + \beta_{(age-18)*dead} + \beta_{gender}$). Hospital mortality was identified as an effect modifier; hence the inclusion of the interaction term ($\beta_{exposure*dead}$). Interaction was identified between age (shifted by -18) and hospital mortality ($\beta_{(age-18)*dead}$). Age ($\beta_{(age-18)}$) was included in the model to ensure it was hierarchically well formulated. Gender (β_{gender}) was kept in the model on the basis of clinical significance. No confounding was identified during the modeling process.

The proposed final model was assessed to ensure that the assumptions for linear regression were not violated and that the model was constructed properly. The first assumption of linear regression is that the residuals of the dependent variable, length of stay, be normally distributed. Since length of stay is a time-dependent variable, naturally is it right skewed; furthermore the residuals were also right skewed. Therefore, length of stay was transformed onto the log-scale to correct for this deficiency. A plot depicting the distribution of pre-transformation residuals can be found in Appendix B (Figure B.1).

Figure 4.6 depicts the normal distribution of the residuals of this model, post transformation. The Standardized Normal Probability plot graphs the residuals of the data against a theoretical normal distribution (represented as the 45^o straight line -black). Any departures from the line indicate departures from normality. The grey points on the graph, representing this dataset, are nearly linear and indicate that the assumption of normality as not been violated and the log distribution is a good fit for this model.

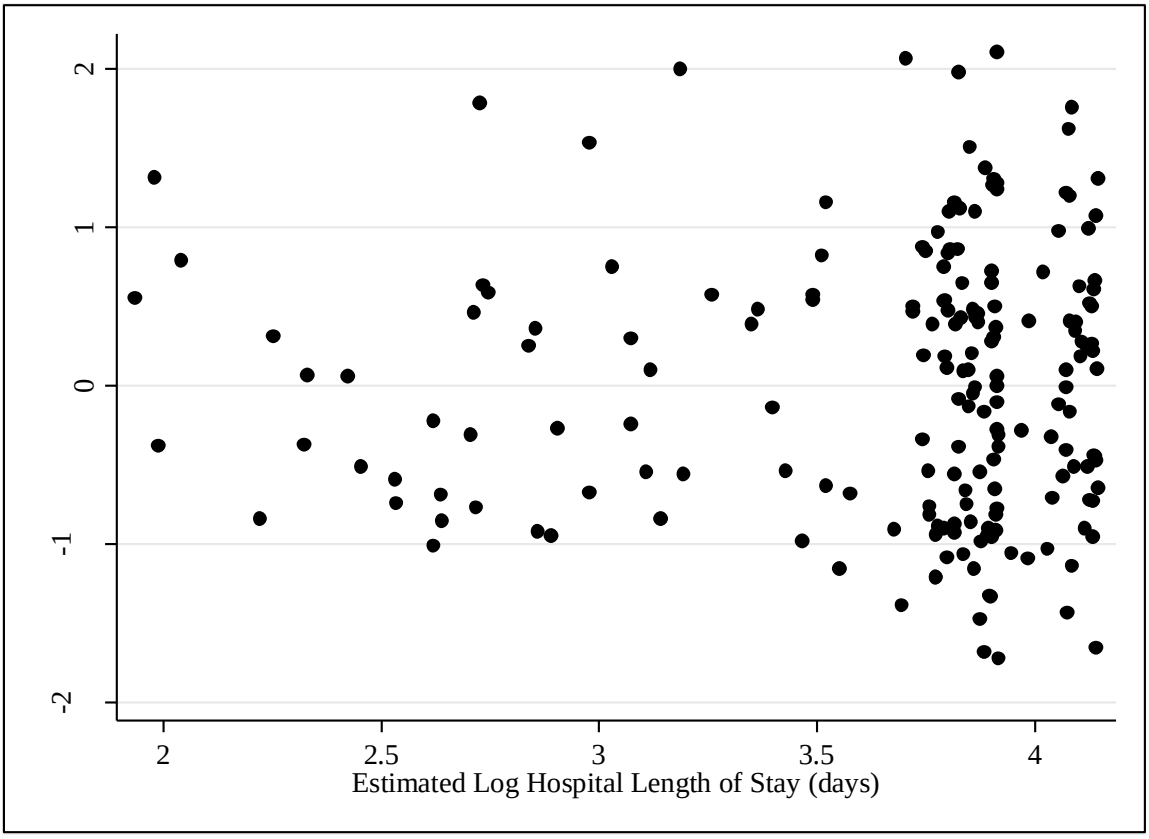
Figure 4.6: Standardized Normal Probability Plot of the Linear Regression Model Residuals (Post-transformation)



The second assumption of linear regression, states that the relationship between the independent (covariates) and dependent (length of stay) variables should be linear. To check for linearity, each continuous independent variable was plotted against the standardized residuals of the model. The standardized residuals were plotted against age (shifted by -18) and the interaction term created to represent age (shifted by -18) multiplied by mortality. Both plots indicated that there was no pattern (i.e. random), meaning that the assumption of linearity was not violated (Appendix B: Age- Figure B.2; Age*Mortality- Figure B.3). Furthermore, the Box-Tidwell test also suggested that there were no linearity issues and none of the variables required further transformation (Age: p=0.122; Age*Mortality: p=0.62).

To test the third assumption, homoscedasticity, the residuals were plotted against the predicted values of the model. The plot shown in Figure 4.7 indicates that there is no pattern (i.e. random) and the residuals are centered on zero. Therefore the variance of the error is constant. This conclusion is duplicated by the Breusch-Pagan/Cook-Weisberg test, which indicates the null hypothesis, that there is constant variance, cannot be rejected (X^2=0.70, p=0.40).

Figure 4.7: Linear Regression Model Residuals against the Estimated Log Hospital Length of Stay (Test for Homoscedasticity)



Similar to the assumption of logistic regression, each of the variables and the individual observations must be independent of one another. Once again, this was accounted for in the design and conduct of the study.

The final assumption for linear regression states that there must not be collinearity between variables. The correlation and variance inflation factor of each unique variable

was tested and there were no concerning violations (exposure= 1.38, mortality= 4.02, age= 1.57, gender =1.06). None of the variable pairings had a correlation value (r) of greater than 0.55 or less than -0.55 (Appendix B: Table B.5).

This model was also assessed for specification errors to see if the model was both meaningful and complete. The Regression Specification Test uses the null hypothesis that there are no missing variables in the model. The result, p=0.22, indicates there are no errors and the null hypothesis cannot be rejected.

Finally, the Goodness of Fit is assessed using the F-statistic, which indicates whether or not the whole model is statistically significant. Secondly the Goodness of Fit can be assessed by the R-squared, which is the proportion of the variance of the outcome, length of stay, that is explained by the model. The above stated model is statistically significant (F=12.06, p=<0.001) and approximately 28% of the variance (of the association) is accounted for.

In all accounts this model proved to be constructed properly and in accordance with the linear regression assumptions. A summary of the model performance results is shown in Table 4.14.

Table 4.14: Summary of Model Performance Indicators for Hospital Length of Stay Linear Regression

Final Proposed Model: $log(Length\ of\ Stay) = \beta_0 + \beta_{exposure} + \beta_{dead} + \beta_{exposure*dead} + \beta_{(age-18)} + \beta_{(age-18)*dead} + \beta_{gender}$

Assumption	Test	Measurement	Significance Threshold	Result
Normally distributed residuals	Standardized Normal Probability Plot	To visualize if the residuals of the dependent variable, log length of stay, are distributed normally.	Linear Distribution	No concern. Pre-transformation: Appendix B: Figure B.1. Post-transformation: Figure 4.6.
Homoscedasticity	Constant Variance	To visualize if the residuals plotted against the predicted values of the model are distributed randomly	Random Distribution	No concern. See Figure 4.7
	Breusch-Pagan/Cook-Weisberg	Ho: There is constant variance	$p<0.05$	p=0.40
Independence of subjects	None	--	--	No concern. Inherent in study design
Independence of Variables (Collinearity)	Correlation	Measure independence of variables from one another	$0.55>r<-0.55$	No concern. See Appendix B (Table B.5).
	Variance Inflation Factor	Measure of how much of the inflation of the standard error is caused by collinearity	>10	Exposure 1.38 Age 1.57 Gender 1.06 Mortality 4.02

Assumption	Test	Measurement	Significance Threshold	Result
Linearity of Independent Variables	Standardized Residual Plots	To visualize if the residuals plotted against the values of each continuous variable are normally distributed.	Random Distribution	No concern. See Appendix B (Age- Figure B.2; Age*Mortality-Figure B.3).
	Box-Tidwell	Ho: Each continuous variable is a linear term (does not need to be transformed)	$p<0.05$	Age 0.122 Age*Mortality 0.167
Specification Errors	Regression Specification Test	Ho: There are no missing variables	$p<0.05$	$p=0.22$ ($F=1.48$)
Goodness of Fit	F-statistic	Ho: The whole model is not statistically significant	$p<0.05$	$p<0.001$ ($F=12.06$)

Note: APACHE=Acute Physiology and Chronic Health Evaluation; Exp=Exposure (Intubation Location); Ho=Null Hypothesis.

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The results of this model are summarized in Table 4.15. The mean length of stay column indicates the additional days of hospitalization associated with one unit change of each variable.

This model indicates that there is a significant association between intubation location and hospital length of stay in the presence of multiple variables. The calculation of length of stay is quite complex as there was effect modification by mortality (p=<0.01) and interaction between age and mortality (p=0.02). Although gender did not act as either an effect modifier or a confounder, it was forced into the model on the premise of clinical significance.

Table 4.15: Mean Hospital Length of Stay for the Final Multivariate Linear Regression Model

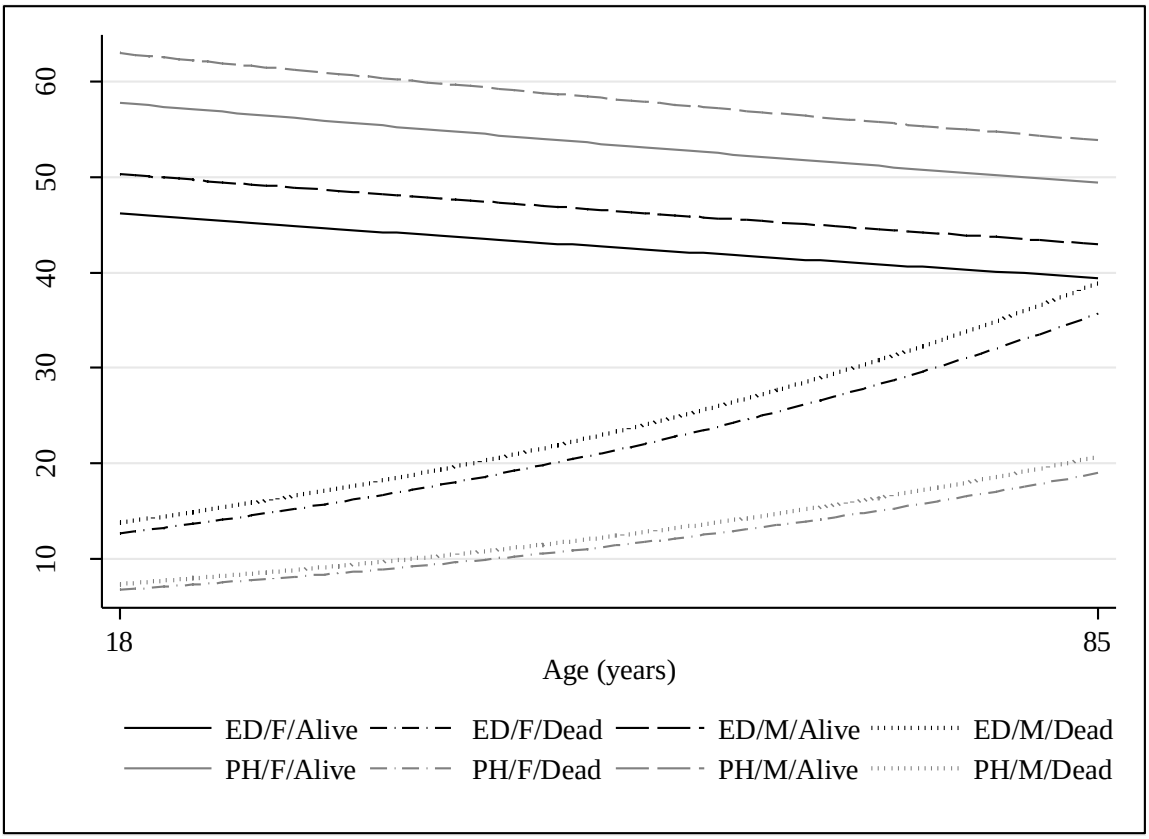
Variable	Data Type	Mean LOS	95% CI	*P*
Exposure	ED=0, PH=1	1.252	0.926-1.693	0.14
Dead	Alive=0, Dead=1	0.273	0.155-0.480	<0.001†
Exposure*Dead	ED=0, PH=1	0.424	0.235-0.767	<0.01†
Age	Continuous (shifted left by 18)	0.998	0.990-1.001	0.57
Dead*Age	Alive=0, Dead=continuous	1.018	1.003-1.033	0.02†
Gender	F=0, M=1	1.090	0.808-1.471	0.57

Note: * indicates the measure was taken upon ICU admission; † indicates Student t-test p-value <0.05; CI=Confidence Interval; ED=Emergency Department; F=Female; LOS=Length of Stay; M=Male; PH=Prehospital.

This model is graphically represented in Figure 4.8. There are two distinct patterns in the data, one group of patients who were discharged deceased and the second group of patients who were discharged alive. Younger patients who were discharged deceased had a shorter length of stay than older patients who were discharged deceased (i.e. they died quicker). Furthermore, patients who were intubated in the Emergency Department (black) had a longer length of stay prior to death than patients intubated in

the Prehospital setting (grey). The opposite is true for patients who survived until hospital discharge. Younger patients had a longer length of stay than their older counterparts. Also Prehospital intubated (grey) patients had a longer length of stay than their Emergency Department intubated (black) counterparts. For all groups, females had a slightly shorter length of stay than males.

Figure 4.8: Estimated Hospital Length of Stay by Age



Note: ED=Emergency Department; F=Female M=Male; PH=Prehospital.

The calculated length of stay for several types of patients is listed in Table 4.16. This table is included to show the numerical values for the mean length of stay, as calculated by this model, for several different scenarios. For example, among 58 year old Male patients who die the hospital utilization, as determined by mean length of stay, is 12 days longer for those who were intubated in the Emergency Department, compared to the Prehospital setting (ED=26 days; PH=14 days). Conversely, 58 year old Male patients

who survive and were intubated in the Prehospital setting have a 11 day longer length of stay than their Emergency Department counterparts (ED=46 days; PH=57 days).

Table 4.16: Mean Hospital Length of Stay for Various Patient Groups

Age (years)	Alive				Dead			
	Female		Male		Female		Male	
	ED	PH	ED	PH	ED	PH	ED	PH
18	46	58	50	63	13	7	14	7
28	45	56	49	62	15	8	16	9
38	44	55	48	60	17	9	19	10
48	43	54	47	59	20	11	22	12
58	42	53	46	57	23	12	26	14
68	41	51	45	56	27	15	30	16
78	40	50	44	55	32	17	35	19
88	39	49	43	53	37	20	41	22

Note: ED=Emergency Department; PH=Prehospital.

Time to Event Analysis

Time to event analysis was used to compare the difference in the timing of death for patients intubated in the Emergency Department to the timing of death for patients intubated in the Prehospital setting.

The results of the previous comparative analysis indicate that the length of stay for patients who remained alive is significantly longer than the length of stay for patient who died regardless of ETI setting (Table 4.5: ED p=<0.01, Table 4.6: PH p=<0.001). This means that patients who die, do so earlier in the hospital stay.

Furthermore, the timing of death is different for patients intubated in the Prehospital setting in comparison to those intubated in the Emergency Department. The stratified analysis concluded that among survivors, Prehospital intubated patients are 28% more likely to stay ≥ 40 days than those intubated in the Emergency Department (Table 4.13: OR=1.28, 95% CI 0.60-2.80). However, among deceased patients, Prehospital intubated patients are 86% less likely to stay ≥40 days compared to those intubated in the Emergency Department (Table 4.13: OR=0.14, 95% CI 0.003-1.23). This result can also

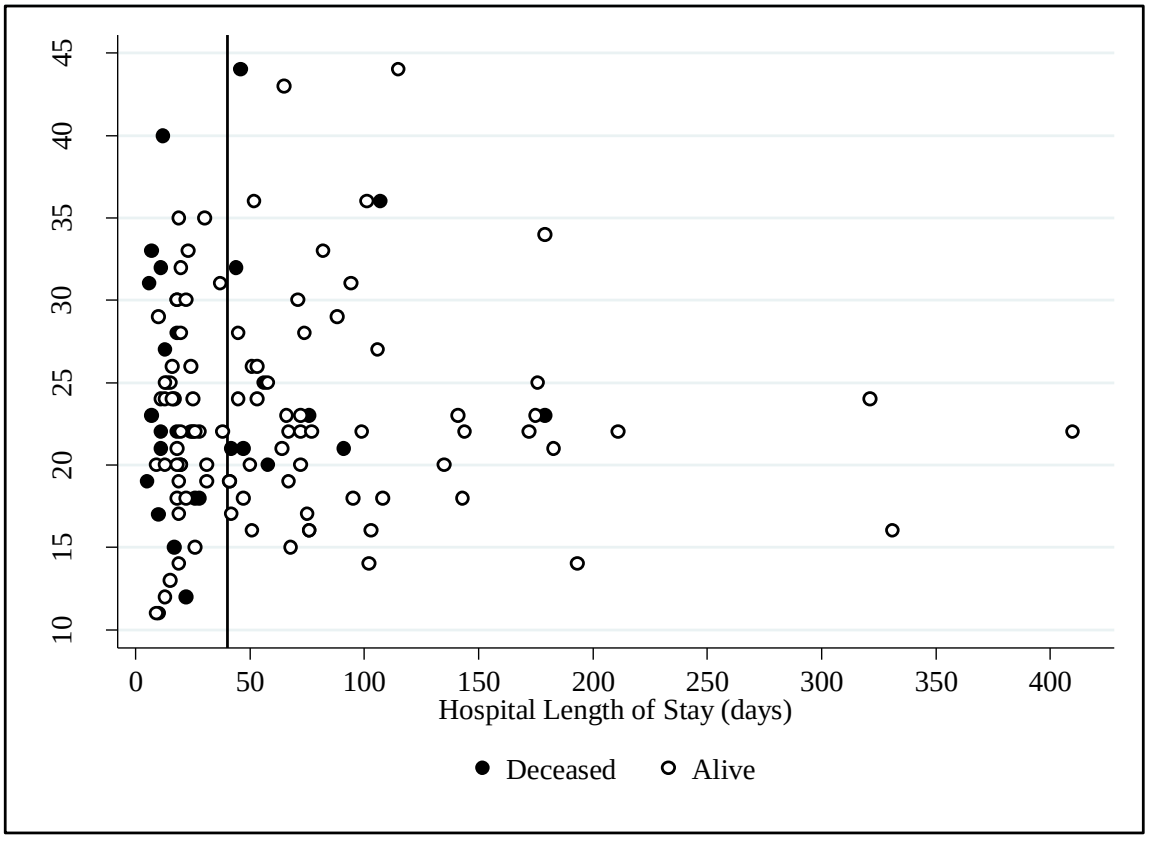
be seen in the estimated hospital length of stay from the linear regression model (Figure 4.8) and in the calculated mean length of stay in Table 4.16.

The relationship between hospital length of stay and discharge status (alive vs. deceased) is plotted against disease severity (APACHE II) for both Emergency Department ETI patients (Figure 4.9) and Prehospital ETI (Figure 4.10). The black dots represent patients who are discharged deceased; while the white dots represent patients who are discharged alive. The median length of stay, 40 days, is indicated by a vertical reference line.

Figure 4.9 shows that in general that length of stay among Emergency Department ETI patients, both alive (white) and deceased (black), are concentrated to the left of the x-axis, indicating a shorter length of stay. Although both groups contain several cases that exceed the reference line, there are numerous patients who are discharged alive in which the length of stay persists well into several hundreds of days.

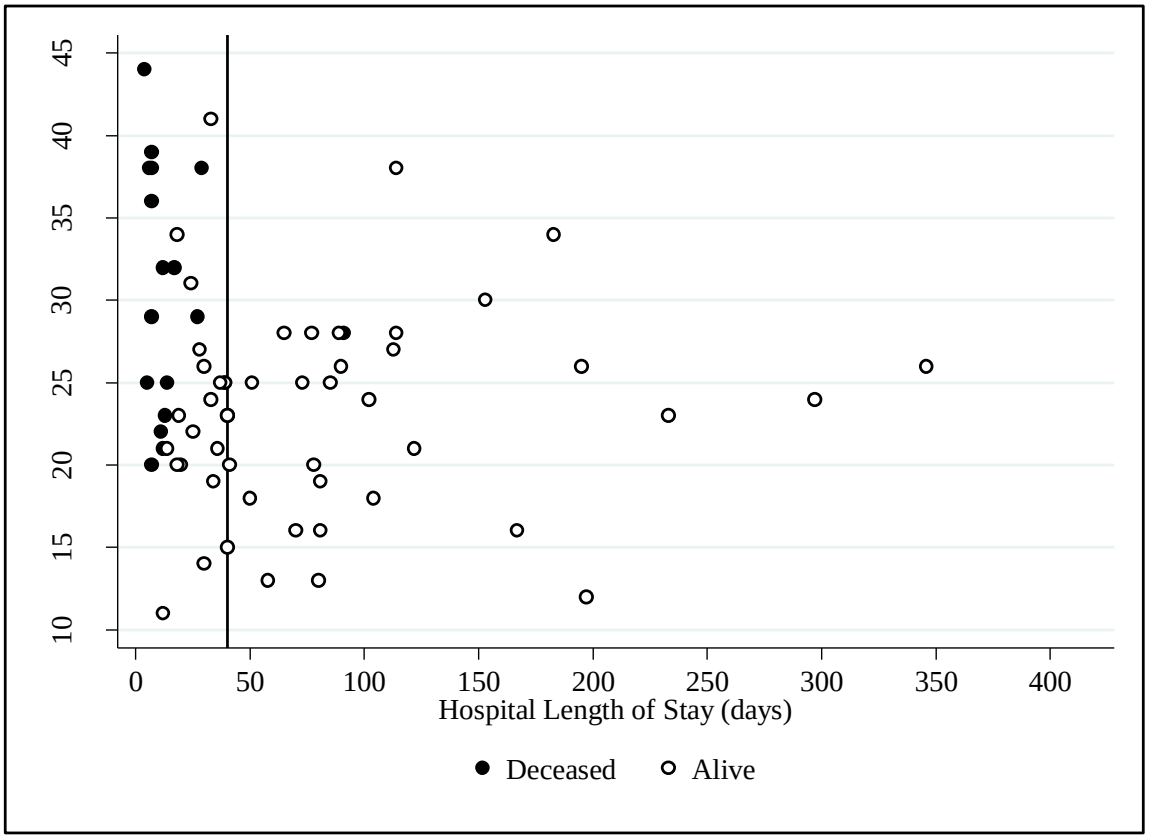
The depiction showing the length of stay among Prehospital intubation patients (Figure 4.10) is very similar to that of the Emergency Department, with the majority of cases clustered below the reference line and several white dots (alive patients) exceeding it. The main difference is that there is only one case in which a Prehospital intubated patient who is discharged deceased had a length of stay greater than 40 days.

Figure 4.9: Hospital Length of Stay versus Acute Physiology and Chronic Health Evaluation II score for Emergency Department Intubated Patients



Note: * indicates the measure was taken upon ICU admission; APACHE=Acute Physiology and Chronic Health Evaluation.

Figure 4.10: Hospital Length of Stay versus Acute Physiology and Chronic Health Evaluation II score for Prehospital Intubated Patients



Note: * indicates the measure was taken upon ICU admission; APACHE=Acute Physiology and Chronic Health Evaluation.

One way to compare time-dependent events is to describe the hazard rates for each group. A hazard rate is a type of incidence rate and is calculated as the number of deaths over the total time at risk (days). The hazard rate for the entire study population is 4.15 $x10^{-3}$ deaths per person-days. The hazard rate for Emergency Department ETI patient 1.12 times the hazard rate of Prehospital ETI patients (ED=4.32 $x10^{-3}$ deaths per person-days, PH=3.87 $x10^{-3}$ deaths per person-days). Even though the hazard rates are quite different for each group, the result is not significant (p=0.36).

Although hazard rate calculations consider the quantity of time at risk, it still does not take into consideration the instantaneous risk of death. The use of hazard ratios is a measure of association that accounts for the risk of death over a finite interval of time.

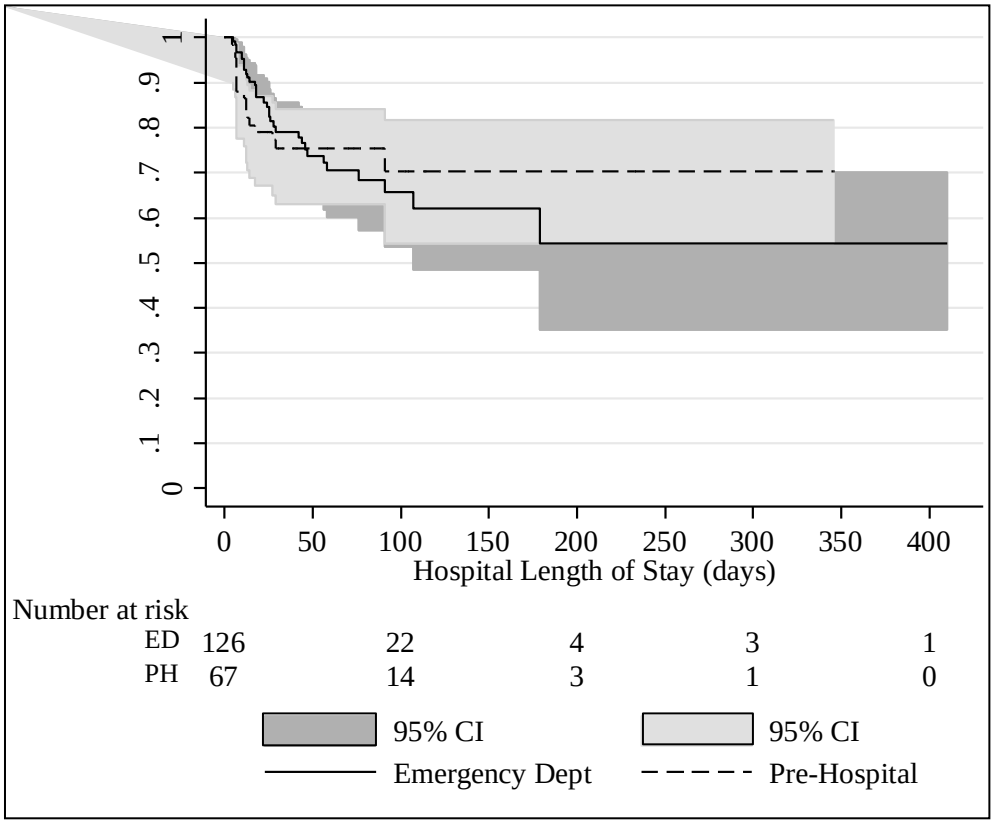
The hazard ratio is a ratio of the hazard rates, over the same time period for two groups with the same risk profile except for intubation location. The hazard ratio represents the instantaneous risk of death anytime during the hospital stay. The crude hazard ratio is 0.95 (95% CI 0.53-1.71). This means that Prehospital intubated patients and Emergency Department intubated patients have equal risk rates as the magnitude of the hazard ratio estimate is close to 1 and the confidence interval crosses the null value.

Hazard ratios can be calculated every time a patient leaves the study (either death or discharge). The series of hazard ratios, converted to survival proportions are represented graphically, called a Kaplan-Meier curve. Figure 4.11 is a pictorial representation of the crude survival curves (with 95% confidence intervals) for each exposure group. They show how the proportional hazards (instantaneous risk) changes over the study period. The calculation is based on the number of deaths at a specific time and the number of patients at risk of death at the same time. The curves are shaped like staircases, where every vertical step downward is the time of death for each individual subject (no cases were censored). The probability of survival (y-axis) is the estimated proportion of patients that survive to a certain time (x-axis).

The curve that represents the Prehospital ETI patients (- - -) shows a quick drop off, and then levels at day 92 (no more deaths occur after that time). The curve that represents the Emergency Department ETI patients (---) shows a more gradual drop off and then levels at day 180. Although the two curves have different shapes, the confidence intervals overlap and the log-rank test for equality of survival functions indicates they are not significantly different (p=0.87).

However, the results of the mortality and length of stay analysis indicate that the effect of the intubation location cannot be fully explained using a crude model. In fact, this relationship is quite complex and requires analysis that can consider multiple variables.

Figure 4.11: Kaplan-Meier Survival Estimates for Emergency Department Endotracheal Intubation and Prehospital Endotracheal Intubation Patients



Note: CI=Confidence Interval; ED=Emergency Department; PH=Prehospital.

Regression Analysis

The technique used to analyze proportional hazards in the presence of multiple variables is called Cox regression. Cox regression provides an estimate of the effect of intubation location on survival after the adjustment of covariates. The crude model included only the effect of the exposure (intubation location).

The baseline model was:

$$log\left(\frac{H(t)}{Ho(t)}\right) = \beta_{exposure}$$

Since no other information is included in this model, the results are the same as the hazard rate ratio above (0.95, 95% CI 0.53-1.71). This model was insufficient in explaining the relationship of intubation location and survival (p=0.87).

Further models were constructed using information from the mortality and length of stay regression analyses. Any variables that were included in either of the final models were considered during cox regression model formation.

Age and APACHE II were considered as continuous variables, whereas gender and trauma admission category were considered dichotomously. The survival time was hospital length of stay and the outcome was hospital discharge status, where death was considered failure. There were no censored observations in this dataset (the outcome of all patients was known).

A forward stepwise selection process was used to determine which of these variables influenced the association between intubation location and time to death in a multivariate model. The entire modelling process is outlined in Appendix B (Table B.6). All of the variables considered were kept in the model.

The proposed final model was:

$$log\left(\frac{H(t)}{Ho(t)}\right) = \beta_{exposure} + \beta_{(age-18)} + \beta_{gender} + \beta_{apache} + \beta_{exposure*apache} + \beta_{trauma}$$

This model was constructed based on the assessment of effect measure modification, confounding and clinical significance of the above stated variables. This equation states that the log hazard ratio of survival is the summation of the exposure effect ($\beta_{exposure}$) and several other patient characteristics ($\beta_{(age-18)} + \beta_{gender} + \beta_{apache} + \beta_{exposure*apache} + \beta_{trauma}$). Acute Physiology and Chronic Health Evaluation II score was identified as an effect modifier; hence the inclusion of the interaction term ($\beta_{exposure*apache}$). Both age (shifted by -18) and trauma admission category confounded the intubation location-survival relationship; while, gender was kept in the model on the basis of clinical significance. There was no interaction identified between variables.

This model was further assessed to ensure that the model was constructed properly and assumptions of cox-proportional hazards regression were not violated. Cox-proportional regression is a non-parametric technique, which is not based on any assumptions concerning the shape of the underlying survival distribution.

However, the model assumes that the underlying hazard rate is a function of the independent variables. (87) In this model the independent variables were age, APACHE II score, gender and trauma admission category. This is the primary assumption of this regression technique, called the proportionality assumption. It states that there must be a multiplicative relationship between the underlying hazard function and the log-linear function of the covariates. (87) This means that for two patients with different covariate values, hazard ratio for those two patients does not depend on hospital length of stay. The Schoenfeld test was used to assess the proportionality of the model as a whole and the proportionality of each covariate separately. The global test indicates a non-significant result (X^2 =1.11, p=0.98). Based on the null hypothesis that there is no violation, we can conclude that the proportionality assumption is upheld. Furthermore, the independent test for each variable also upheld the assumption (exposure p=0.61, age p=0.52, gender p=0.90, APACHE II p=0.88, trauma p=0.70).

Finally the Goodness of Fit was assessed using the log likelihood chi^2 test which indicates that the above stated model, as a whole, is statistically significant (X^2=152.58, p-value=<0.001).

In all accounts this model proved to be constructed properly and in accordance with the linear regression assumptions. A summary of the model performance results is shown in Table 4.17.

Table 4.17: Summary of Model Performance Indicators for Survival Cox Proportional Hazards Regression

Final Proposed Model: $log\left(\frac{H(t)}{Ho(t)}\right) = \beta_{exposure} + \beta_{(age-18)} + \beta_{gender} + \beta_{apache} + \beta_{exposure*apache} + \beta_{trauma}$

Assumption	Test	Measurement	Significance Threshold	Result	
Proportionality	Schoenfeld	Ho: there is proportionality	p<0.05	Global	p=0.98 (X^2=1.11)
				Exposure	p=0.61
				Age	p=0.52
				Gender	p=0.90
				APACHE II	p=0.88
				Trauma	p=0.70
Goodness of Fit	Log Likelihood chi^2	Ho: The whole model is not statistically significant	p<0.05	p<0.001 (X^2=152.58)	

Note: APACHE=Acute Physiology and Chronic Health Evaluation; Ho=Null Hypothesis.

The results of the model are summarized in Table 4.18. The hazard ratio column indicates the change in hazard for Prehospital patients over the change is hazard for Emergency Department patients for every one unit change of each variable. This model shows that the estimated hazard in the Prehospital ETI group is 70.15 times that of the Emergency Department group; that is a significant increase in the risk of death after adjustment of the other explanatory variables in the model (p<0.001).

This model indicates that there is a significant association between intubation location and time of death in the presence of multiple variables. It was found that there was effect measure modification by APACHE II score (p=<0.001).

Table 4.18: Hazard Ratios for the Final Multivariate Cox-Proportional Regression Model

Variable	Data Type	HR	95% CI	*P*
Exposure	ED=0, PH=1	70.15	(17.85-275.71)	<0.001†
Age	Continuous (shifted left by 18)	0.98	(0.98-0.99)	<0.001†
Gender	F=0, M=1	1.04	(0.70-1.54)	0.85
APACHE II score*	Continuous	1.00	(0.97-1.03)	0.94
Exposure*APACHE II*	ED=0, PH=continuous	0.85	(0.80-0.90)	<0.001†
Trauma admission	No=0, Yes=1	6.37	(3.96-10.22)	<0.001†

Note: * indicates the measure was taken upon ICU admission; † indicates Wald test p-value <0.05; APACHE=Acute Physiology and Chronic Health Evaluation; CI=Confidence Interval; ED=Emergency Department; HR=Hazard Ratio; F=Female; M=Male; PH=Prehospital.

As previously mentioned age and admission due to trauma were both found to confound the intubation location-mortality relationship. This was determined via the comparison of nested models using likelihood ratio tests. The p-value and chi square statistics were significant when for both of the variables (Age: $p<0.001$, $X^2=1143.60$; Trauma: $p=<0.01$, $X^2=8.39$; Appendix B: Table B.6)

The survival curves associated with this model can also be depicted alike the simple Kaplan-Meier curves. These survival curves represent the probability of surviving as a function of time (length of stay) with the consideration of age, APACHE II score, gender and trauma admission. Figure 4.12 depicts the survival curve for an 18 year old female patient who did not suffer trauma, who had an APACHE II score of zero and was intubated in the Emergency Department (grey). This curve represents the baseline group; it is the survival curve when exposure status and all covariates are zero.

Additionally this graph shows the effect of each covariate on the survival curve. Since the coefficients of the continuous variables were small, the effects of APACHE II and age have each been multiplied by 20 to show a meaningful change in magnitude.

For example, the thin solid black line indicates the survival curve for an 18 year old female patient who did not suffer trauma, who had an APACHE II score of 20 and

was intubated in the Emergency Department (all covariates equal their intercept, except APACHE II=20). The thick solid black line represents a one unit change in gender from baseline (18 year old male patient who did not suffer trauma, who had an APACHE II score of zero and was intubated in the Emergency Department). The dotted line represents a 20 unit change in age from baseline (38 year old female patient who did not suffer trauma, who had an APACHE II score of zero and was intubated in the Emergency Department). Finally, the long-short-long dotted line indicates a one unit change in trauma status from baseline (18 year old female patient who did suffer trauma, who had an APACHE II score of zero and was intubated in the Emergency Department).

The only covariate that changes the survival curve in a clinically meaningful way was a patient having suffered a trauma.

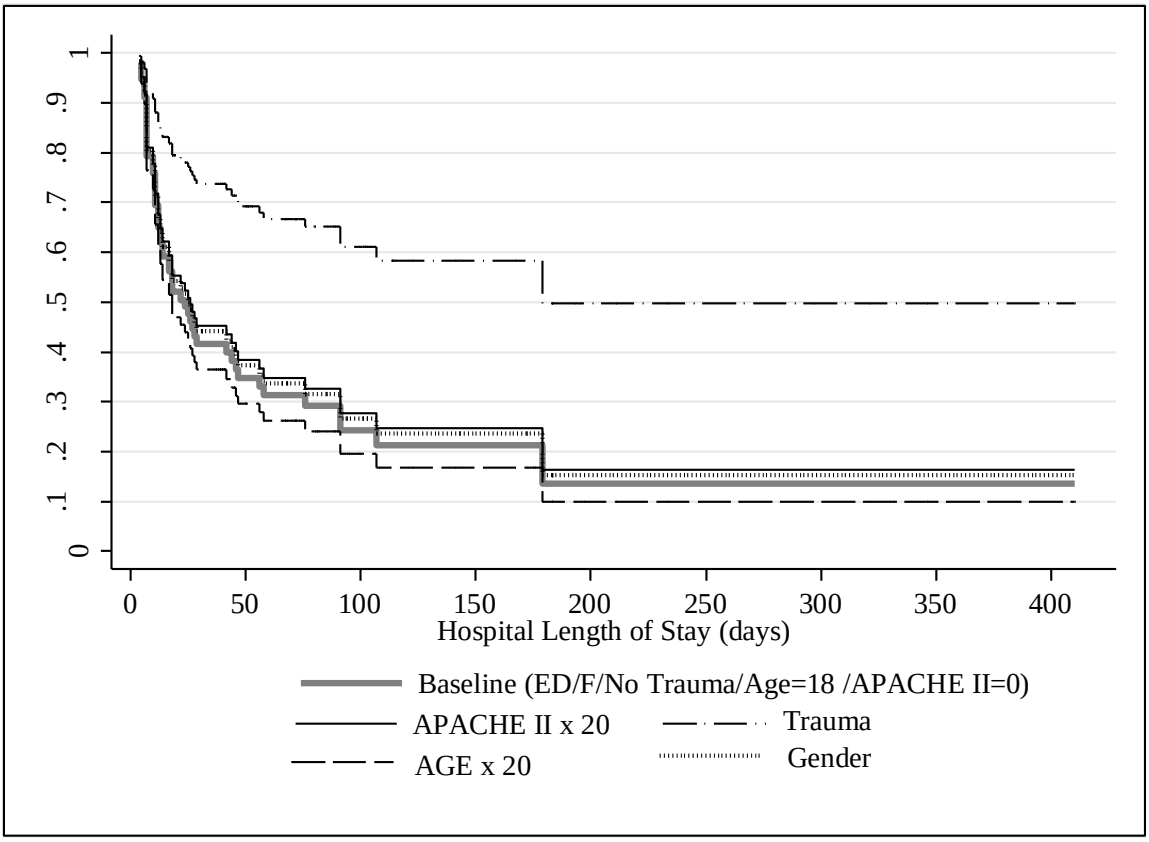
To further demonstrate the results of this model, Figure 4.13 shows survival curves for four different patient groups (variables that are not specified are held at their mean; age=43, APACHE II=24).

Firstly, patients intubated in the Prehospital setting with (dotted line) and without trauma (solid line) are depicted in grey. Patients who experience trauma have a more gradual decline in the probability of survival over time than patients who do not experience trauma.

Secondly, patients intubated in the Emergency Department with (dotted line) and without trauma (solid line) are depicted in black. Once again, patients who experience trauma have a more gradual decline in the probability of survival over time than patients who do not experience trauma.

Patients intubated in the Prehospital setting have a much higher probability of surviving than Emergency Department ETI patients at any time throughout the hospital stay, regardless of admission type (when removing the effects of age and APACHE II score). Furthermore, the difference in survival probability between traumatic and non-traumatic patients is much larger for Emergency Department ETI patients than Prehospital ETI patients.

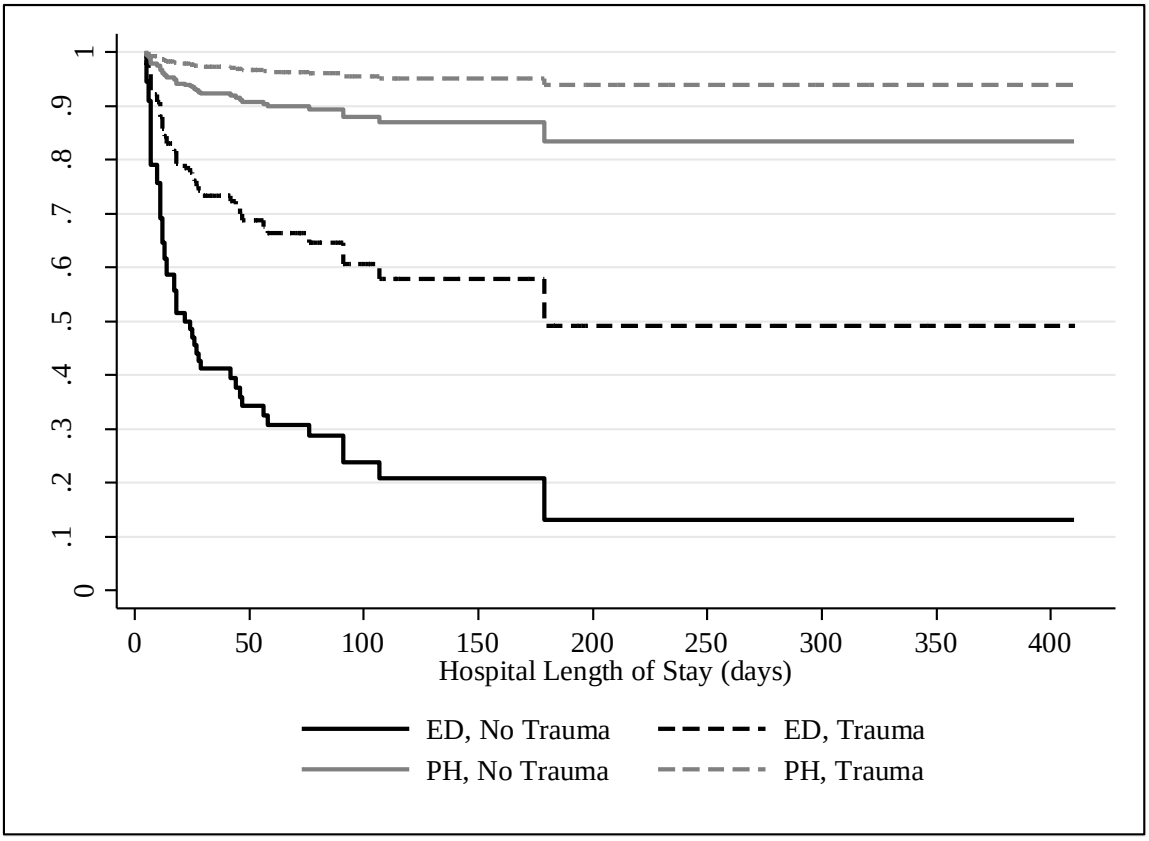
Figure 4.12: Estimated Baseline Probability of Survival & Individual Effect of Each Covariate



Note: APACHE=Acute Physiology and Chronic Health Evaluation; ED=Emergency Department; F=Female.

Figure 4.13: Estimated Probability of Survival by Intubation Location and Admission Category Type

(Age=43, APACHE II=24)



Note: ED=Emergency Department; PH=Prehospital.

CHAPTER FIVE: SECONDARY RESULTS

This chapter addresses the secondary objectives of this project: to describe the differences in ventilator-associated pneumonia (VAP) etiology and microbiology of disease between Prehospital Endotracheal Intubation (ETI) patients and Emergency Department ETI patients. Two characteristics will be explored in this analysis are: time to VAP diagnosis; and primary pathogen associated with VAP.

This chapter begins with the descriptive and comparative statistics for time to VAP diagnosis; followed by a detailed stratified and linear regression analysis. The second half of this chapter is devoted to the exploration of the primary microbial pathogen associated with VAP among the study sample.

Time to Ventilator-Associated Pneumonia Diagnosis

Descriptive and Comparative Statistics

In the previous description, it was determined that there was no difference in time to VAP diagnosis between Emergency Department ETI and Prehospital ETI patients (Table 4.4: ED=7.62±SD9.12 vs. PH=6.83±SD4.83, p=0.51). Additionally, for patients intubated in the Prehospital setting there was no difference in time to VAP diagnosis between those who lived and those who died (Table 4.6: Alive=7.00±SD5.11 vs. Died=6.35±SD4.01, p=0.64). However, for patients intubated in the Emergency Department, the time to VAP diagnosis was significantly different between those who lived and those who died (Table 4.5: Alive=6.36±SD6.90 vs. Died=11.15±SD13.15, p=0.01).

To further described the characteristics of patients with early and late on-set VAP a basic comparative analysis was completed (Table 5.1). Among Emergency Department ETI patients who developed early VAP, a higher proportion were older (ED≥65=19%vs. PH≥65=0%, p=0.02), and a lower proportion were male (ED=79% vs. PH=96%, p=0.05) than their Prehospital ETI counterparts.

Table 5.1: Means and Proportions of Characteristics of Patients Intubated in the Emergency Department compared to Patients Intubated in the Prehospital Setting by Time of Ventilator-Associated Pneumonia Onset

	Early On-set (<5 days)			Late On-set VAP (≥5 days)		
	Emerg Dept. n=42	Prehospital n=27	*P*	Emerg Dept. n=84	Prehospital n=40	*P*
DEMOGRAPHICS & DISEASE STATE						
Age (years), mean±sd	40.98±18.85	37.15±14.73	0.37	45.96±20.23	43.35±18.52	0.49
<65	34(81%)	27(100%)	-	63(75%)	31(78%)	-
≥65	8(19%)	0(0%)	0.02†	20(25%)	9(22%)	0.72
Gender						
Female	9(21%)	1(4%)	-	25(30%)	9(23%)	-
Male	33(79%)	26(96%)	0.05†	58(70%)	31(77%)	0.42
APACHE II score*, mean±sd	21.19±5.30	24.14±6.50	0.04†	24.48±7.21	25.60±7.85	0.43
<25	32(76%)	13(48%)		49(58%)	19(48%)	-
≥25	10(24%)	14(52%)	0.02†	34(42%)	21(52%)	0.30
SOFA Score*, mean±sd	7.02±2.77	8.59±2.99	0.03†	8.33±3.44	8.52±3.30	0.77
<7	20(47%)	8(29%)	-	29(34%)	11(28%)	-
≥7	22(52%)	19(70%)	0.14	54(65%)	29(72%)	0.44
Admission category by primary diagnosis						
Medical	3(7%)	2(7%)	1.00	28(33%)	11(28%)	0.57
Trauma	34(81%)	24(89%)	0.37	45(55%)	24(60%)	0.60
Neurological	5(12%)	1(4%)	0.25	10(12%)	5(12%)	1.00
VAP ETIOLOGY						
Pathogen¥						
Gram Negative Bacteria (unspecified, not *H. influenzae*)	7(17%)	7(26%)	0.36	23(27%)	12(30%)	0.72

	Early On-set (<5 days)			Late On-set VAP (≥5 days)		
	Emerg Dept. n=42	Prehospital n=27	*P*	Emerg Dept. n=84	Prehospital n=40	*P*
Haemophilus influenzae	13(31%)	6(22%)	0.41	11(13%)	7(18%)	0.46
Staphlyococcus aureus	10(24%)	13(48%)	0.04†	28(33%)	11(28%)	0.57
Streptococcus spp.	9(21%)	1(4%)	0.05†	6(7%)	4(10%)	0.56

Note: All results are represented as "n (%)", unless otherwise stated; * indicates the measure was taken upon ICU admission; † indicates p-value <0.05; ¥ indicates that the pathogen category is not complete, only the four most frequent pathogens are listed; APACHE= Acute Physiology and Chronic Health Evaluation; sd= Standard Deviation; SOFA= Sequential Organ Failure Assessment; VAP= Ventilator-Associated Pneumonia.

However, the mean Acute Physiology and Chronic Health Evaluation (APACHE) II score and proportion of patients who scored ≥25 was higher for patients who were intubated in the Prehospital setting (ED=21.19±SD5.30 vs. PH=24.14±SD6.50, p=0.04, ED=24% vs. PH=52%, p=0.02). Similarly, the mean SOFA score was higher for patients intubated in the Prehospital setting (ED=7.02±SD2.77 vs. PH=8.59±SD2.99, p=0.03) The proportion of patients who were diagnosed with *Staphylococcus aureus* was much lower in the Emergency Department ETI group than the Prehospital ETI group (ED=24% vs. PH=48%, p=0.04). Conversely, a higher proportion of Emergency Department ETI patients were diagnosed with *Streptococcus* species (ED=21% vs. PH=4%, p=0.05). There were no significant differences between the Emergency Department ETI and Prehospital ETI groups among the patients who developed late onset VAP.

Stratified Analysis

A classic stratified analysis was performed to analyze the potential effects of covariates on the relationship between intubation location and time to VAP diagnosis. Odds ratios were employed to quantify the measure of association. The odds ratio was calculated as the odds of late onset VAP for those intubated in the Prehospital setting over the odds of late onset VAP for those intubated in the Emergency Department. The

outcome of the stratified analysis was used to determine which variables should be included in the linear regression analysis.

The results of the stratified analysis are listed in Table 5.2.The estimated crude odds ratio for late onset VAP is 0.75 (95% CI 0.39-1.45). This means that the odds of late onset VAP is 25% lower among Prehospital intubated patients than the odds of late onset VAP for Emergency Department intubated patients. Basically, Prehospital ETI patients are less likely to get late onset VAP. Conversely, they are more likely to experience early onset VAP. However, the precision of this estimate is quite poor and the confidence interval crosses the null value. Therefore, the null hypothesis that the odds of late onset VAP does not differ by intubation location, cannot be rejected (p=0.36). This crude estimate does not account for important covariates that may alter this relationship. To further evaluate the odds of late onset VAP by intubation location, a stratified analysis was performed.

Gender and pathogen type were the only covariates in which the stratum specific estimates varied greatly. The odds ratio for late onset VAP was much higher among females (3.24 95% CI 0.34-157.53) than males (0.68 95% CI 0.32-1.41, p=0.18); however there was only one female that was intubated in the Prehospital setting that had early onset VAP. Caution, for the same reason, should also be used when interpreting the different ORs for the *Streptococcus* species stratum. The odds ratio for developing late onset VAP for patients who are diagnosed with *Streptococcus* species is much higher (6.00 95% CI 0.41-327.55) than those who are not diagnosed with *Streptococcus* species (0.61 95% CI 0.030-1.23, p=0.07). The effect modification seen by the *Staphylococcus aureus* stratum is rather plausible, as reasonable cells sizes allow for an accurate comparison. The odds ratio for late onset VAP is higher among patients who are not diagnosed with *Staphylococcus aureus* (1.25 95% CI 0.54-2.96) than those who are (0.30 95% CI 0.09-1.01, p=0.03). There is a substantial difference in both magnitude and direction of the relationship.

Table 5.2: Stratified Analysis of Covariates Effect on the Relationship between Intubation Location and Odds Ratio of Late Ventilator-Associated Pneumonia Onset

		Odds Ratio (95% CI)	MH Combined (95% CI)	*P*
Crude Estimate		0.75 (0.39-1.45)	-	0.36
DEMOGRAPHICS & DISEASE STATE				
Age (years)				
<65		0.62 (0.30-1.27)	0.62 (0.30-1.27)	-
≥65		----- (----------)		
Gender				
Female		3.24 (0.34-157.53)	0.81 (0.43-1.522)	0.18‡
Male		0.68 (0.32-1.41)		
APACHE II score*				
<25		0.95 (0.38-2.42)	0.69 (0.37-1.29)	0.24
≥25		0.44 (0.15-1.30)		
SOFA score*				
<7		0.94 (0,2903.25)	0.71 (0.39-1.33)	0.53
≥7		0.62 (.27-1.43)		
Admission category by primary diagnosis				
Medical	No	0.82 (0.40-1.70)	0.79 (0.42-1.50)	0.75
	Yes	0.60 (0.06-8.05)		
Trauma	No	1.12 (0.23-7.40)	0.82 (0.43-1.55)	0.63
	Yes	0.76 (0.36-1.65)		
Neurological	No	0.68 (0.34-1.37)	0.75 (0.41-1.40)	0.30
	Yes	2.50 (0.18-141.52)		
VAP ETIOLOGY				
Pathogen¥				
Gram Negative	No	0.84 (0.39-1.84)	0.75 (0.41-1.40)	0.51

		Odds Ratio (95% CI)	MH Combined (95% CI)	*P*
Bacteria (unspecified, not *H.influenzae*)	Yes	0.52 (0.12-2.23)		
Haemophilus influenzae	No	0.65 (0.31-1.39)	0.76 (0.41-1.42)	0.33
	Yes	1.38 (0.29-6.62)		
Staphlyococcus aureus	No	1.25 (0.54-2.96)	0.77 (0.42-1.42)	0.03‡
	Yes	0.30 (0.09-1.01)		
Streptococcus spp.	No	0.61 (0.30-1.23)	0.75 (0.40-1.37)	0.07‡
	Yes	6.00 (0.41-327.55)		

Note: All results are represented as "n (%)", unless otherwise stated; * indicates the measure was taken upon ICU admission; ‡ indicates p-value <0.20; ¥ indicates that the pathogen category is not complete, only the four most frequent pathogens are listed; APACHE= Acute Physiology and Chronic Health Evaluation; MH=Mantel Haenszel; sd= Standard Deviation; SOFA= Sequential Organ Failure Assessment; VAP= Ventilator-Associated Pneumonia.

This suggests that odds of late onset VAP is 25% higher for PH ETI patients than ED ETI patients among those who develop VAP with a pathogen that is not *Staphylococcus aureus* and the odds of late onset VAP is 70% lower for PH ETI patients than ED ETI patients among those who do develop VAP with *Staphylococcus aureus*. None of the Mantel-Haenszel combined estimates differed significantly from the crude odds ratio; therefore, confounding was not identified as a concern for any of the other covariates.

Although the results of the descriptive and stratified analyses considered a dichotomized time to VAP diagnosis, they provided valuable information as to which variables might influence the relationship between intubation location and hospital length of stay.

The descriptive analysis indicated that age, gender and APACHE II and SOFA score all differed significantly between Prehospital ETI and Emergency Department ETI patients among those who had early on-set VAP. The stratified analysis revealed that certain pathogen types may also affect the relationship (*Staphylococcus aureus* and *Streptococcus* species).

Since time to VAP diagnosis was captured as a continuous variable, a large amount of information regarding this association is lost upon dichotomization. Linear regression was performed to further describe the association between mean time to VAP diagnosis and intubation location in a multivariate model.

Regression Analysis

Linear regression was used to calculate the mean time to VAP diagnosis with a multivariate model while adjusting for multiple variables. The crude model included only the effect of the exposure (intubation location).

The baseline model was:

$$Time\ to\ VAP\ diagnosis = \beta_0 + \beta_{exposure}$$

This model indicates that the mean time to diagnosis is a function of a baseline time (β_0=7.62) and the exposure ($\beta_{exposure}$=-0.79). Since no other information is included in this model, the results are the same as the previous descriptive statistics (Table 4.2). The mean time to diagnosis for patients intubated in the Emergency Department is 7.62 days; and the mean time to diagnosis for patients intubated in the Prehospital setting is 6.83 days. This model was insufficient in explaining the relationship of intubation location and time to VAP diagnosis (p=0.51).

Further models were constructed based on the information obtained from the descriptive and stratified analyses. Age, APACHE II and SOFA scores were used as continuous variables in the regression analysis even though they were used dichotomously in the stratified analysis. The other four variables evaluated, gender, gram negative bacteria, trauma and neurological admission category, remained dichotomous.

A forward step-wise approach was used to determine which variables influenced the model. The entire modelling process is outlined in Appendix B (Table B.7). Neither APACHE II score, SOFA score, nor pathogen type changed the model significantly and were therefore removed. The outcome, time to VAP diagnosis, was transformed onto the log scale to rectify the problem of non-normality of the residuals.

The proposed final model was:

$$log(time\ to\ VAP\ diagnosis) = \beta_0 + \beta_{exposure} + \beta_{(age-18)} + \beta_{gender} + \beta_{trauma}$$

This model was constructed based on the assessment of effect measure modification, confounding and clinical significance of the above stated variables. This equation states that the log mean time to VAP diagnosis is the summation of some baseline effect (β_0) plus the exposure effect ($\beta_{exposure}$) and several other patient characteristics ($\beta_{(age-18)} + \beta_{gender} + \beta_{trauma}$). There was no effect modification or interaction identified during the modeling process. Both age (shifted by -18) and trauma admission category confounded the intubation location-time to VAP diagnosis relationship. The exposure variable, intubation location, was forced into the model; while gender was kept in the model on the basis of clinical significance.

The assumptions of linear regression were tested in the same manner as the hospital length of stay regression above. The assumptions of normality, linearity, independence, and non-collinearity were not violated. The model, however, proved to have a non-constant variance, even whilst using robust techniques and transformations (Appendix B: Figure B.7). This means that the standard errors of the coefficients are most likely biased, and caution must be used when interpreting confidence intervals to avoid a type II error.

This model, as a whole, is statistically significant (F=6.88, p=<0.001), and approximately 12% of the variance of time to VAP diagnosis is explained. A summary of the model performance results is shown in Table 5.3. The plots used to assess the assumptions of linear regression can found in Appendix B (Figures B.4, B.5, B.6, B.7; Table B.8).

Table 5.3: Summary of Model Performance Indicators for Time to Ventilator-Associated Pneumonia Diagnosis Linear Regression

Final Proposed Model: $log(time\ to\ VAP\ diagnosis) = \beta_0 + \beta_{exposure} + \beta_{(age-18)} + \beta_{gender} + \beta_{trauma}$

Assumption	Test	Measurement	Significance Threshold	Result
Normally distributed residuals	Standardized Normal Probability Plot	To visualize if the residuals of the dependent variable, log length of stay, are distributed normally.	Linear Distribution	No concern. Pre-transformation: Appendix B: Figure B.4; Post-transformation: Appendix B: Figure B.5
Homoscedasticity	Constant Variance	To visualize if the residuals plotted against the predicted values of the model are distributed randomly	Random Distribution	Concerning Results. See Appendix B (Figure B.7).
	Breusch-Pagan/Cook-Weisberg	Ho: There is constant variance	$p<0.05$	Concerning Results. $p<0.001$
Independence of subjects	None	--	--	Inherent in study design
Independence of Variables (Collinearity)	Correlation	Measure independence of variables from one another	$0.55>r<-0.55$	No concern. See Appendix B
	Variance Inflation Factor	Measure of how much of the inflation of the standard error is caused by collinearity	>10	Exposure 1.02 Age 1.14 Gender 1.20 Trauma 1.37
Linearity of Independent Variables	Standardized Residual Plots	To visualize if the residuals plotted against the values of each continuous variable are normally distributed.	Random Distribution	No concern. See Appendix B (Figure B.6).
	Box-Tidwell	Ho: Each continuous variable is a linear term (does not need to be transformed)	$p<0.05$	Age $p=0.35$

Assumption	Test	Measurement	Significance Threshold	Result
Specification Errors	Regression Specification Test	Ho: There are no missing variables	$p<0.05$	$p=0.04$ ($F=2.85$)
Goodness of Fit	F-statistic	Ho: The whole model is statistically significant	$p<0.05$	$p<0.001$ ($F=6.88$)

Note: Ho=Null Hypothesis ; VAP=Ventilator-Associated Pneumonia.

The results of this model are summarized in Table 5.4. The mean length of stay column indicates the additional days of hospitalization associated with one unit change of each variable.

This model indicates that there is no significant difference in time to VAP diagnosis between Emergency Department ETI and Prehospital ETI patients (p=0.96). Age and trauma admission category were both found to confound the relationship and there was no effect modification or interaction. Although gender was not identified as either an effect modifier or confounder, it was forced into the model on the basis of clinical significance.

Table 5.4: Mean Hospital Time to Ventilator-Associated Pneumonia Diagnosis for the Final Multivariate Linear Regression Model

Variable	Data Type	Mean TTD	95% CI	*P*
Exposure	ED=0, PH=1	1.005	0.844-1.196	0.96
Age	Continuous (shifted left by 18)	1.005	1.000-1.009	0.04†
Gender	F=0, M=1	0.961	0.776-1.191	0.79
Trauma	NT=0, T=1	0.706	0.580-0.860	0.001†

Note: † indicates Student t-test p-value <0.05; TTD=time to VAP diagnosis; CI=Confidence Interval; ED=Emergency Department; F=Female; M=Male; NT= No Trauma; PH=Prehospital; T=Trauma; TTD=Time to VAP Diagnosis.

As previously mentioned age and admission due to trauma were both found to confound the intubation location-time to VAP diagnosis relationship. This was determined using F-tests at the 5% significance level (Age: F=3.36, p=0.001; Trauma: F=-3.48, p=0.001; Appendix B: Table 4.6).

The mean time to VAP diagnosis increases in a linear fashion as age increases. Figure 5.1 demonstrates the linear relationship for eight distinct patient groups. . There is a separate line for each combination of intubation location, gender and trauma status.

Prehospital ETI patients are represented by grey lines; while Emergency Department ETI patients are represented by black lines.

It is evident that patients who experienced trauma have a much shorter time to VAP diagnosis than patients who do not experience trauma. Furthermore, male patients seem to have a slightly shorter time to VAP diagnosis than their female counterparts, regardless of intubation setting or trauma status. This relationship is true for both Prehospital ETI and Emergency Department ETI patient groups. However, the difference between Prehospital ETI and Emergency ETI time to VAP diagnosis is not statistically or clinically significant as all the paired lines overlap.

Figure 5.1: Estimated Time to Ventilator-Associated Pneumonia Diagnosis by Age

Note: ED=Emergency Dept.; PH=Prehospital; F= female; M=male; NT= no trauma; T=trauma.

The calculated time to VAP diagnosis for several types of patients is listed in Table 5.5. This table is included to show the numerical values of the mean time to VAP diagnosis as calculated by this model, for several different scenarios. For example, the mean time to VAP diagnosis for a female patient who is admitted without trauma is nearly the same for both the Emergency Department (6.65 days) and Prehospital setting (6.68 days) The biggest difference in mean time to diagnosis is among elderly (88 years old) females who are intubated in the Prehospital setting; those who experience trauma acquire VAP approximately 2.75 days sooner than their non-traumatic counterparts.

Table 5.5: Mean Time to Ventilator-Associated Pneumonia Diagnosis for Various Patient Groups

Age (years)	No Trauma				Trauma			
	Female		Male		Female		Male	
	ED	PH	ED	PH	ED	PH	ED	PH
18	6.65	6.68	6.39	6.42	4.70	4.72	4.51	4.53
28	6.97	7.01	6.71	6.74	4.93	4.95	4.74	4.76
38	7.32	7.35	7.04	7.07	5.19	5.19	4.97	4.99
48	7.68	7.71	7.38	7.42	5.42	5.45	5.21	5.24
58	8.06	8.09	7.75	7.78	5.69	5.72	5.47	5.50
68	8.45	8.49	8.13	8.16	5.97	6.00	5.74	5.77
78	8.87	8.91	8.53	8.57	6.27	6.29	6.02	6.05
88	9.31	9.35	8.95	8.99	6.57	6.60	6.32	6.35

Note: ED=Emergency Department; PH=Prehospital.

Primary Pathogen

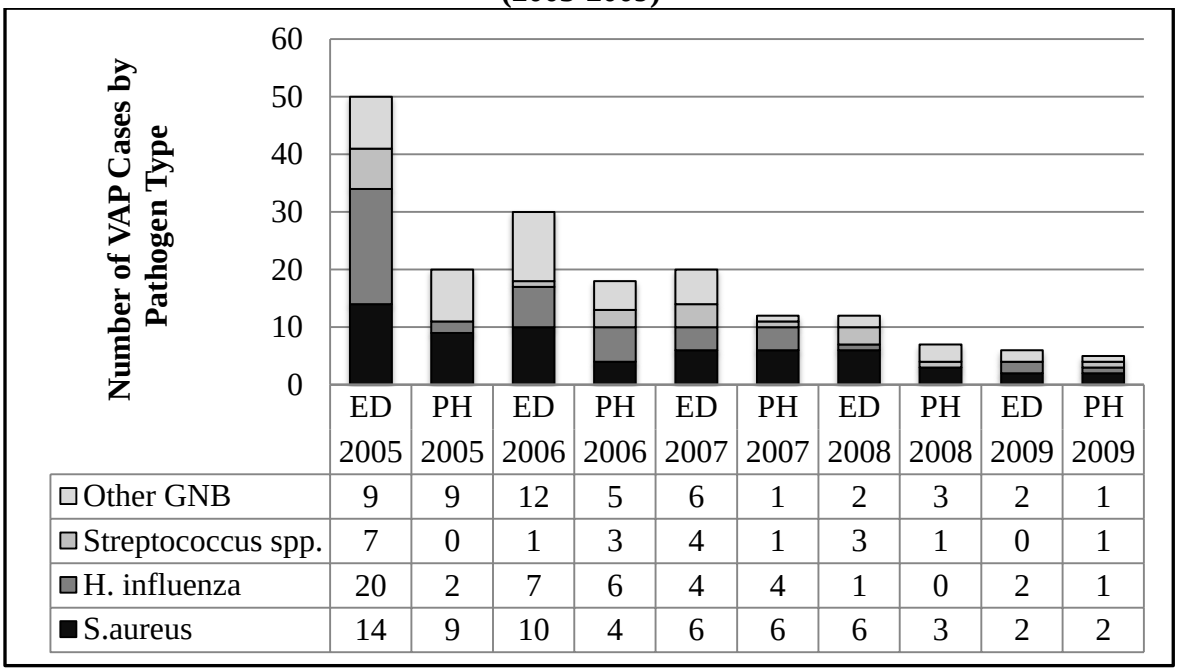
To further describe the VAP etiology for the study sample, the primary microbial pathogen associated with VAP diagnosis was described and compared, followed by a stratified analysis.

Descriptive and Comparative Statistics

The distribution and frequency of pathogen type is important to understanding the burden of disease. Figure 5.2 depicts the number and pathogen type of VAP cases per year by intubation location for the four most frequent pathogens. The incidence of VAP

for both the Prehospital and Emergency Department ETI groups is clearly declining, regardless of pathogen type, as time progresses.

Figure 5.2: Number of Ventilator-Associated Pneumonia Cases per year by Pathogen Type and Intubation Location (2005-2009)



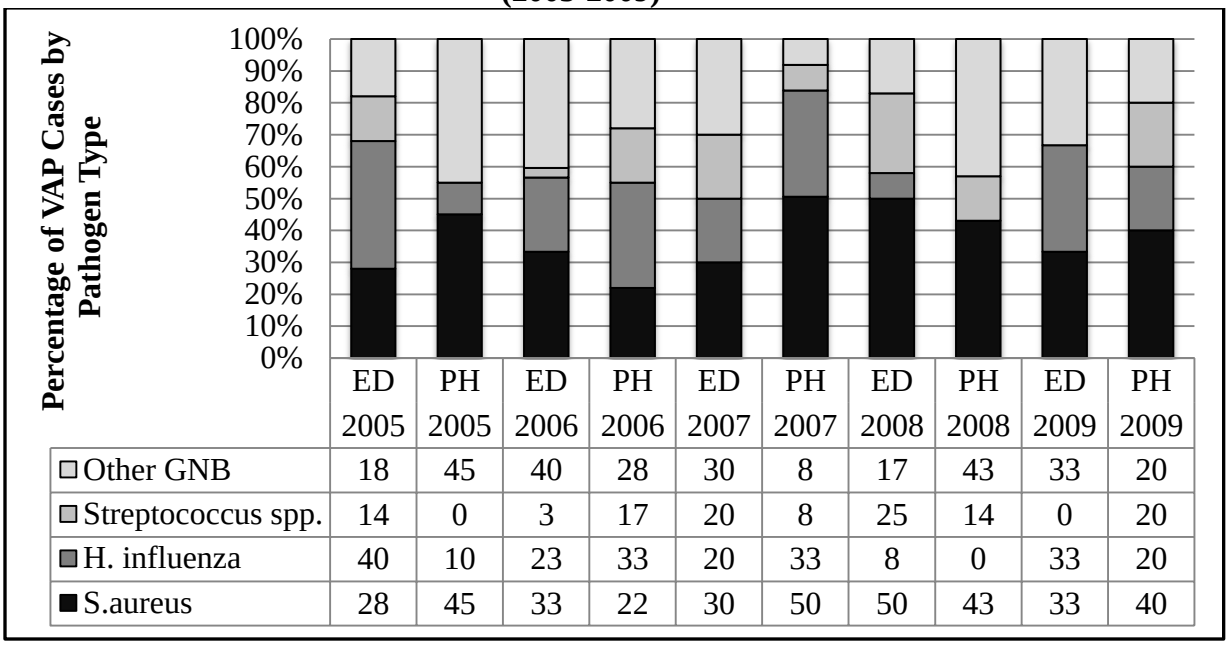
	ED 2005	PH 2005	ED 2006	PH 2006	ED 2007	PH 2007	ED 2008	PH 2008	ED 2009	PH 2009
Other GNB	9	9	12	5	6	1	2	3	2	1
Streptococcus spp.	7	0	1	3	4	1	3	1	0	1
H. influenza	20	2	7	6	4	4	1	0	2	1
S.aureus	14	9	10	4	6	6	6	3	2	2

Note: The pathogen category is not complete, only the four most frequent pathogens are listed; ED=Emergency Department; GNB=Gram Negative Bacteria; PH=Prehospital; VAP=Ventilator-Associated Pneumonia.

The relative proportion of each pathogen type by year is demonstrated in Figure 5.3. *Staphylococcus aureus* (*S. aureus*) represents the largest burden of disease as it has the highest proportion for both the Emergency Department ETI and Prehospital ETI groups. The average proportion of disease caused by *Staphylococcus aureus* over the five year timeframe is 35% (range 28-50) for the Emergency Department ETI patients; which is slightly lower for the proportion of disease caused by *Staphylococcus aureus* for the PH ETI patients (average=40%, range 22-50). The second most frequent pathogen is *Haemophilus influenzae* (*H.influenzae*). Over the five year study period, the average proportion of disease caused by *Haemophilus influenzae* is slightly higher for the Emergency Department ETI (average=25%, range 8-40%) than the Prehospital ETI

patients (average=19%, range 0-33%). Although the relative proportion of gram negative bacteria (GNB) is higher than that of *Haemophilus influenzae* (ED average=28%, range 17-40%, PH average=19%, range 8-45%), it contains a mixture of many pathogens which cannot be separately analyzed. The fourth most common pathogen is the group of *Streptococcal* species (ED average=12%, range 2-35%, PH average=12, range 0-20%).

Figure 5.3: Relative Proportion of Pathogen Type per year by Intubation Location (2005-2009)



	ED 2005	PH 2005	ED 2006	PH 2006	ED 2007	PH 2007	ED 2008	PH 2008	ED 2009	PH 2009
Other GNB	18	45	40	28	30	8	17	43	33	20
Streptococcus spp.	14	0	3	17	20	8	25	14	0	20
H. influenza	40	10	23	33	20	33	8	0	33	20
S.aureus	28	45	33	22	30	50	50	43	33	40

Note: The pathogen category is not complete, only the four most frequent pathogens are listed; ED=Emergency Department; GNB=Gram Negative Bacteria; PH=Prehospital; VAP=Ventilator-Associated Pneumonia.

Previous analyses indicated that there was no significant difference in pathogens isolated for the Emergency Department ETI patients compared to the Prehospital ETI patients (Table 4.2). A lower proportion of Prehospital patients died when a gram negative bacteria (unspecified, not *Haemophilus influenzae*) was isolated compared to Emergency patients (Table 4.5: ED Alive=26% vs. Deceased=22%, p=0.65; Table 4.6: PH Alive=36% vs. Deceased=6%, p=0.02).

The previous stratified analysis that compared the odds of mortality for intubation location identified a significant difference between the gram negative bacteria strata.

Patients who were intubated in the Prehospital setting were 36% more likely to die than their Emergency counterparts if any other pathogen besides a gram negative bacteria was isolated (Table 4.7: Not GNB OR=1.36, 95% CI 0.59-3.07); whereas Prehospital intubated patients were 81% less likely to die than their ED counterparts if a gram negative bacteria was isolated (Table 4.7: GNB OR=0.19, 95% CI 0.004-1.75, p=0.09).

Sub-analysis was performed on the two most commonly isolated pathogens: *S.aureus*; and *H. influenzae.* The results of the comparative analysis are listed in Table 5.6.

For VAP cases where *S.aureus* was the primary pathogen, the relative proportion of male patients differed between Prehospital ETI and Emergency Department ETI patients. A higher proportion of Prehospital ETI patients were male compared to their Emergency Department ETI counterparts (p=0.04). There were no significant differences among Prehospital ETI and Emergency Department ETI patients who were diagnosed with *H.influenzae*.

To further evaluate the relationship between intubation location and primary VAP pathogen, a stratified analysis was completed for *S.aureus* and *H.influenzae*.

Table 5.6: Means and Proportions of Demographic & Disease State Characteristics by VAP Pathogen for Patients who were Intubated in the Emergency Department compared to those were Intubated in the Prehospital Setting

	S. aureus			*H. influenzae*		
	Emerg Dept. n=38	Prehospital n=24	*P*	Emerg Dept. n=24	Prehospital n=13	*P*
Age (years), mean±sd	39.53±21.48	39.86±18.68	0.95	39.59±15.62	34.00±10.40	0.26
<65	29(76%)	21(88%)	-	22(91%)	13(100%)	-
≥65	9(24%)	3(12%)	0.24	2(8%)	0(0%)	0.29
Gender						
Female	10(26%)	1(4%)	-	2(8%)	3(23%)	-
Male	28(74%)	23(95%)	0.04†	22(91%)	10(77%)	0.24
APACHE II score*, mean±sd	22.21±6.15 (1 missing value)	25.12±8.87	0.13	21.39±5.14	23.92±6.56	0.20
<25	27(71%)	12(50%)	-	18(75%)	7(54%)	-
≥25	11(29%)	12(50%)	0.10	6(25%)	6(46%)	0.19
SOFA Score*, mean±sd	7.60±2.99	8.29±3.52	0.41	8.38±2.76	8.39±2.75	0.99
<7	17(45%)	10(42%)	-	6(25%)	2(15%)	-
≥7	21(55%)	58(58%)	0.81	18(75%)	11(84%)	0.52
Admission category by primary diagnosis						
Medical	10(26%)	5(21%)	0.65	0(0%)	0(0%)	-
Trauma	24(85%)	16(67%)	0.10	21(88%)	11(85%)	0.80
Neurological	4(11%)	3(12%)	0.90	3(12%)	2(15%)	0.80

Note: All results are represented as "n (%)", unless otherwise stated; * indicates the measure was taken upon ICU admission; † indicates p-value <0.05; APACHE= Acute Physiology and Chronic Health Evaluation; sd= Standard Deviation; SOFA= Sequential Organ Failure Assessment.

Stratified Analysis

Separate stratified analyses were performed on the two most prevalent pathogens. The purpose was to analyze the potential effects of covariates on the relationship between intubation location and both *Staphylococcus aureus* and *Haemophilus influenzae*. Odds ratios were employed to quantify the measure of association. The odds ratio was calculated as the odds of being diagnoses with a specific pathogen for those intubated in the Prehospital setting over the odds of being diagnoses with a specific pathogen for those intubated in the Emergency Department.

The results of the stratified analysis are listed for both *Staphylococcus aureus* and *Haemophilus influenza*, in Table 5.7 and Table 5.8 respectively. The estimated crude odds ratio for being diagnosed with *S.aureus* is 1.26 (95% CI 0.64-2.47, p=0.47). This means that the odds of being diagnosed with *S.aureus* among Prehospital intubated patients are 26% higher than the odds of being diagnosed with *S.aureus* among Emergency Department intubated patients. There was effect modification by gender (p=0.11). The estimated odds ratio for females (0.24, 95% CI 0.01-2.28) is much lower and in the opposite direction as the estimated odds ratio for males (1.55, 95% CI 0.73-3.26). There was no confounding identified by any of the other variables.

The estimated crude odds ratio for being diagnosed with *H.influenzae* is 1.00 (0.43-2.24, p=0.93). This means that the odds of being diagnosed with *H.influenzae* were the same for both intubation locations. The only variable in which the stratum specific estimates varied greatly was gender. Among females the odds ratio is 6.43 (95% CI 0.59-85.66), whereas among males the odds ratio is 0.68 (95% CI 0.26-1.66, p=0.03). The magnitude and direction of these estimates are quite different, indicating effect measure modification. There was no confounding identified by any of the other variables; however, many associations were not calculated due to zero cell sizes.

Table 5.7: Stratified Analysis of Covariates Effect on the Relationship between Intubation Location and Odds Ratio of Ventilator-Associated Pneumonia with *Staphylococcus aureus*

		Odds Ratio (95% CI)	MH Combined (95% CI)	*P*
Crude Estimate		1.26 (0.64-2.47)	-	0.47
Age (years)				
<65		1.31 (0.62-2.76)	1.26 (0.67-2.39)	0.81
≥65		1.06 (0.14-6.45)		
Gender				
Female		0.24 (0.01-2.28)	1.22 (0.65-2.30)	0.11‡
Male		1.55 (0.73-3.26)		
APACHE II score*				
<25		1.18 (0.45-2.98)	1.33 (0.70-2.53)	0.67
≥25		1.56 (0.53-4.66)		
SOFA Score*				
<7		2.09 (0.62-7.04)	1.34 (0.71-2.55)	0.32
≥7		1.06 (0.43-2.53)		
Admission category by primary diagnosis				
Medical	No	1.28 (0.58-2.76)	1.27 (0.68-2.39)	0.98
	Yes	1.25 (0.25-5.77)		
Trauma	No	1.56 (0.44-5.38)	1.28 (0.68-2.40)	0.67
	Yes	1.17 (0.50-2.68)		
Neurological	No	1.17 (0.57-2.39)	1.27 (0.67-2.37)	0.48
	Yes	2.50 (0.22-27.06)		

Note: All results are represented as "n (%)", unless otherwise stated; * indicates the measure was taken upon ICU admission; ‡ indicates p-value <0.20; APACHE= Acute Physiology and Chronic Health Evaluation; MH=Mantel Haenszel; sd= Standard Deviation; SOFA= Sequential Organ Failure Assessment.

Table 5.8: Stratified Analysis of Covariates Effect on the Relationship between Intubation Location and Odds Ratio of VAP with *Haemophilus influenzae*

		Odds Ratio (95% CI)	MH Combined (95% CI)	*P*
Crude Estimate		1.00 (0.43-2.24)	-	0.93
Age (years)				
<65		0.97 (0.42-3.35)	----- (----------)	-
≥65		----- (----------)		
Gender				
Female		6.43 (0.59-85.66)	0.94 (0.44-1.97)	0.03‡
Male		0.68 (0.26-1.66)		
APACHE II score*				
<25		0.96 (0.30-2.80)	1.09 (0.50-2.34)	0.70
≥25		1.31 (0.31-5.45)		
SOFA Score*				
<7		0.84 (0.08-5.37)	0.92 (0.43-1.97)	0.94
≥7		0.94 (0.36-2.39)		
Admission category by primary diagnosis				
Medical	No	0.92 (0.39-2.13)	----- (----------)	-
	Yes	----- (----------)		
Trauma	No	1.60 (0.12-15.26)	0.92 (0.43-1.99)	0.53
	Yes	0.83 (0.32-2.06)		
Neurological	No	0.67 (0.18-2.13)	----- (----------)	-
	Yes	----- (----------)		

Note: All results are represented as "n (%)", unless otherwise stated; * indicates the measure was taken upon ICU admission; ‡ indicates p-value <0.20; APACHE= Acute Physiology and Chronic Health Evaluation; MH=Mantel Haenszel; sd= Standard Deviation; SOFA= Sequential Organ Failure Assessment.

Further regression models were not used to explain the relationship between intubation location and pathogen type as gender was the only influencing covariate. Therefore, the stratum specific odds ratios for each gender represent the most accurate estimate of the association.

CHAPTER SIX: DISCUSSION

This thesis concludes with a chapter devoted to a discussion of the results and their implications, the strengths and limitations of this research, and recommendations for clinical practice and future research.

Key Results and Interpretation

The purpose of this study was to describe and quantify the morbidity and mortality of patients who are intubated in the Emergency Department or Prehospital setting and acquire ventilator-associated pneumonia (VAP). Using a retrospective cohort design, rigorous methodology and informed decisions based on literature and clinical significance, several comparisons and analyses were performed to calculate the most precise estimate of the effect of intubation location on the aforementioned outcomes.

A summary of the characteristics described and compared for the sampling frame are listed in Table 6.1. All of the patients included in this study acquired VAP during their Intensive Care Unit (ICU) stay. The VAP population had more severe disease, were younger and included a higher proportion of male patients in comparison to their non-VAP counterparts. Cook et al. (1998) performed a prospective Canadian cohort study to evaluate the risk factors associated with VAP which demonstrated similar findings with regards to age and gender. However, they did not find a significant difference in severity as measured by the Acute Physiology and Chronic Health Evaluation (APACHE) II score. (52) The VAP population in this study also experiences higher hospital mortality and longer hospitalizations than patients without VAP. This parallels the literature regarding the morbidity and mortality among VAP patients. (17,20,23,25,42,51) Therefore, the VAP population from which the sample came is very similar to other previously studied VAP populations.

This study found that patients intubated in the Prehospital setting were very similar to patients intubated in the Emergency Department with regards to basic demographic and admission characteristics. This is a very key result, as the validity of the

comparisons between the groups is pivotal to the groups being the same in all but one category – exposure (intubation location).

Although a higher proportion of patients intubated in the Prehospital setting had an APACHE II score (upon ICU admission) greater than 25 compared to Emergency Department Endotracheal Intubations (ETI) patients, the mean APACHE II score did not differ. Several previous studies have also used Emergency Department ETI patients as an appropriate comparison group for Prehospital ETI patients. (2,12,38-40)

Table 6.1: Summary of Descriptive and Comparative Statistics for Sampling Frame

Reference Group	Comparison Group	Age	Gender (% male)	APACHE II Score*	SOFA Score*	Admission Category	Diagnostic Criteria	Pathogen	Time to Diagnosis	Hospital LOS	Hospital Mortality
No VAP	VAP	↓	↑	↑	NA	NA	NA	NA	NA	↑	↑
ED ETI	PH ETI	=	=	↑	=	=	=	=	=	=	=
Included	Excluded	=	=	=	NA	NA	NA	NA	NA	=	=

Note: * indicates the measure was taken upon ICU admission; APACHE=Acute Physiology and Chronic Health Evaluation; ED=Emergency Department; ETI=Endotracheal Intubation; LOS=Length of Stay; PH=Prehospital; NA= not assessed; SOFA= Sequential Organ Failure Assessment; VAP=Ventilator-Associated Pneumonia

Primary Objective

Hospital Mortality

The odds of hospital mortality were evaluated using a multivariate logistic regression model. Age and admission due to trauma were found to confound this relationship and APACHE II score, a surrogate for illness severity, was found to modify the measure of effect.

For patients who have an APACHE II score (upon ICU admission) of less the 25 points, the odds of death among Prehospital ETI patients is lower than the odds of death among Emergency Department ETI patients. However, once the presenting illness is severe enough and the APACHE II score is above 25 points, the odds of death among Prehospital ETI patients' increases exponentially relative to the odds of death among Emergency Department ETI patients of the same acuity.

Although several other studies have evaluated the odds ratio of mortality between these two groups, they have included a wider subset of patients. This study only included patients who have survived long enough to be admitted to the ICU and develop VAP, whereas previous studies have included all Prehospital and Emergency Department ETI patients. Since this study only includes a fraction of the same patients evaluated in other studies, comparisons of the results are difficult. Nevertheless, for severe patients the results consistently reveal that odds of mortality are higher among Prehospital ETI patients. (2,38,39)

Acute Physiology and Chronic Health Evaluation II Score

Interestingly, the relationship of APACHE II score and mortality is different between the two exposure groups. Previous studies have evaluated the use and timing of various severity scores. APACHE II, taken upon admission, has been demonstrated to be valuable in predicting mortality among ICU patients. (88,66,89) Furthermore, the use of this scoring system has similar value among VAP patients. (67) In general, as the APACHE II score increases so do the odds of mortality.

The regression results for the odds ratio of mortality found there to be effect modification by APACHE II score. In this study, this means that the magnitude of the odds ratio of mortality increased as APACHE II score increased. However, upon further investigation of the APACHE II score- odds of mortality association (Figure 4.4), it is noted that the typical prediction pattern can only been seen for Prehospital ETI patients. The odds of mortality do not increase with severity for patients intubated in the Emergency Department.

This is a novel finding and suggests that perhaps APACHE II score, taken upon ICU admission, is not useful in predicting mortality among Emergency Department ETI patients. One explanation for the disparity in these results (as compared to previous literature) is that the previous studies did not take into consideration the effect of intubation location. This would confound the results of previous studies and the estimates would be a mixture of the effect of Prehospital and Emergency Department intubations together.

Hospital Length of Stay

The mean length of hospitalization was assessed using a multivariate linear regression model. The combined effect of age and mortality modified the association. Patients who were discharged alive had a significantly longer hospitalization than patients who were discharged deceased.

Furthermore, among those who were discharged deceased, younger patients died quicker than older patients and females died quicker than males. However, regardless of age or gender, patients who were intubated in the Prehospital setting died earlier than their Emergency Department counterparts.

Among those who were discharged alive, younger patients had longer hospitalizations than older patients, and male patients had longer hospitalizations than female patients. Once again this association was different based on intubation location. Regardless of age and gender, among those who remained alive, patients intubated in the Prehospital setting had longer hospitalizations that their Emergency Department counterparts.

An increased length of stay has many negative impacts for both healthcare system and the patient. Longer hospitalization results in increased healthcare utilization and cost as well as increased morbidity and missed days of work for patients.

Among survivors, both young and old Prehospital ETI patients have the longest hospitalization followed closely by young Emergency Department ETI patients. However, elderly Emergency Department ETI patients have similar hospitalization regardless of their outcome status.

There are many factors which influence hospital length of stay. Currently there are no studies which evaluate the length of hospitalization for patients who acquire VAP based on intubation location to compare these results to. Therefore, this information provides a basic foundation for further research in this area.

Time to Event

The instantaneous risk of death was evaluated using Cox-proportional multivariate regression modelling. Hospital discharge status was analysed as a time-

dependent variable based on hospital length of stay. APACHE II score was found to modify the association; while age and trauma were identified as confounders.

The instantaneous risk of death, and inversely the probability of surviving, was the worst among Emergency Department ETI patients who were admitted for a non-trauma related illness, followed by Emergency Department ETI patients who were admitted for a traumatic injury. The probability of surviving was much better for patients intubated in the Prehospital setting (while controlling for age and APACHE II score). Similarly, the probability was higher for those who suffered a trauma compared to those who did not.

This is a unique way to evaluate the risk of mortality during hospitalization. It appears that Prehospital ETI patients with VAP have a higher probability of surviving than their Emergency Department ETI counterparts, regardless of admission diagnosis. No other studies have been completed that calculate the proportional hazard ratios for these groups and therefore no comparisons can be made.

Secondary Objective

Time to Ventilator-Associated Pneumonia Diagnosis

Time to VAP diagnosis and primary pathogen were assessed to describe the etiology of VAP between the two groups. Linear regression was used to evaluate difference in time to VAP diagnosis. Although age, gender and admission for trauma altered the mean time to VAP diagnosis, intubation location did not affect the estimate.

The mean time to VAP diagnosis increased linearly with age. VAP onset was shorter for patients who were admitted with trauma and slightly shorter for males regardless of admission category.

Although interaction was not found, it is plausible to accept that age, male gender and traumatic injury could all be related; young males have the highest likelihood of being in a traumatic accident. Giard et al. (2008) has also reported that age and gender affect the mean time to VAP diagnosis and has suggested a similar link to traumatic injuries. (50)

Primary Pathogen

The distribution of pathogens associated with VAP is very similar between Prehospital and Emergency Department ETI groups. *Staphylococcus aureus* and *Haemophilus influenzae* are the two most commonly isolated pathogens for both groups. Gender modified the odds ratio for both outcomes. The odds ratio for being diagnosed with *Staphylococcus aureus* was much lower for females than for males. This means that among males, patients intubated in the Prehospital setting are more likely to be diagnosed with *Staphylococcus aureus* than their Emergency Department counterparts; whereas Prehospital ETI female patients are less likely to be diagnosed with *Staphylococcus aureus* than their Emergency Department counterparts.

The opposite is true for patients diagnosed with *Haemophilus influenzae*. The odds ratio was much higher for females than for males. This means that among females, patients intubated in the Prehospital setting are more likely to be diagnosed with *Haemophilus influenzae* than their Emergency Department counterparts; whereas Prehospital ETI male patients are less likely to be diagnosed with *Haemophilus influenzae* than their Emergency Department counterparts.

Strengths and Limitations

The methodology used throughout this study resulted in several contextual strengths and weaknesses, which warrant discussion.

Firstly, this study was completed with the utmost care for measurement accuracy and methodological rigor. This study was designed and executed by the sole author. This was imperative as the subject matter and intent remained constant throughout the study process. The sole author also completed all of the chart reviews, which eliminated bias and data errors that may have been introduced in the presence multiple reviewers.

Secondly, the retrospective nature of this study has several benefits; it allowed for the exploration of multiple outcomes in the presences of multiple covariates, while studying a rare exposure. This resulted in a comprehensive assessment of the effects of intubation location, while considering several demographic and physiological

characteristics. This study design also resulted in a larger sample size than a prospective study of the same timeframe. Additionally, this study was easy to administer and relatively inexpensive to complete.

This study identified VAP patients using a well-established local surveillance database. This program uses a clearly defined clinical diagnosis of VAP that is generalizable to innumerable ICU settings. Additionally, all patients are screened and evaluated in the same way which eliminates the concern for diagnostic selection bias.

Another key strength of this study is the use of multiple data sources. This study used information taken at the beginning of the patient encounter all the way to the end. Not only did this result in a complete dataset and zero attrition (the outcome status of all patients was known), it also highlighted the need for more comprehensive charting for emergent invasive procedures and the introduction of electronic health records. The use of several data sources also ensured that specific data elements were accurate and valid.

The in-depth analyses provided in chapters four and five provide a comprehensive and robust assessment of the aforementioned relationship using several statistical techniques. Furthermore, the results from the detailed comparisons and stratified analysis were used to explore and inform multivariate regression models. Regression techniques allowed for the simultaneous adjustment of confounding variables, while also including interaction terms for effect modification.

Finally, the results of this study are a novel contribution to the emergent intubation and VAP literature. This study is the first to compare the outcomes of intubation location among patients who acquire VAP during their hospital stay. In addition, this study provides insight for all Prehospital ETI patient types, not just trauma patients as is prevalent in the literature.

Due to the uncontrolled observational nature of this research, a degree of random and systematic error is likely to be present. Both of these types of error reduce the accuracy of the estimates calculated in the analysis.

Random Error

All measurements are prone to error. Random error is the variability in measurement that cannot be explained by other means. Variance is used as a common measure of random variation. (84) Although the variance of the descriptive statistics was quite high and the precision of the stratified analysis effect estimate was poor (wide confidence intervals), the regression analysis provided reasonable error rates that did not cross the null hypothesis.

Sparse data was categorized into larger groups to assess for effect measure modification and confounding (i.e. admission category and pathogen type). This increased the precision of the effect estimates, therefore decreasing the variability. Additionally, the significance level was set to 5% for all tests to reduce the probability that the null hypothesis would be falsely rejected.

Power

The power of a study is the ability to detect an effect of a specified size given a predetermined sample size and significance level. It is represented as the probability of correctly rejecting the null hypothesis. The *a priori* power calculation suggested that approximately 187 patients were required for each exposure group. This sample size would have resulted in 90% power to detect a 50% difference in mortality between Prehospital and Emergency Department ETI patients. Trending introduced by advances in medical diagnostics and techniques as well as the use of current data was also considered in determining the proposed sample size.

It was decided that five years of ICU data would be included. The incidence of VAP during the study was lower than expected and declined over time, which resulted in a lower number of VAP cases over the study period. This oversight resulted in a decreased number of cases arising from both the Emergency Department and Prehospital settings, and therefore a smaller number of included subjects. All VAP cases were reviewed and the final dataset included a sample of only 193 patients.

Although this study was underpowered with regards to the original calculation, significant results were achieved using regression techniques. The results of the stratified

analyses, however, should be interpreted with caution. The insufficient sample size led to a high degree of variability and low precision of estimates. Wide confidence intervals and high standard errors indicate a high type II error rate (accepting the null when in fact it is false). This suggests that the power of the study was insufficient to detect statistical differences, even if they did truly exist.

The results of the secondary analysis should also be viewed with caution. As the data was sub-divided there were several zero cells, which resulted in imprecise estimates with wide confidence intervals and the inability to calculate portions of the stratified analysis.

Future studies examining this relationship would require a larger sample size. Since the incidence of VAP is declining, and the proportion of patients intubated in the Prehospital setting is so low almost 15 years of data would be required to have a sample size with approximately 200 patients in each group. This is not only unrealistic for both retrospective and prospective studies, it is impractical as trending would introduce significant bias. Instead, future studies should attain a larger sample size by including multiple large-urban cities that have a primary Emergency Medical Service and tertiary-level hospital care (with similar VAP surveillance systems).

Systematic Error

Unlike random error, systematic error occurs due to improper study design or conduct. There are three types of systematic error which affect the internal validity of the study: selection bias; information bias; and confounding. Selection and information bias are of particular concern during the data collection phase, and cannot be corrected for in the analysis; whereas confounding can be adjusted for in the analysis, provided the confounder is known and measured. (84)

Selection Bias

Selection bias is a distortion of the measure of association based on how the subjects were selected into the study. This bias may be of issue if the criteria for inclusion into the study were applied differently between groups in a way that is associated with both intubation location and outcome. (84) Unequal selection could result in a

misrepresentation of the exposure distribution in the source population that gave rise to the VAP study sample as well as an incorrect effect estimate.

Diagnosis of VAP is the point of entry into this study cohort. The descriptive analysis showed that the diagnostic criteria were not different for the two groups. Therefore, the way in which patients were diagnosed and then selected into the study was not systematically different. However, it is important to reflect on which patients are considered for diagnosis.

The surveillance program uses time-sensitive microbiological triggers as the primary method for case finding. Automated microbial surveillance has been shown to capture just as many or more cases in comparison to comprehensive surveillance. (70-72) There are three plausible reasons as to why patients may be missed using this type of surveillance: (1) the microbial cultures are not taken; (2) microbial cultures that are taken fail to grow anything; or finally, (3) the duration of mechanical ventilation for Emergency Department and Prehospital patients is slightly different.

Microbial cultures are ordered at the attending physician's discretion based on clinical suspicion of infection. Patients may be missed because they are either too sick (i.e. likely to die soon and treatment will not affect the outcome) or not sick enough. However, the severity of illness (APACHE II score) and organ dysfunction (SOFA score) were not clinically different between the Prehospital ETI and Emergency Department ETI groups. These similarities are plausibly extrapolated to the extremely sick and not-so-sick patients as well. Therefore this bias is likely not of concern.

The second indication as to why patients may be missed is based on testing or laboratory error. Firstly, when a microbial culture is taken it may be taken incorrectly. For example, a sputum sample may have too many epithelial cells and the lab cannot test it. Secondly, assuming the culture is taken correctly the lab may incorrectly conclude that there was no growth, when in fact there was a microbe present. However this bias is minimized as the clinicians that are taking the samples and the laboratory processing them are the same for all ICU patients.

The definition for VAP requires that the patient receive at least 48 hours of continuous invasive mechanical ventilation prior to the sentinel x-ray. Theoretically, there is a slightly longer duration of mechanical ventilation for patients intubated in the Prehospital setting compared to those intubated in the Emergency Department. In this dataset the median time to ICU admission post-intubation is 217 minutes (Interquartile Range 127-293) for the Prehospital ETI patients and 183 minutes (Interquartile Range 131-300) for the Emergency Department ETI patients. This difference, 34 minutes, is neither clinically nor statistically significant and would likely not result in a difference in application of the definition and not cause selection bias.

One key limitation of the study is the retrospective design, particularly in relation to the chart review. The data collected in the chart review is limited to information that was previously documented, and cannot be confirmed once the patient has left the hospital. The chart review was the sole information source to classify exposure status (intubation location). There were seven charts in which the intubation location could not be identified. These patients were classified as exposure unknown and excluded from the study. The discharge outcome for all the patients is known (Alive=4, Dead=3). There are several scenarios in which these seven patients could alter the crude effect estimate. The results of the sensitivity analysis explaining the impact of this bias are listed in Table 6.2.

Firstly, based on all 323 chart reviews, approximately 60% of all VAP patients were intubated in either the Emergency Department or Prehospital setting (40% and 20% respectively). This would translate to four (of seven) unknown patients that should have been included in the study. Based on the distribution of exposure and mortality, three of these patients would have been intubated in the Emergency Department (Alive=2, Dead=1) and one would have been intubated in the Prehospital setting (Alive=1). The estimate of the odds ratio of hospital mortality would shift slightly away from the null (0.93, 95% CI 0.44-1.91); however the change in magnitude from the crude is not clinically or statistically significant as the confidence intervals overlap (Table 4.7: Crude= 0.98, 95% CI 0.45-1.98).

It is likely, however, that all of the unknown intubation locations took place within an emergency setting as charting is less reliable and transfer of patients may result in lost charts. Therefore, if all seven patients were included in the study the effect estimate (hospital mortality odds ratio) would be slightly higher (0.97, 95% CI 0.47-1.96) than the crude value towards the null, but again not substantially enough to invalidate the crude estimate.

In the extreme case, it is plausible to accept that all seven patients were intubated in the Prehospital setting. Patients who are intubated in the Prehospital setting have an additional chart (Patient Care Record from the Paramedics) and an additional transfer of care (Prehospital to Emergency Department) compared to their Emergency Department counterparts. These additional points of care could increase the error rate of lost or missing information. If all of the patients were in fact from the Prehospital setting, the odds ratio of hospital mortality would now be higher in the Prehospital than the Emergency Department (1.04, 95% CI 0.51-2.08), and in the opposite direction from the crude. Although the direction of the associations has changed, the magnitude and precision of the estimate do not change the overall interpretation.

Table 6.2: Selection Bias Sensitivity Analysis

	Outcome	Intubation Location		OR (95% CI)
		ED	PH	
Crude	Alive	93	50	0.96 (0.45-1.98)
	Dead	33	17	
Scenario 1 (+4)	Alive	93+2	50+1	0.93 (0.44-1.91)
	Dead	33+1	17	
Scenario 2 (+7)	Alive	93+3	50+1	0.97 (0.47-1.96)
	Dead	33+2	17+1	
Scenario 3 (PH+7)	Alive	93	50+4	1.04 (0.51-2.08)
	Dead	33	17+3	

Note: CI=Confidence Interval; ED=Emergency Department; OR=Odds Ratio; PH=Prehospital.

Information Bias

Information bias occurs when subjects are systematically misclassified with regards to either the exposure (intubation location) or the outcome (mortality/length of

stay). There are two types of information bias: non-differential; and differential. Non-differential misclassification occurs when information regarding either the exposure or the outcome is incorrect, resulting in a dilution of the effect estimate towards the null. (84) Differential misclassification occurs when the correctness of the exposure information depends on outcome classification or visa-versa. The result of differential misclassification is circumstantial. If the missing or incorrect information is equivalent for both outcomes and does not vary with exposure then the effect estimate is likely unbiased. The best way to prevent information bias is to record objective, accurate and complete measurements from valid data sources.

In this study, exposure status, as determined by the manual chart review, was assigned based on the location in which the first successful intubation took place. Misclassification of the exposure could occur if the documentation suggested that the intubation was successful, when in reality it was not. This misclassification is most likely to occur in the Prehospital setting as the diagnostic techniques for intubation confirmation are limited. Prehospital ETI placement is based on self-report and indirect verification procedures (i.e. auscultation). This error is unlikely to occur in the Emergency Department as a chest x-ray and other definitive confirmation techniques are available and used to ensure proper endotracheal tube placement. Research by Bair, Smith and Lichty (2005) suggests that approximately 2% of Prehospital intubations which are declared as successful are determined to be non-tracheal by the receiving ED physician. (90) The impact of this estimate on this study would result in only two patients (2% of 67=1.34) that were misclassified as Prehospital when in fact the first successful intubation would have been performed in the Emergency Department. The sensitivity analysis performed to explore the possibility of information bias with respect to the exposure is summarized in Table 6.3.

Since approximately 75% of both Emergency Department and Prehospital patients survived, it is most likely that the two shifted patients would also remain alive. The magnitude and direction of the effect estimate slightly change (1.02, 95%CI 0.48-

2.11). Nevertheless the interpretation remains the same due to the poor precision and wide confidence interval.

Perhaps patients who have an attempted intubation in the Prehospital setting (then go on to success in the Emergency Department) have a risk profile alike the true Prehospital intubation patients and have higher odds of dying. If the two patients both died, then the estimate would trend away from the null (0.80, 95% CI 0.37-1.67) and infer that Prehospital intubation is protective against mortality. However, this scenario is unlikely as the results from the previous investigation and multivariate regression analysis suggest that the odds of mortality are significantly higher amongst Prehospital ETI patients than Emergency Department ETI patients.

As a side note to the issue of misclassifying intubation location, a sensitivity analysis was calculated based on patients who had an unsuccessful intubation attempt in the Prehospital Setting that went on to have a successful intubation in the Emergency Department. These patients were originally classified as not exposed as their first successful intubation location was the Emergency Department. If in fact the "exposure" was an intubation attempt, these patients should been classified as "exposed". Changing the exposure definition would results in 16 misclassified patients (Alive=13, Dead=3). These patients have the same outcome profile as the rest of the study sample and therefore the estimated odds ratio (0.84, 95% CI 0.41-1.70) would not change significantly from the crude.

Table 6.3: Information Bias Sensitivity Analysis

	Outcome	Intubation Location		OR (95% CI)
		ED	PH	
Crude	Alive	93	50	0.96 (0.45-1.98)
	Dead	33	17	
2% Non-tracheal in PH (alive)	Alive	93+2	50-2	1.02 (0.48-2.11)
	Dead	33	17	
2% Non-tracheal in PH (dead)	Alive	93	50	0.80 (0.37-1.67)
	Dead	33+2	17-2	
Unsuccessful in PH	Alive	93-13	50+13	0.84 (0.41-1.70)
	Dead	33-3	17+3	

Note: CI=Confidence Interval ED=Emergency Department; OR=Odds Ratio; PH=Prehospital.

There were two primary outcomes used in this study: hospital discharge status and hospital length of stay. Hospital discharge status was measured as dead or alive, by both the VAP Surveillance program and the chart review. There was 98% agreement between the two data sources ($z=13.24$, $p<0.001$). Of the four patients in which there was disagreement, all were identified as deceased by visualization of the death record in the chart review. These patients were likely captured as alive by the VAP surveillance database because they were transferred from the hospital in which they acquired VAP to another Calgary area hospital for the remainder of their care. Because this data element was captured by both data sources and verified upon disagreement, it is unlikely that there is misclassification of hospital discharge status.

Hospital length of stay was measured as the number of days from primary intubation to death or discharge from a Calgary area hospital. These specific hospitals were used as a surrogate for tertiary level hospitals, which provide more-acute care than other facilities. Although the majority of patients who were discharged alive, were likely discharged home or to a step-down facility, it is plausible to accept that some patients were transferred to another tertiary care facility. The discharge location was not readily available from the VAP Surveillance database, nor was it reliably documented in the chart, therefore a precise estimate of the magnitude of this bias is unattainable. However, since the both the acuity and proportion of patients assigned to each admission category were similar for both exposure groups, it is likely that they were equally effected and this bias would most likely have a null effect.

Confounding

The final source of systematic error is due to confounding. The retrospective nature of this study makes it vulnerable to bias due to inadequate measurement of potential confounders. A confounding factor is an unmeasured or poorly measured variable that causes a distortion in the relationship between the outcome and exposure. In this study, a confounder would be a factor that is related both to the intubation location and outcome but not in the casual pathway (between intubation location and outcome).

This study was designed to measure and account for several known potential confounders. A list of potential confounders was created *a priori* based on current literature, clinical importance and availability. Stratified analysis and regression modelling were used to control for confounding factors that were measured, such as age, gender and admission category.

There are three types of residual confounding: (1) misclassification due to poor measurement; (2) differences within a broad category; and (3) unmeasured factors.

There were three potential confounders that were measured poorly in this study: number of intubation attempts; number of complications; and rapid sequence induction (RSI) technique. These data elements collected but not included in the description or analysis due to insufficient data.

The literature suggests that the number of intubation attempts is higher among Prehospital clinicians than Emergency Department clinicians. (6-10) Of the data that was collected (n=68), the mean number of attempts was lower in the Prehospital setting than in the Emergency Department. However, this data element is very poorly documented and subject to reporting bias. An increased number of attempts may indicate a difficult airway, which is related to death. However, Wang et al. (2009) confirmed that Prehospital ETI errors were not associated with mortality, and therefore not in the causal pathway. (41) The same rationale can be applied to the number of reported ETI complications.

Rapid sequence induction is a pharmacologically induced sedation and paralysis performed just prior to endotracheal intubation. It is a quick and complex procedure with a variety of dosing requirements. Charting the use of pharmaceutical agents during ETI was not standardized between the Emergency Department and Prehospital settings, therefore it was not captured in this study. Rapid sequence induction is a technique that is performed in both the Emergency Department and Prehospital setting. Rapid-sequence induction is performed on patients who have a higher level of consciousness than those who already have an altered level of consciousness; meaning that the severity (which modifies outcome) is different for these patient groups. In addition to using rapid

sequence induction for conscious patients, this technique is also used on patients in whom the first attempt was unsuccessful, therefore relating rapid sequence induction to the risk of Prehospital ETI failure (leading to an increase in primary ETI success in the Emergency Department).

The change in the magnitude and direction of the effect estimate caused by these confounding variables is difficult to quantify. These variables would be more readily obtainable using a prospective study design and by the consistent use of standardized charting templates.

The second category of confounding applies to an inappropriate definition used to measure or classify patients. In this study, there is potential for confounding in the definitions used to classify patients based on their primary diagnosis into four distinct admission categories. The concern, in particular, is regarding the trauma category. This category includes two patient groups –those with and those without a brain injury. Trauma patients who suffer a brain injury may be more difficult to intubate due to anatomical deformities, and studies have suggested that the risk of death is higher for patients who experience a brain injury. (91) Also, the length of stay may be longer for patients who have a brain injury due to extended rehabilitation. These patients have injury qualities that are both traumatic and neurological in nature. Approximately 67% of patients in the trauma admission group were admitted with a traumatic brain injury (TBI). A sensitivity analysis was not performed as there were zero patients that were intubated in the Prehospital setting that suffered a non-brain related traumatic injury (non-TBI) who died. A larger sample size would be needed to explore the confounding effect of combining these two patient groups.

Variables that remain unmeasured represent the third category of confounding. One particular factor that was not examined in this study was the presence of a concomitant bloodstream infection at time of VAP diagnosis. This data element was not available to be extracted from the VAP Surveillance database, and is a difficult and complex element to extract from a chart review. Bloodstream infections have been identified as an important risk factor of mortality among VAP patients. (66, 92) Research

that compares the location of intravenous cannulation, suggests that there is no difference in the bloodstream infection rate between PH and ED patients. (93,94) However, bacteremia can be caused by a variety of mechanisms, not just cannulation of an artery or vein. There has been no research conducted to investigate whether bloodstream infections are related to Prehospital intubation. Therefore, confounding of the effect measure in this way cannot be ruled out.

A discussion regarding confounding would be remiss if it did not include the possibility of surrogacy. Since a definite conclusion regarding causation cannot be stated, it is theoretically plausible to accept that "intubation location" may be a surrogate marker for the general difference between Prehospital and Emergency Department patients. There may be an unknown confounder that occurs prior to intubation in the Prehospital setting that would provide a more accurate explanation of this association. One example of this confounding bias may be a "healthy patient (worker) effect".

This would mean that patients intubated in the Emergency Department must meet a minimum health status (high enough to make it to the hospital without medical intervention) that the Prehospital patients do not meet. Prehospital patients are theoretically getting medical attention sooner than their Emergency Department counterparts. Perhaps some patients would not have survived long enough to make it to the Emergency Department if it was not for the intervention of intubation in the Prehospital setting. However, the magnitude and impact of this bias is difficult to quantify and, as seen throughout the literature, Emergency Department patients are the best comparison group for the Prehospital population. Further research in this subject matter would be needed to exclude this possible bias.

Summary

Although the methodological issues discussed here are numerable, the results are both coherent and clinically important. The strength of the association between intubation location and mortality is large enough that the magnitude of the potential shift caused by these biases provides little threat to the validity of the final model. Even though this study was not able to account for all of the confounding factors, the results

and their interpretation provide a plausible explanation and set the foundation for future exploratory research. In conclusion, this study has reasonable internal validity because the theoretical and actual errors in estimation are quite small.

Future Research

The current study is the first to explore the association of intubation location and outcomes among VAP patients. Although the results in this study are significant, several limitations have been identified. Additional research that replicates these finding is essential to draw concrete conclusions about the effect of intubation location on both all-cause hospital mortality and length of stay.

Ensuring accurate and detailed collection of exposure and covariate variables is necessary. One way to facilitate this would be to implement a standardized reporting for intubations in both the Prehospital and inpatient settings. A report mirroring the data collection form used in this study (Appendix A) would adequately capture key covariates.

A case control study design would improve efficiency and decrease the required sample size. The use of matching and/or restricting while selecting the sample would control for confounding of concerning variables, such as age and trauma admission.

Regardless of methodology, all studies require a sufficient sample size and power to calculate an accurate measure of the association. A larger sample size has many benefits. The point estimates would be more precise and confidence intervals narrower; which would in turn decrease both the type I and type II error rates. As mentioned above, a larger sample should be sought from the use of multiple sites instead of extending the study time frame.

Implications

Although the results of this study need to be confirmed by further research, there are several conclusions that may impact patient care and require discussion.

Several data elements were not able to be considered due to poor charting. This highlights a major concern about the consistency of recording essential details about

invasive procedures. In addition to standardized charting for ETI as mentioned above, an integrative electronic charting system would ensure accurate and complete information.

An electronic health record that is accessible in all patient care settings would facilitate better communication among clinicians and also ensure that data is not lost during transfer of care. Furthermore, it would guarantee comprehensive datasets for future research. Currently the Government of Alberta is working towards the implementation of a province-wide electronic health record. It is imperative that data elements discussed in this thesis are included in the record template.

Two previous studies have documented that Prehospital ETI patients are more likely to develop nosocomial pneumonia than Emergency Department ETI patients. (12,41) Aspiration is one of the most common causes of VAP (95), and of particular concern for Prehospital intubated patients. Perhaps immediately implementing precautions (in the ambulance) to reduce the risk of aspiration right away may also reduce VAP as well as mortality. Such interventions may include raising the head of the stretcher by 30^{o}, or the use of an endotracheal tube with silver-ion lining or subglottic secretion drainage. (96,97)

If these results are valid and replicated, perhaps preventing ETI in the Prehospital setting or postponing ETI until Emergency Department, would result in decreased hospital mortality. In 2008, Thompson et al. studied the use of continuous positive airway pressure as an alternative to ETI in the Prehospital setting. (98) This study was conducted in a similar setting as Calgary, a large Canadian urban city with short transport times. They found that continuous positive airway pressure reduced the need for ETI by 30% and also reported a reduction in mortality of 20%. (98) These finding are supported by literature that suggests that Paramedics should focus on adequate oxygenation regardless of means, opposed to successful tracheal intubation. The use of continuous positive airway pressure is one alternative that could lower the mortality rate among patients who would otherwise be intubated in the Prehospital setting.

Patients who are intubated in the Prehospital may further benefit from in-hospital interventions to reduce the impact of VAP. This subset of patients would be good

candidates for expensive therapies, treatments or prophylaxes that are reserved for high risk patients. One example may be the use of silver-coated endotracheal tubes. Kollef and colleagues (2008) concluded that the use of silver-coated endotracheal tubes lower the incidence of VAP that resulted in the 36% relative risk reduction. (97) Instituting the use of silver-coated endotracheal tubes in the Prehospital setting may achieve not only reduced VAP, but also reduced mortality.

Conclusion

This study provides several novel conclusions about the association between intubation location and morbidity and mortality among patients who acquire VAP in the ICU. Patients who suffer severe illness or injury are more likely to die if they are intubated in the Prehospital setting compared to the Emergency Department. Furthermore, Prehospital ETI patients who die, do so sooner than Emergency Department ETI patients; whereas Prehospital ETI patients who survive, have longer hospitalizations than their Emergency Department counterparts. Although the time to VAP diagnosis is similar between the two groups, the primary microbial pathogen may differ.

APACHE II score, taken upon ICU admission, which served as a surrogate severity in this study and was shown to modify the intubation location –mortality relationship. Age and traumatic injury have proven to be important confounding factors that necessitate consideration when assessing these associations.

Since this study is the first to analyse these objectives, there are no comparative studies in the literature. Despite the limitations observed and described these results are important for future research. A large prospective multi-site nested case-control study would improve efficiency and provide better control over confounding factors.

This study may improve patient care in several ways. Firstly, this study has highlighted the need for consistent and comprehensive reporting for invasive procedures, such as ETI. Secondly, these results provide further evidence that suggests that patients who are cared for in the Prehospital setting may benefit from non-invasive ventilation techniques. Finally, those who are intubated in the Prehospital setting represent a small

subset of patients who would be good candidates for expensive therapies that are proven to reduce mortality among VAP patients.

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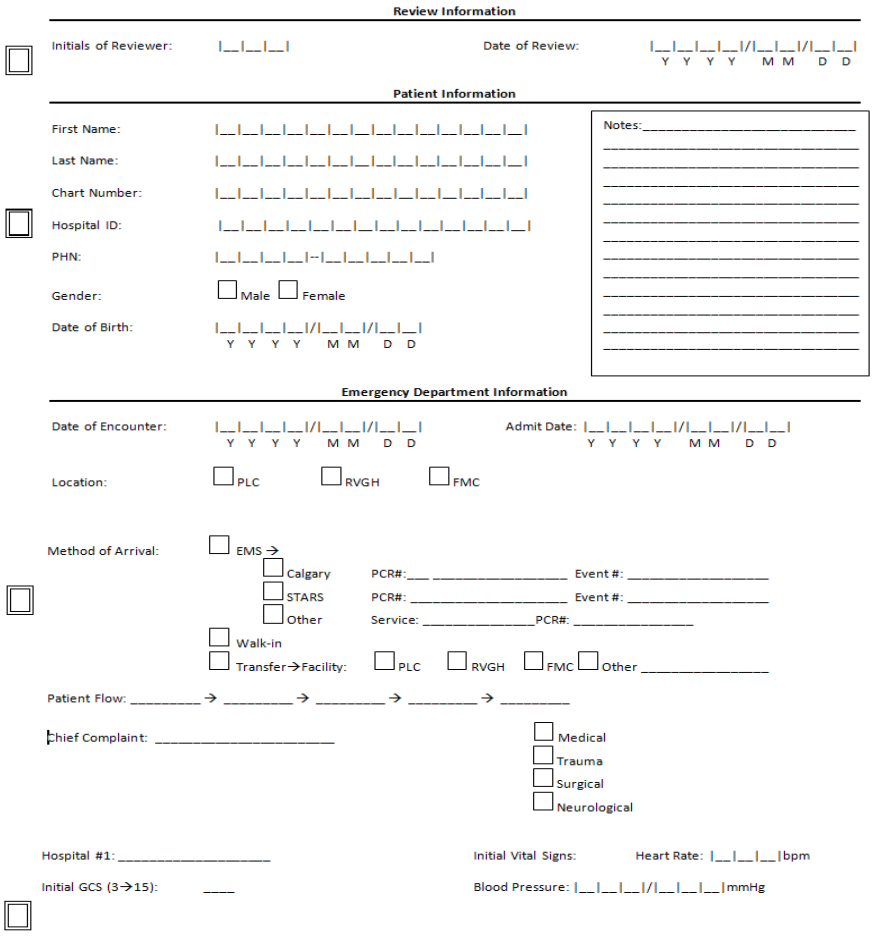
APPENDIX A: CHART REVIEW DATA COLLECTION FORM



Review Information

Initials of Reviewer: |__|__|__| Date of Review: |__|__|__|__|/|__|__|/|__|__| (Y Y Y Y M M D D)

Patient Information

First Name: |__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|

Last Name: |__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|

Chart Number: |__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|

Hospital ID: |__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|

PHN: |__|__|__|__|--|__|__|__|__|__|

Gender: ☐ Male ☐ Female

Date of Birth: |__|__|__|__|/|__|__|/|__|__| (Y Y Y Y M M D D)

Notes:_____

Emergency Department Information

Date of Encounter: |__|__|__|__|/|__|__|/|__|__| (Y Y Y Y M M D D) Admit Date: |__|__|__|__|/|__|__|/|__|__| (Y Y Y Y M M D D)

Location: ☐ PLC ☐ RVGH ☐ FMC

Method of Arrival: ☐ EMS → ☐ Calgary PCR#:___ _____ Event #: _____ ☐ STARS PCR#: _____ Event #: _____ ☐ Other Service: _____PCR#: _____ ☐ Walk-in ☐ Transfer→Facility: ☐ PLC ☐ RVGH ☐ FMC ☐ Other _____

Patient Flow: _____ → _____ → _____ → _____ → _____

Chief Complaint: _____ ☐ Medical ☐ Trauma ☐ Surgical ☐ Neurological

Hospital #1: _____ Initial Vital Signs: Heart Rate: |__|__|__|bpm

Initial GCS (3→15): ____ Blood Pressure: |__|__|__|/|__|__|__|mmHg

(Page 1 of 2)

Hospital #2: _____ Initial Vital Signs: Heart Rate: |__|__|__|bpm

Initial GCS (3→15): ____ Blood Pressure: |__|__|__|/|__|__|__|mmHg

Intubation Information

Date of Initial Intubation: |__|__|__|__|/|__|__|/|__|__|
Y Y Y Y M M D D

Intubation time: |__|__|:|__|__| (24 hours) ☐ Unknown/Not Documented

Number of Attempts: |__|__| ☐ Unknown/Not Documented Size: _____french Depth: _____cm

Intubation Location: ☐ Pre-Hospital → ☐ Calgary ☐ STARS ☐ Other _____
☐ Emergency Department→ Hospital Name: _____
☐ ICU
☐ OR
☐ Other: _____

Provider: _____ ☐ Unknown/Not Documented

Complications: _____ ☐ Unknown/Not Documented

Type: ☐ Oral-tracheal ☐ Naso-tracheal ☐ Cricotomy

RSI: ☐ Yes ☐ No ☐ Unknown

Drug Used: _____

Discharge Date: |__|__|__|__|/|__|__|/|__|__| Discharge Outcome: ☐ Dead ☐ Alive
Y Y Y Y M M D D

Missing Data

Description of missing data elements: _____

Completion

☐ Complete ☐ Validated ☐ Entered in Database

APPENDIX B: SUPPLIMENTARY ANALYSIS INFORMATION

This appendix contains supplementary material to fully explain the model formation process and performance of the regression analyses presented in this thesis. This appendix follows the same flow as the primary and secondary results sections (Chapter four and five). Refer to Chapter three (Methodology) for a description of the analysis performed and model formation process used.

Details pertaining to the logistic regression model for hospital mortality will be presented followed by the linear regression model for hospital length of stay, cox proportional hazards regression for the survival analysis, and finally linear regression model for time to ventilator-associated pneumonia (VAP) diagnosis.

Modeling Process

A detailed table is provided for each regression analysis to explain the modeling process. The model number, right side of the equation, goodness of fit (either X^2 or F statistic), goodness of fit significance (Prob>X^2 or Prob>F) and p-value are denoted for each model. The p-value denotes the level of significance for the coefficient of the covariate that is **bolded** (multiple p-values are listed in the order of the bolded covariates in the equation).

Each coefficient is represented by beta (B) and subscript letters, which represent covariates. A Table B.1 is a legend of all the subscript letters used. Confounding is measured by evaluating the coefficient of a covariate by itself (example: B_A=age). Any covariate that is combined with exposure (E) represented an effect modification term (example: B_{AE}=age*exposure). Any covariate that is combined with either one or several other covariate subscripts is a term that is used to assess for interaction (example: B_{AG}=age*gender).

Table B.1: Coefficient Legend

Subscript	Variable	Data Type
A	Age	Continuous (shifted left by 18)
B	Gram-negative bacteria	0=Not GNB, 1=GNB
D1	Medical admission	0=Not Medical, 1=Medical
D2	Trauma admission	0=Not Trauma, 1=Trauma
D3	Neurology admission	0=Not Neuro, 1=Neuro
E	Exposure	ED=0, PH=1
G	Gender	F=0, M=1
M	Mortality	0=Alive, 1=Deceased (upon discharge)
O	Baseline (log odds or estimated mean - conditional on zero values for all unspecified coefficients in model)	
P	APACHE II score	Continuous
S	SOFA score	Continuous
T	Time to VAP diagnosis	Continuous

Note: APACHE=Acute Physiology and Chronic Health Evaluation; ED=Emergency Department; F=Female; GNB=Gram Negative Bacteria; M=Male; PH=Prehospital; VAP=Ventilator-Associated Pneumonia.

Log likelihood ratio tests are used for the hospital mortality logistic regression and the survival analysis cox proportional hazards regression. These tests assess the ratio of the log likelihood chi square statistics of two nested models. A significant p-value indicates that the models are different; whereas a non-significant p-value indicates the models are not different.

The proposed final model for each regression analysis is boarded and appears in *italics.* Details for these models, including the values of each coefficient and p-value, can be found in the corresponding results chapter.

Hospital Mortality Logistic Regression

Table B.2 is a detailed description of the modeling process used to analyze the association between intubation location and hospital mortality in the presence of multiple covariates. The left side of the model equation is the log odds ratio of mortality for Prehospital intubations over Emergency Department intubations.

Many variables were considered during the construction of this model. The interaction terms associated with gram-negative bacteria and time to VAP diagnosis were not able to be assessed due to the high number of iterations. Models with the aforementioned interaction terms did not achieve convergence.

Table B.2: Hospital Mortality Logistic Regression Model Formation

Model	Equation (Right Side Only)	LR X^2	Prob $>X^2$	P-value†
1	B_O+**B_E**	0.02	0.90	0.90
2	B_O+B_E+B_A+**B_{AE}**	9.13	0.03	0.85
-	Nested Models: M1 M2	9.11	0.01	-
3	B_O+B_E+**B_A**	9.09	0.01	<0.01
-	Nested Models: M2 M3	0.04	0.85	-
-	Nested Models: M1 M3	9.07	<0.01	-
4	B_O+B_E+B_A+B_G+**B_{GE}**+**B_{AG}**	13.96	0.16	0.26 0.12
-	Nested Models: M3 M4	4.87	0.18	-
5	B_O+B_E+B_A+**B_G**	10.07	0.02	0.32
6	B_O+B_E+B_A+B_G+B_P+B_{PE}+B_{GP}+**B_{AP}**+B_{AGP}	27.98	<0.001	0.44
-	Nested Models: M5 M6	23.95	<0.001	-
7	B_O+B_E+B_A+B_G+B_P+B_{PE}+B_{GP}+**B_{AGP}**	27.38	<0.001	0.09
-	Nested Models: M6 M7	0.60	0.44	-
8	B_O+B_E+B_A+B_G+B_P+B_{PE}+**B_{GP}**	24.36	<0.01	0.19
-	Nested Models: M7 M8	3.02	0.08	-
9	B_O+B_E+B_A+B_G+B_P+**B_{PE}**	22.51	<0.001	0.03
-	Nested Models: M8 M9	1.85	0.17	-
-	Nested Models: M5 M9	18.48	<0.001	-
10	B_O+B_E+B_A+B_G+B_P+B_{PE}+B_S+**B_{SE}**+B_{SA}+B_{SG}+B_{SP}+B_{AGS} +B_{APS}+B_{GPS}+B_{AGPS}	30.70	<0.01	0.31
-	Nested Models: M9 M10	8.20	0.51	-
11	B_O+B_E+B_A+B_G+B_P+B_{PE}+B_S+**B_{SA}+B_{SG}+B_{SP}+B_{AGS} +B_{APS}+B_{GPS}+B_{AGPS}**	29.65	<0.01	0.16 0.20 0.23 0.24 0.11 0.11

Model	Equation (Right Side Only)	LR X^2	Prob $>X^2$	P-value†
				0.13
-	Nested Models: M10 M11	1.05	0.31	-
12	$B_O+B_E+B_A+B_G+B_P+B_{PE}+\mathbf{B_S}$	23.01	<0.01	0.48
-	Nested Models: M11 M12	6.64	0.47	-
-	Nested Models: M10 M12	7.69	0.46	-
-	Nested Models:M9 M12	0.50	0.48	-
13	$B_O+B_E+B_A+B_G+B_P+B_{PE}+B_{D2}+\mathbf{B_{D2E}}+B_{D3}+\mathbf{B_{D3E}}$ Baseline group is considered D1=1 (exhaustive indicators)	36.65	<0.001	0.77 0.18
-	Nested Models: M9 M13	14.14	<0.01	-
14	$B_O+B_E+B_A+B_G+B_P+B_{PE}+B_{D2}+\mathbf{B_{D3}}$	34.14	<0.001	0.84
-	Nested Models: M13 M14	2.51	0.29	-
15	$B_O+B_E+B_A+B_G+B_P+B_{PE}+B_{D2}$	*34.09*	*<0.001*	*0.05*
-	Nested Models: M13 M15	2.55	0.47	-
-	Nested Models: M9 M15	11.59	<0.001	-
16	$B_O+B_E+B_A+B_G+B_P+B_{PE}+B_{D2}+\mathbf{B_{AD2}}+\mathbf{B_{GD2}}+\mathbf{B_{PD2}}+\mathbf{B_{AGD2}}+\mathbf{B_{APD2}}+B_{GPD2}+\mathbf{B_{AGPD2}}$	48.16	<0.001	0.83 0.18 0.40 0.18 0.40 0.47 0.65 0.34
-	Nested Models: M15 M16	14.07	0.05	-
17	$B_O+B_E+B_A+B_G+B_P+B_{PE}+B_{D2}+\mathbf{B_{GPD2}}$	34.10	<0.001	0.96
-	Nested Models: M15 M17	0.00	0.96	-
18¥	$B_O+B_E+B_A+B_G+B_P+B_{PE}+B_{D2}+B_B+\mathbf{B_{BE}}$	35.67	<0.001	0.45
-	Nested Models: M15 M18	1.58	0.45	-
19	$B_O+B_E+B_A+B_G+B_P+B_{PE}+B_{D2}+\mathbf{B_B}$	35.20	<0.001	0.30

Model	Equation (Right Side Only)	LR X^2	Prob $>X^2$	P-value†
-	Nested Models: M15 M19	1.10	0.29	-
20¥	$B_O+B_E+B_A+B_G+B_P+B_{PE}+B_{D2}+B_T+\mathbf{B_{TE}}$	37.75	<0.001	0.78
-	Nested Models: M15 M20	4.24	0.12	-
21	$B_O+B_E+B_A+B_G+B_P+B_{PE}+B_{D2}+\mathbf{B_T}$	34.37	<0.001	0.56
-	Nested Models: M20 M21	3.37	0.07	-
-	Nested Models: M15 M21	0.86	0.35	-

Note: †indicates p-value associated with **bolded** variable; ¥-Models with additional interaction terms did not achieve convergence; LR=Log likelihood Ratio; X^2=chi square.

The second assumption of logistic regression is the absence of collinarity. This means that the values of all variables are independent of one another (i.e. gender does not influence age). This was assessed by testing the correlation of the variables.

The resultant of variable pairings is a correlation value of "r". Variable pairings that have a correlation value (r) of greater than 0.55 or less than -0.55 would be concerning, and the variables would be deemed collinear. Variable pairings that have a correlation value (r) between -0.55 and 0.55 are not concerning, and collinarity can be dismissed.

The variables used in the final proposed model for the hospital mortality logistic regression were: exposure (intubation location); age; gender; Acute Physiology and Chronic Health Evaluation (APACHE) II score; and trauma. There were no concerning pairs in this model.

Table B.3: Hospital Mortality Logistic Regression Assessment of Collinearity

	Exposure	Age	Gender	APACHE II	Trauma
Exposure	1.0000				
Age	-0.0885	1.0000			
Gender	0.1440	-0.1505	1.0000		
APACHE II	0.1137	0.1712	-0.0350	1.0000	
Trauma	0.0832	-0.3044	0.4007	-0.2714	1.0000

Note: APACHE=Acute Physiology and Chronic Health Evaluation.

Hospital Length of Stay Linear Regression

Table B.4 is a detailed description of the modeling process used to analyze the association between intubation location and hospital length of stay in the presence of multiple covariates. The left side of the model equation is the log mean length of stay (days).

Due to the amount of variables included in this model, the number of interaction terms was limited. In following convention, a limit of 5 coefficient terms was followed based on the sample size (number of deaths=50).

Table B.4: Hospital Length of Stay Linear Regression Model Formation

Model	Equation (Right Side Only)	F	Prob >F	P-value†
1	B_O+**B_E**	0.01	0.94	0.94
2	B_O+B_E+B_M+**B_{ME}**	21.14	<0.001	<0.01
3	B_O+B_E+B_M+B_{ME} +B_A+**B_{AE}**+B_{MA}	12.26	<0.001	0.28
4	B_O+B_E+ B_M+B_{ME} +B_A+**B_{MA}**	14.47	<0.001	0.01
5	B_O+B_E+ B_M+B_{ME} +B_A+B_{MA}+B_G+**B_{GE}**	10.41	<0.001	0.43
6	*B_O+B_E+ B_M+B_{ME} +B_A+ B_{MA}+**B_G***	*12.06*	*<0.001*	*0.57*
7	B_O+B_E+ B_M+B_{ME} +B_A+ B_{MA}+B_G+B_P+**B_{PE}**	8.83	<0.001	0.91
8	B_O+B_E+ B_M+B_{ME} +B_A+ B_{MA}+B_G+**B_P**	10.14	<0.001	0.75
9	B_O+B_E+ B_M+B_{ME} +B_A+ B_{MA}+B_G+B_S+**B_{SE}**	9.08	<0.001	0.45
10	B_O+B_E+ B_M+B_{ME} +B_A+ B_{MA}+B_G+**B_S**	10.32	<0.001	0.67
11	B_O+B_E+ B_M+B_{ME} +B_A+ B_{MA}+B_G +B_{D2}+**B_{D2E}**	9.07	<0.001	0.41
12	B_O+B_E+ B_M+B_{ME} +B_A+ B_{MA}+B_G +**B_{D2}**	10.29	<0.001	0.95
13	B_O+B_E+ B_M+B_{ME} +B_A+ B_{MA}+B_G +B_B+**B_{BE}**	8.98	<0.001	0.60
14	B_O+B_E+ B_M+B_{ME} +B_A+ B_{MA}+B_G+ **B_B**	10.26	<0.001	0.27

Note: †indicates p-value associated with **bolded** variable.

Several assumptions of linear regression were assessed with the graphs, which were not included in the main text of the thesis. The primary assumption is called linearity. This means that the residuals of the dependent variable (length of stay) are normally distributed.

Figure B.1 depicts the normal distribution of the residuals of the crude model, pre-transformation. The Standardized Normal Probability plot graphs the residuals of the data against a theoretical normal distribution (represented as the 45^o straight line –black). Any departures from the line indicate departures from normality. The grey points on the graph, representing this dataset, are not linear and indicate that the assumption of normality has been violated and transformation is required.

Refer to chapter four for information regarding the reasons for transformation and the post-transformation Standardized Normal Probability Plot (Figure 4.6).

The second assumption of linear regression is called linearity. Linearity means that the relationship between each continuous independent variable and the dependent variable should be linear. To assess linearity, the standardized residuals (y-axis) of the proposed final model were plotted against both age and the effect modification term age*mortality (x-axis).

A graph that indicates that the linearity assumption has not be violated has no pattern and the residuals (grey dots) centered around zero. Figures B.2 and B.3 are the graphs for age and age*mortality respectfully. The assumption of linearity has not been violated in either case. Therefore, it is correct to assume that the log mean length of stay has a linear relationship with both age and age*mortality.

Figure B.1: Standardized Normal Probability Plot of the Hospital Length of Stay Linear Regression Model Residuals (Pre-transformation)

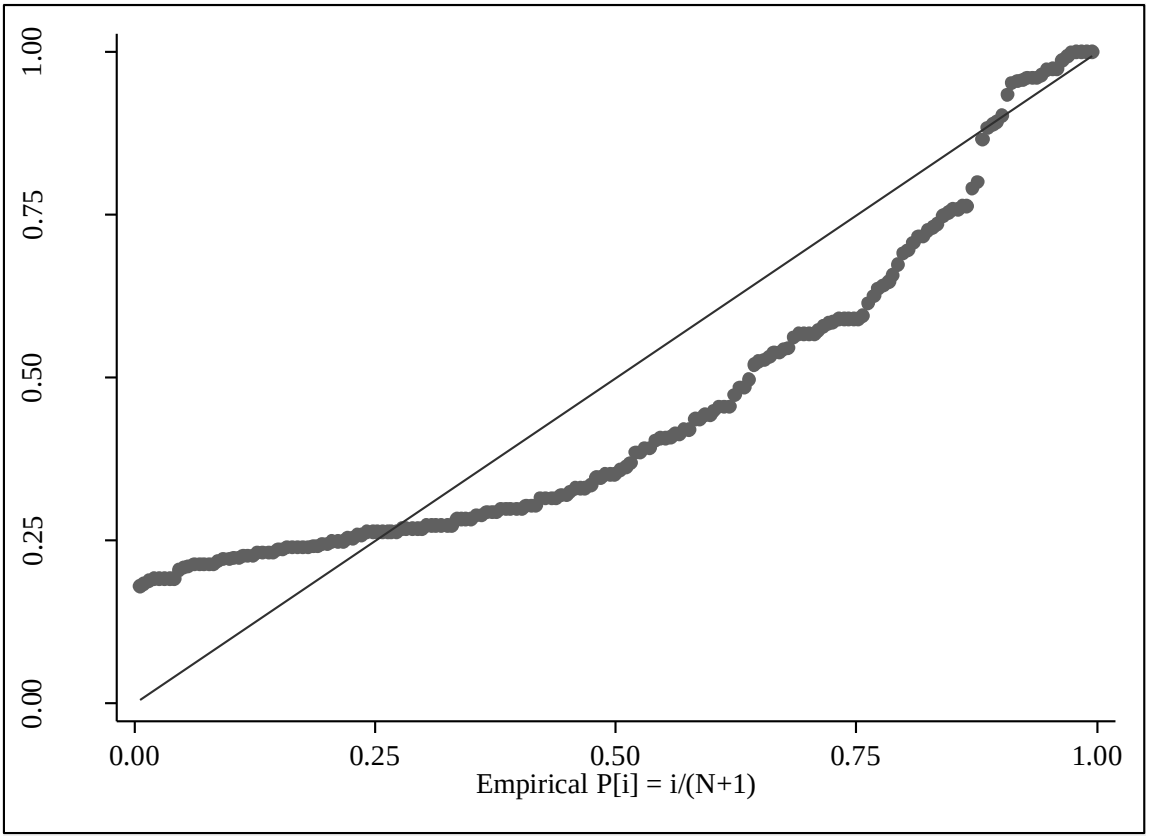


Figure B.2: Hospital Length of Stay Linear Regression Model Residuals against Age

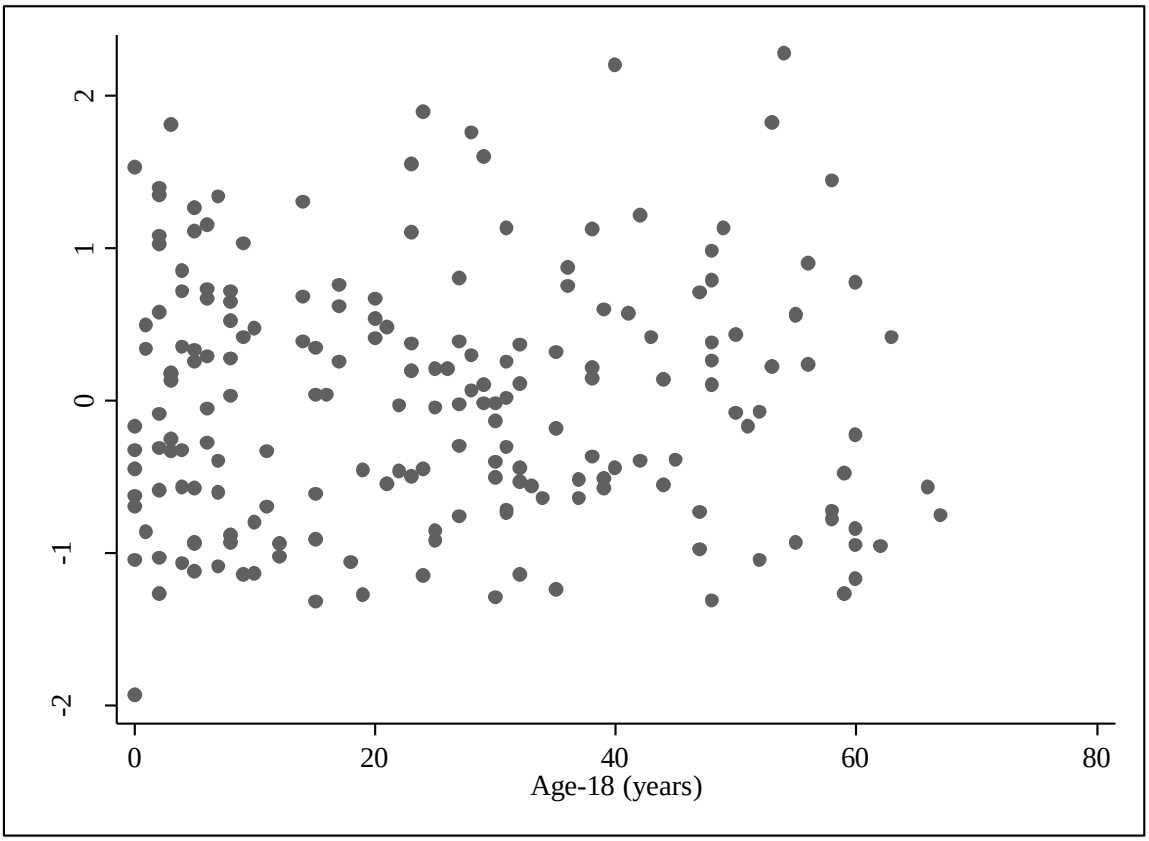
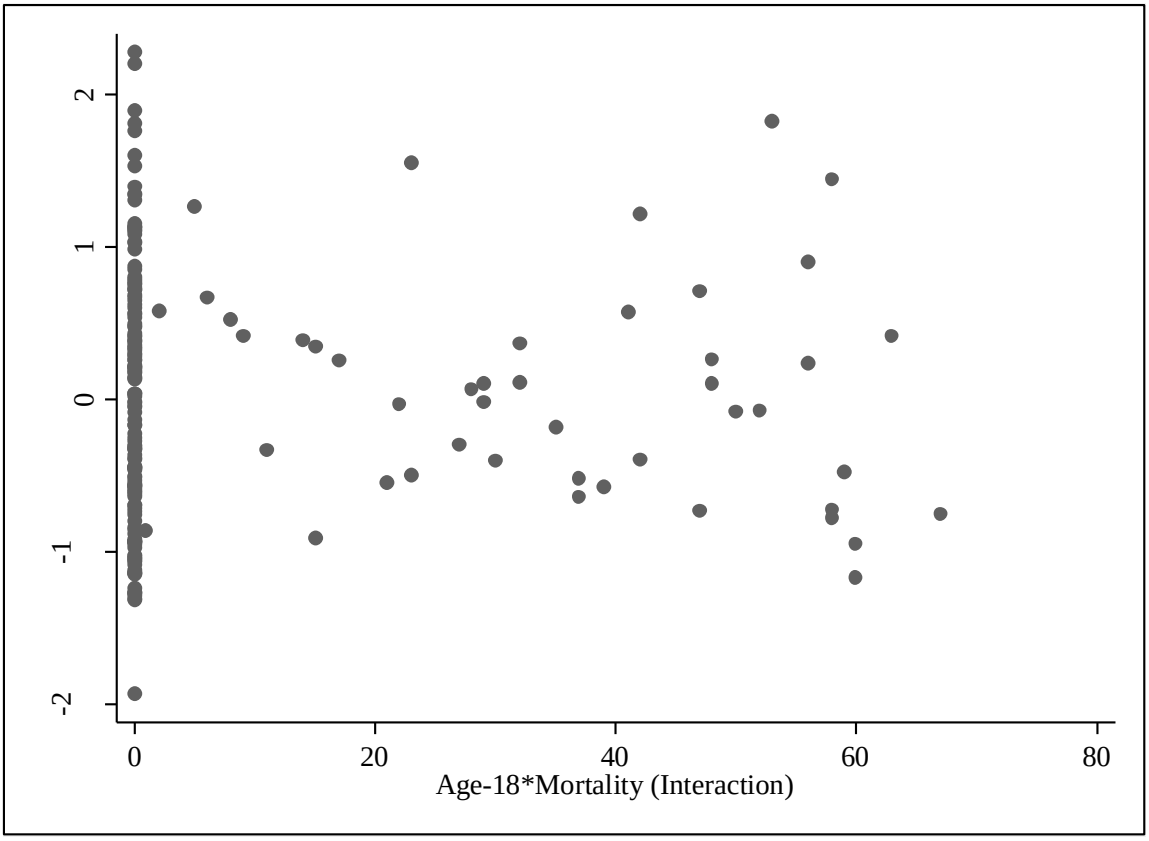


Figure B.3: Hospital Length of Stay Linear Regression Model Residuals against Age*Mortality



The final assumption of linear regression is the absence of collinarity. The explanation for collinearity and correlation is the same as stated above for logistic regression.

The variables used in the final proposed model for the hospital length of stay linear regression were: exposure (intubation location); hospital discharge status (alive vs. dead); age; and gender. There were no concerning pairs in this model.

Table B.5: Hospital Length of Stay Linear Regression Assessment of Collinearity

	Log LOS	Exposure	Age	Gender	Dead
Log LOS	1.0000				
Exposure	0.0055	1.0000			
Age	-0.0441	-0.0915	1.0000		
Gender	0.1053	0.1368	-0.1464	1.0000	
Dead	-0.4604	-0.0089	0.2176	-0.1015	1.0000

Note: LOS=Length of Stay.

Time to Event Cox Proportional Hazards Regression

Table B.6 is a detailed description of the modeling process used to analyze the association between intubation location, hospital mortality and length of stay in the presence of multiple covariates. The term time-to-event refers to the length of stay until discharge, where death is the event being analyzed. The result is a ratio of the survival probabilities. The left side of the model equation is the log hazard ratio of mortality for Prehospital intubations over Emergency Department intubations.

Table B.6: Time to Event Cox Proportional Hazards Regression Model Formation

Model	Equation (Right Side Only)	LR X^2	Prob $>X^2$	P-value†
1	$\mathbf{B_E}$	0.03	0.87	0.87
2	$B_E+B_A+\mathbf{B_{AE}}$	7.71	0.05	0.58
-	Nested Models: M1 M2	7.69	0.02	-
3	$B_E+\mathbf{B_A}$	7.41	0.02	<0.01
-	Nested Models: M2 M3	0.31	0.58	-
-	Nested Models: M1 M3	7.38	<0.01	-
4	$B_E+B_A+B_G+B_{GE}+\mathbf{B_{AG}}$	12.67	0.03	0.08
-	Nested Models: M3 M4	5.26	0.15	-
5	$B_E+B_A+B_G+B_{GE}$	9.65	0.05	0.31
-	Nested Models: M4 M5	3.02	0.08	-
6	$B_E+B_A+\mathbf{B_G}$	8.61	0.04	0.26
-	Nested Models: M5 M6	1.04	0.31	-
-	Nested Models: M3 M6	1.20	0.27	-
7	$B_E+B_A+B_G+B_P+B_{PE}+B_{GP}+\mathbf{B_{AP}}+B_{AGP}$	28.30	<0.001	0.19
-	Nested Models: M6 M7	40.20	<0.001	-
8	$B_E+B_A+B_G+B_P+B_{PE}+B_{GP}+\mathbf{B_{AGP}}$	26.56	<0.001	0.15
-	Nested Models: M7 M8	1.74	0.19	-
9	$B_E+B_A+B_G+B_P+B_{PE}+\mathbf{B_{GP}}$	24.42	<0.001	0.12
-	Nested Models: M7 M9	3.89	0.14	-
10	$B_E+B_A+B_G+B_P+\mathbf{B_{PE}}$	22.00	<0.001	<0.01
-	Nested Models: M7 M10	6.30	0.10	-
-	Nested Models: M6 M10	33.90	<0.001	-
11	$B_E+B_A+B_G+B_P+B_{PE}+B_S+B_{SE}+\mathbf{B_{SA}+B_{SG}+B_{SP}+B_{AGS}}$	25.02	<0.001	0.50 0.36 0.15
-	Nested Models: M10 M11	3.02	0.69	-

Model	Equation (Right Side Only)	LR X^2	Prob $>X^2$	P-value†
12	$B_E+B_A+B_G+B_P+B_{PE}+B_S+\mathbf{B_{SE}}$	22.86	<0.001	0.40
-	Nested Models: M11 M12	2.16	0.54	-
-	Nested Model: M10 M12	0.86	0.65	-
13	$B_E+B_A+B_G+B_P+B_{PE}+\mathbf{B_S}$	22.11	<0.001	0.73
-	Nested Models: M12 M13	0.75	0.39	-
-	Nested Models: M10 M13	0.11	0.74	-
14	$B_E+B_A+B_G+B_P+B_{PE}+B_{D2}+B_{D2E}+\mathbf{B_{D3}+B_{D3E}}$ Baseline group is considered D1=1 (exhaustive indicators)	33.12	<0.001	0.24 0.61
15	$B_E+B_A+B_G+B_P+B_{PE}+B_{D2}+\mathbf{B_{D2E}}$	30.72	<0.001	0.57
-	Nested Models: M14 M15	1.40	0.50	-
16	$B_E+B_A+B_G+B_P+B_{PE}+B_{D2}+\mathbf{B_{AD2}+B_{GD2}+B_{PD2}+B_{AGD2}}$	34.25	<0.001	0.28 0.18 0.20
-	Nested Models: M10 M16	12.24	0.31	-
-	Nested Models: M15 M16	3.53	0.32	-
17	$B_E+B_A+B_G+B_P+B_{PE}+\boldsymbol{B_{D2}}$	*30.39*	*<0.001*	*<0.01*
-	Nested Models: M16 M17	3.86	0.43	-
-	Nested Models: M10 M17	8.39	<0.01	-
18	$B_E+B_A+B_G+B_P+B_{PE}+B_{D2}+B_B+\mathbf{B_{BE}}$	32.08	<0.001	0.42
-	Nested Models: M17 M18	1.69	0.43	-
19	$B_E+B_A+B_G+B_P+B_{PE}+B_{D2}+\mathbf{B_B}$	31.43	<0.001	0.31
-	Nested Models: M18 M19	0.65	0.42	-
-	Nested Models: M17 M19	1.04	0.31	-

Note: †indicates p-value associated with **bolded** variable; LR=Log likelihood Ratio; X^2=chi square.

Time to Ventilator-Associated Pneumonia Diagnosis Linear Regression

Table B.7 is a detailed description of the modeling process used to analyze the association between intubation location and time to VAP diagnosis in the presence of multiple covariates. The left side of the model equation is the log mean time to VAP diagnosis (days).

Table B.7: Time to Ventilator-Associated Pneumonia Diagnosis Linear Regression Model Formation

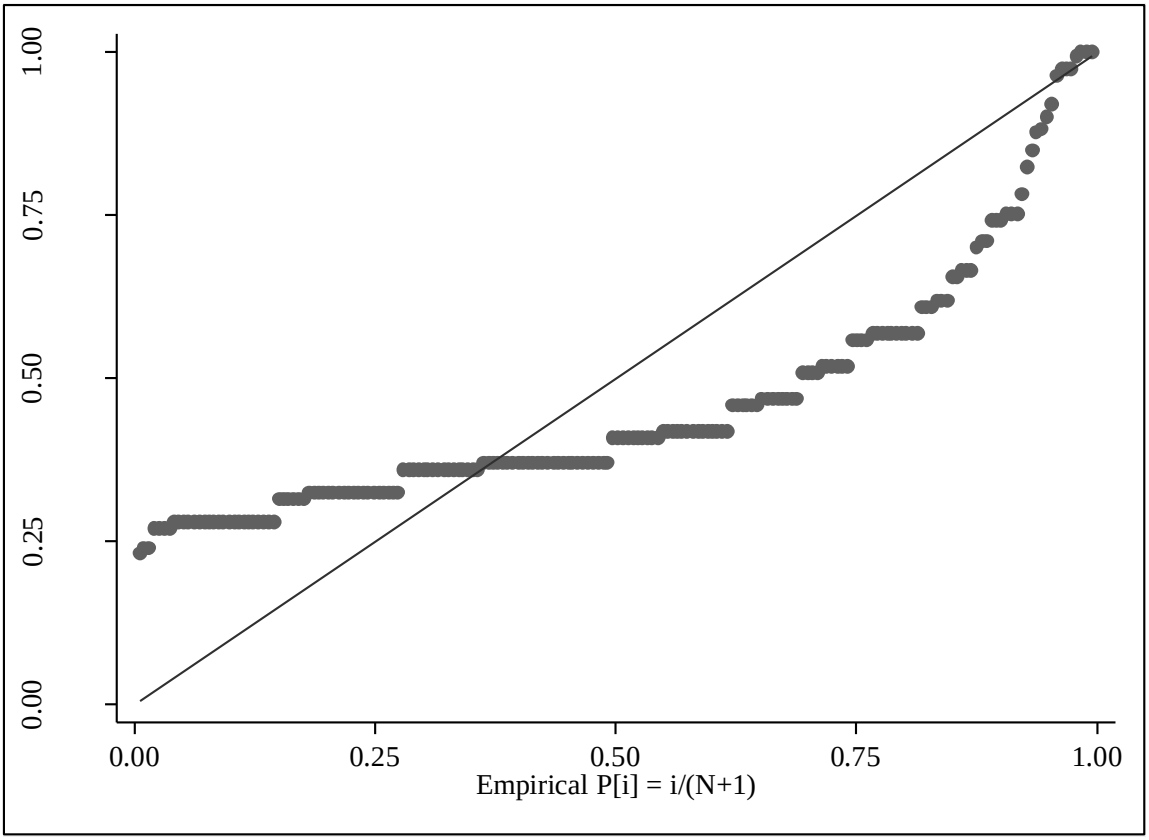
Model	Equation (Right Side Only)	F	Prob >F	P-value†
1	B_O+**B_E**	0.25	0.62	0.62
2	B_O+B_E+B_A+**B_{AE}**	3.96	<0.01	0.55
3	B_O+B_E+**B_A**	5.77	<0.01	<0.001
4	B_O+B_E+B_A+B_G+B_{GE}+**B_{AG}**	3.19	<0.01	0.30
5	B_O+B_E+B_A+B_G+**B_{GE}**	3.71	<0.01	0.58
6	B_O+B_E+B_A+**B_G**	4.86	<0.01	0.09
7	B_O+B_E+B_A+B_G+B_P+B_{PE}+**B_{GP}+B_{AP}+B_{AGP}**	2.53	<0.01	0.84 0.56 0.39
8	B_O+B_E+B_A+B_G+B_P+**B_{PE}**	3.93	<0.01	0.21
9	B_O+B_E+B_A+B_G+**B_P**	4.50	<0.001	0.06
10	B_O+B_E+B_A+B_G +B_{D2}+B_{D2E}+**B_{AD2}+B_{GD2}+B_{AGD2}**	4.87	<0.001	0.13 0.79 0.96
11	B_O+B_E+B_A+B_G +B_{D2}+**B_{D2E}**	6.05	<0.001	0.11
12	B_O+B_E+B_A+B_G +**B_{D2}**	6.88	<0.001	<0.001

Note: †indicates p-value associated with **bolded** variable.

Several assumptions of linear regression were assessed with the graphs, which were not included in the main text of the thesis. The primary assumption is called linearity. This means that the residuals of the dependent variable (time to VAP diagnosis)

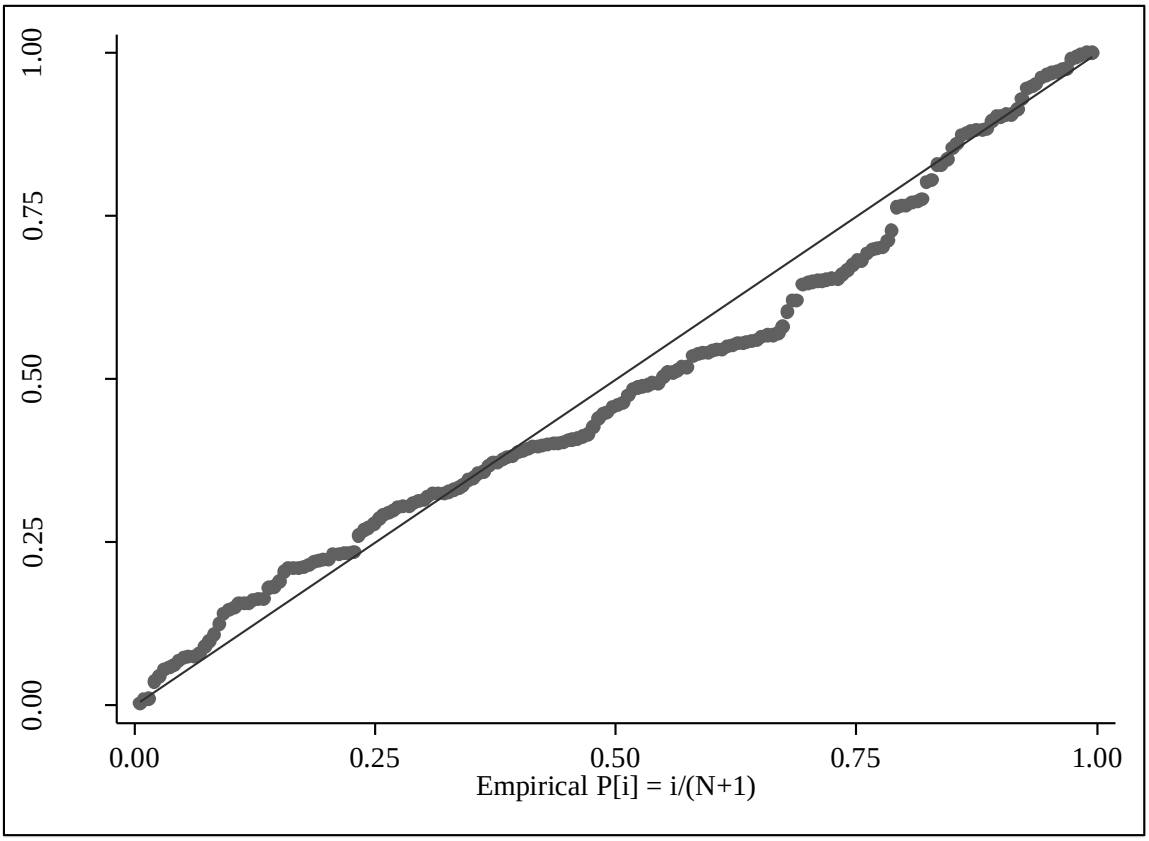
are normally distributed. Figure B.4 depicts the normal distribution of the residuals of the crude model, pre-transformation.

Figure B.4: Standardized Normal Probability Plot of the Time to Ventilator-Associated Pneumonia Diagnosis Linear Regression Model Residuals (Pre-Transformation)



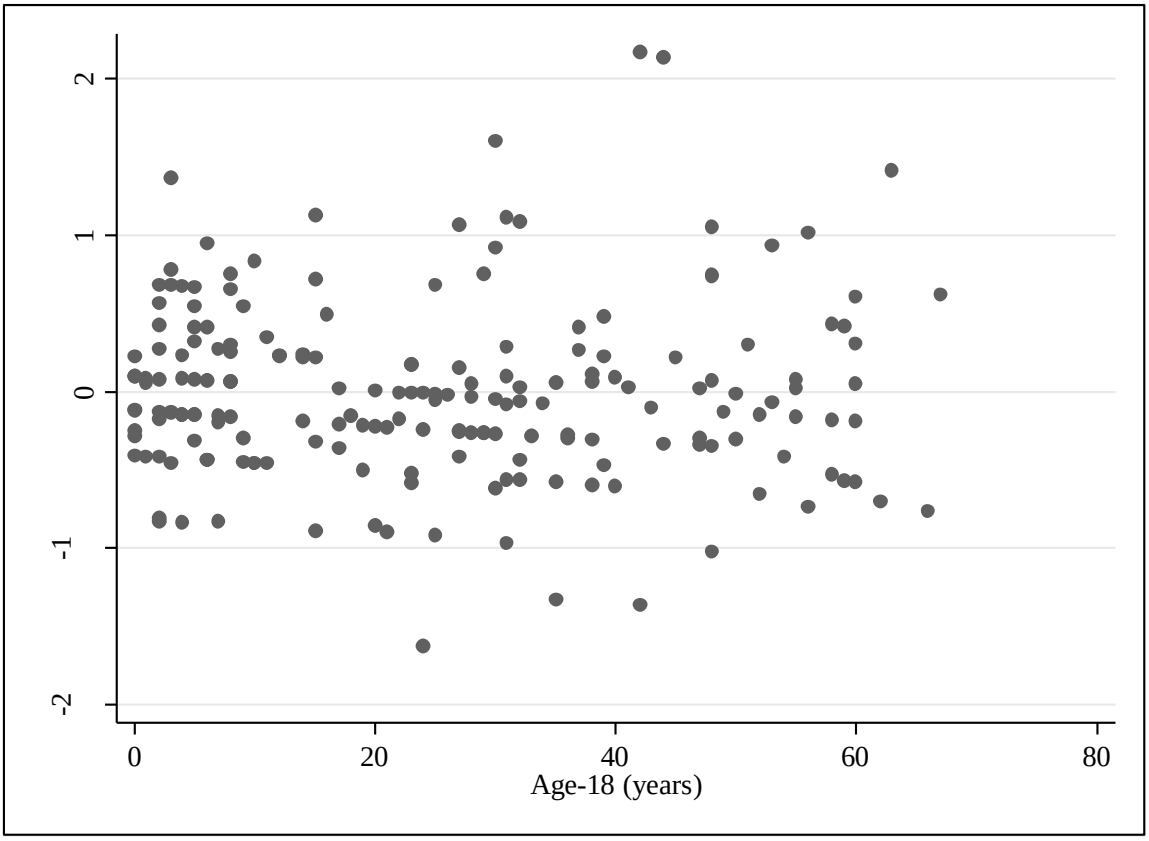
Since length of stay is a time-dependent variable, naturally is it right skewed; furthermore the residuals were also right skewed. Therefore, time to VAP diagnosis was transformed onto the log-scale to correct for this deficiency. Figure B.5 is a plot depicting the distribution of the post-transformation residuals.

Figure B.5: Standardized Normal Probability Plot of the Time to Ventilator-Associated Pneumonia Diagnosis Linear Regression Model Residuals (Post-Transformation)



Linearity, the second linear regression assumption, can also be depicted using plots of residuals. The standardized residuals of the proposed final model are plotted against age, the only continuous variable. The assumption of linearity has not been violated. Therefore, it is correct to assume that the log mean time to VAP diagnosis has a linear relationship with age.

Figure B.6: Time to Ventilator-Associated Pneumonia Diagnosis Linear Regression Model Residuals against Age



The third assumption of linear regression is the absence of collinarity. The explanation for collinearity and correlation is the same as stated above for logistic regression.

The variables used in the final proposed model for the time to VAP diagnosis linear regression were: exposure (intubation location); age; gender; and trauma. There were no concerning pairs in this model.

Table B.8: Time to Ventilator-Associated Pneumonia Diagnosis Linear Regression Assessment of Collinearity

	Log TTD	Exposure	Gender	Age	Trauma
Log TTD	1.0000				
Exposure	-0.0361	1.0000			
Gender	-0.1559	0.1392	1.0000		
Age	0.2394	-0.0864	-0.1517	1.0000	
Trauma	-0.3278	0.0850	0.3955	-0.3193	1.0000

Note: TTD=Time to Ventilator-Associated Pneumonia Diagnosis.

The final assumption of linear regression is called homoscedasticity. This means that the variance of the residuals is constant. To assess this assumption the standardized residuals of the final proposed model were plotted against the fitted values. A graph that does not violate the assumption of homoscedasticity depicts has no pattern (random) and the values are centered on zero.

The homoscedasticity plot for the log time to VAP diagnosis linear regression models indicates that there is not constant variance. The variance of the residuals gets wider as the fitted values increase. This indicates that the standard errors of the coefficients are most likely biased, and may warrant caution in their interpretation. This may be due to a small sample size.

The plot indicates that there is a non-constant variance. Additionally the Breusch-Pagan/Cook-Weisberg test, which is another method to assess homoscedasticity, also indicates that the assumption has been violated ($p<0.001$).

Figure B.7: Linear Regression Model Residuals against the Estimated Log Time to Ventilator-Associated Pneumonia Diagnosis (Test for Homoscedasticity)