ISSN: 2410-1397

MODELLING SURVIVAL FOR PATIENTS IN RELATION TO CENTRAL VENOUS CATHETER AND NOSOCOMIAL BLOOD STREAM INFECTIONS: A CASE STUDY OF AGA KHAN UNIVERSITY HOSPITAL, NAIROBI

MASTERS OF SCIENCE IN SOCIAL STATISTICS

KIRORO FRANCIS MAINA

Supervisor:

Ms. Anne WANG'OMBE

Dr. Majid TWAHIR

Research Project in Social Statistics

I56/74919/2014

School of Mathematics

College of Biological and Physical Sciences

UNIVERSITY OF NAIROBI

DECLARATION

I Kiroro Francis Maina, hereby declare that this is my original work and has not been presented for a degree in any other university

Kiroro Francis Maina (I56/74919/2014)

……. …….

Signature Date

The proposal has been submitted for examination with my approval as University supervisor.

Anne Wang'ombe

Senior Lecturer, University of Nairobi

MPhil (Stockholm University), MSc (UoN), BSc (UoN), PhD (Ongoing)

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Signature Date

In addition, the proposal has been submitted for examination with my approval as institutional supervisor.

Dr Majid Twahir,

MBChB (UoN), MMED (UoN), MBA(SBS), DBA(Ongoing)

Associate Dean and Chief of Staff,

Aga Khan University Hospital, Nairobi

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Signature Date

ACKNOWLEDGEMENT

Thanks to Almighty God for the gift of life and strength that enabled me complete this project. My sincere regards go to my supervisors, Anne Wang'ombe (School of Mathematics, University of Nairobi) and Dr Majid Twahir (Associate Dean and Chief of Staff, Aga Khan University Hospital, Nairobi [AKUH, N]) for their encouragement, guidance, fruitful advice and suggestions that led to the successful completion of this project. I also commend the Department of Medicine and Critical Care leadership of the Aga Khan University Hospital, Nairobi; in particular, Hellen Munyi the Program Administrator, special thanks to Cornelia Ouma (Clinical Practice Educator, Intensive Care Unit [ICU]) and Dorcus Kipsang (Infection Control Specialist, ICU) for their dedication, time and fruitful deliberations.

My other thanks go to my family and relatives for the love and encouragement during my post graduate studies period. To my course mates and friends, I appreciate your love, friendship, advice and all the encouragement.

ABSTRACT

Background

Study was focussed on survival rates of patients admitted in acute care units who utilized medical devices known as Central Venous Catheters (CVC). CVC are useful devices in clinical care, however some infections such as Central Line Associated Bloodstream Infections (CLABSI) may occur which are associated with increased lengths of stay and costs as wells as higher morbidity and mortality rates.

Aim

The overall objective was to determine the survival probabilities and hazard rates for patients who used CVC devices and compare the subgroups by infection status.

Methodology

The study was focused on all patients who were admitted in Critical Care Units between 8th December, 2012 and 31st March, 2016 and utilized CVC devices. It was a retrospective study. Survival analysis techniques, test of equality of proportions, Man-Whitney test and Chi–square test of independence were used.

Results

A total 363 out of 1089 patients included in the study died during hospitalization. 47 patients developed nosocomial CLABSI. The average duration of 18.19 days and median of 12 days was taken by patients who did not develop a nosocomial CLABSI compared to an average of 56.79 days and a median of 51 days for those who developed. There was a significantly higher proportion of mortality by those who developed nosocomial CLABSI compared to the rest (p-value=0.01379).The results indicate that there was a significant association between infection status and the event status as well as significant difference between the survival rates of the patients based on infection status.

Conclusions

There is a significant impact on mortality and morbidity to the patients who develop the nosocomial CLABSI. The length of stay by the patients who developed CLABSI was significantly higher compared to the duration taken by patients who did not develop CLABSI, this leads to increased cost of hospitalization.

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ACRONYMS

AIC	Akaike Information Criterion
AKU	Aga Khan University
AKUH,N	Aga Khan University Hospital, Nairobi
BSc	Bachelor of Science
BSI	Bloodstream Infection
CAUTI	Catheter Associated Urinary Tract Infection
CCU	Coronary Care Unit
CDC	Centers for Disease Control
CHG	Chlorhexidine Gluconate
CI	Confidence Interval
CIC	Cumulative Incidence Curve
CLABSI	Central Line-Associated Bloodstream Infection
Cox PH	Cox Proportional Hazard
CTICU	Cardiothoracic Intensity Care Unit
CVC	Central Venous Catheter
DBA	Doctor of Business Administration
df	Degrees of Freedom
dp	Decimal place
ECMO	Extracorporeal Membrane Oxygenation
ERC	Ethics and Research committee
FH	Fleming-Harrington
HAI	Healthcare Associated Infection
HDU	High Dependency Unit
ICU	Intensive Care Unit
ICP	Infection Control Practitioner
IHI	Institute for Healthcare Improvement
IT	Information Technology
IV	Intravenous
LML	Log minus log/log - log
LOS	Length of Stay

MBA	Master of Business Administration
MBChB	Bachelor of Medicine and Surgery
MMed	Master of Medicine
MPhil	Master of Philosophy
MSc	Master of Science
NICU	Neonatal Intensive Care Unit
NNIS	National Nosocomial Infection Surveillance
UoN	University of Nairobi
PhD	Doctor of Philosophy
PICU	Paediatric Intensive Care Unit
s.e	Standard Error
SSI	Surgical Site Infection
UK	United Kingdom
US	United States
USA	United States of America
USIU	United States International University
VAP	Ventilator Associated Pneumonia

DEFINITION OF OPERATION TERMS

Admission	: date a patient is admitted into a Critical Care Unit
Critical Care Unit	: refers to acute care units in the hospital namely, Intensive Care Unit, Coronary Care Unit, High Dependency Unit and Cardiothoracic – Intensive Care Unit
Discharge	: date of discharge from the hospital by a patient on follow up, it also marks the date of patient's demise or transfer to another facility
Event	: it's a failure; in this case it refers to the death of a patient who is being followed up
Intensivist	: also known as a critical care physician is a medical doctor with special training and experience in treating critically ill patients.
Length of stay	: duration between patient's admission and discharge
Nosocomial infection	: infections that occur to a patient while still admitted in a hospital
Pathogenesis	: the origination of a disease or infection
Survival analysis	: a collection of statistical procedures for analysing data for which the outcome variable of interest is time until an event occurs
Transfer	: transfer of patients from hospital to other health facilities

CHAPTER 1

INTRODUCTION

1.0 Background

Central Line Associated Bloodstream Infection (CLABSI) is a type of infection which affects patients who utilize Central Venus Catheter (CVC) during their hospitalization. CVC refers to any central venous access device inserted into the internal jugular, sub-clavian or femoral vein that terminates in the inferior vena cava or right atrium (Vineet Chopra et al, 2013). CVCs are commonly used in Critical Care units such as the Intensive Care Unit (ICU). In accordance to The Joint Commission (2012), the CVCs are imperative in health care provision as they facilitate administration of medications, intravenous (IV) fluids, blood products, parenteral nutrition, hemodialysis and providing means of hemodynamic monitoring (The Joint Commission, 2012).The most widespread risk associated with CVCs in the hospitals is central line-associated bloodstream infections (CLABSIs) caused by microbes which colonize at the external surface of the central line device or within the fluid pathway during insertion or while the device is in use (Institute for Healthcare Improvement [IHI], 2012). According to the IHI (2012), about 90% of all CLABSIs occur due to CVCs use, resulting in increased lengths of stay, increased costs and higher morbidity and mortality rates. CLABSIs are healthcare-associated infections (HAI) associated with CVC utilization. HAI refer to infections which occur in course healthcare management in any setting (e.g., hospitals of different sizes and levels, nursing homes as well as home care). In particular, the infections acquired in hospitals during admission are referred to as nosocomial infections (Siegel et al, 2007).

In the United States of America, about 75% of all HAIs are mainly as a result of four types of infections namely; catheter associated urinary tract infections (CAUTI), CLABSI, Ventilator associated pneumonia (VAP) and the surgical site infections (SSI) (The Joint Commission, 2012). US Centers for Disease Control and Prevention (2016) observed that there was a 46% decrease in central line-associated bloodstream infections (CLABSIs) in hospitals across the U.S.A from year 2008 to 2013, however, about 30,100 CLABSIs still occur in critical care units and wards of U.S. CLABSIs are severe infections which are associated with prolongation of

length of hospitalization and increased health management cost and increased morbidity and mortality. There was a declaration by the European Union that policy on HAIs prevention be prioritized in 2008 (European Commission., 2008).

Even though Central venous catheterization may cause different complications such as infections, haemorrhage or thrombosis, the biggest danger with catheter-related infections lies in the mortality and the costs involved (Lorente et al, 2005). In the developed countries studies regarding the impact on mortality and length of stay have been done, in contrast, very few of such studies in the developing countries such as Kenya.

This proposed study is intended to provide results that explain survival for patients who use CVC devices and develop CLABSI during their duration of hospitalization and compare with those who do not develop the infection. The study shall provide results from a Kenyan private hospital, from which further future related studies can be compared with.

1.2 Statement of the problem

CLABSIs are severe infections associated with increased cost and length of hospitalization, morbidity and mortality (US Centers for Disease Control and Prevention, 2016). Globally, the risk associated with the nosocomial CLABSI is dire, even though there has been application of various strategies to reduce the impact on patients, it remains a crucial problem. Most of the published studies have been carried out in developed countries as compared to developing countries. Most of these studies have not adequately addressed the issue of survival among patients who utilize CVC as well as a result of nosocomial CLABSI.

1.3 Objectives

The overall aim is to determine the survival probabilities and hazard rates for patients who use CVC and establish factors affecting their survival and assess how they differ with the subset of the population that develops central line associated blood stream infection.

More specifically, our objectives are

1. To assess the survival probabilities for persons with CLABSI
2. To compare the survival of patients with CLABSI and central line catheterized patients with no CLABSI during the time of follow up.

3. To determine whether there is an association between infection status and event status.
4. To determine whether the proportions of experiencing the event of interest were significantly different between the two groups
5. To determine factors that affect survival of patients with CLABSI

1.4 Research questions/hypotheses

1. How does the survival probabilities for patients with nosocomial CLABSI compare with those who do not develop CLABSI.
2. Is there any significant association between the infection status and the event status?
3. How does the hazard rates for patients with CLABSI compare to those without CLABSI?
4. What are the factors that influence survival for patients who utilize CVC devices?

1.5 Justification

By conducting this study, the results shall help in identifying how survival probabilities and hazard rates compare between the infected and infection free central line catheterized patients as well as presenting the difference in the length of hospitalization between the group infected by CLABSI and the group not infected. There is little published literature in regard to CVCs use and CLABSI in developing countries as well as absence of literature especially in relation to survival analysis for patients who utilize CVC devices from those countries. De Angelis et al (2010) observed that many published studies suffered from study design aptness (De Angelis et al, 2010).

1.6 Scope

The study was conducted at Aga Khan University Hospital, Nairobi which has an adult11-bedmedical-surgical ICU, 6-bed CCU, 4-bed CT-ICU and 16-bed HDU. The study particularly focused on acute care admitted patients who utilized CVC access devices. The data was obtained retrospectively for all patients admitted between 8thDecember, 2012 and 31stMarch, 2016. Data for all patients who utilized CVC during hospitalization was included in the study.

CHAPTER 2:

LITERATURE REVIEW

2.1 Introduction

This chapter provides an assessment of available literature that is relevant to the study as well as proposed conceptual framework. The literature review contains the following sections namely; the theoretical and empirical review, conceptual framework, pathogenesis of CLABSI, critique of the existing literature and finally the research gaps.

2.2 Theoretical and empirical review

Central venous catheters (CVCs) are crucial in the current healthcare provision, allowing for the administration of medications, IV fluids, blood products, parenteral nutrition, hemodialysis and providing means of hemodynamic monitoring (The Joint Commission, 2012). CVCs are used both in-patient and out-patient clinical care management. In USA about 300 million catheter devices are used yearly; approximately 3 million of these are CVCs. CVCs are also referred to as central lines. In the United Kingdom (UK), nearly 250,000 CVCs are used annually (Iwamoto, 2009). However, use of CVCs is linked with the risk of bloodstream infection caused by microorganisms that colonize the external surface of the device used or the fluid pathway when the device is inserted or manipulated after insertion. These serious infections, termed central line–associated bloodstream infections, or CLABSIs, are associated with increased morbidity, mortality and health care associated costs.

CLABSI's risk factors according to The Joint Commission (2012) can be intrinsic or extrinsic the former referring to characteristics that cannot be modified such as age, gender, underlying morbidities or co-morbidities and the latter referring to factors which may be modified which are related to CVCs insertion or their maintenance (The Joint Commission, 2012).

According to The Joint Commission (2012), there are a variety of CVCs available in various sizes as well as different catheter materials. The CVCs can be single or multi-lumen (double, triple or quadruple lumen). Another categorization by design classifies them as tunnelled catheters, non-tunnelled catheters, peripherally inserted central catheters (PICC) and implantable ports (The Joint Commission, 2012). The choice of catheter is as a result of defined need and

preferences of the clinical care giver or the patient. Every catheter device carries with it some risk of infection, however, the extent of risk depends on the type catheter used (Maki DG et al, 2006).

Several studies have reported that, in the intensive care unit (ICU), bloodstream infections are associated with an increase in morbidity, mortality (10%-40%), length of hospital stay, and finally in medical costs. However, the consequences induced by catheter-related bloodstream infections on morbidity and mortality have not been clearly evaluated and remain under debate (Smith et al, 1991), (Martin et al, 1989), (Harley et al, 1980), Soufir et al (1999) and (Pittet et al, 1994). These controversial results are explained in part by the difficulties in estimating the mortality attributable to the blood stream infections (Soufir et al, 1999). A study on trends in Bloodstream Infections among Human Immunodeficiency Virus (HIV)–infected adults by Gilly et al (2001) in Kenya concluded that bacterium and mycobacterium were significantly associated with an underlying HIV infection (Gilly et al, 2001). A study by Blomberg et al (2007) in Tanzania among children population on antimicrobial resistance with BSI found that the mortality rate from Gram-negative BSI (45.6%) was more than twice that of Malaria (20.2%) and Gram-positive BSI (16.7%), however these figures were not particularly regarding nosocomial bloodstream infection(Blomberg et al, 2007). In another study conducted in Egypt, the CLABSI rate in Paediatric Intensive Care Unit (PICU) was 18.8 (95% CI10.9—29.9) per 1000 CL-days (O. Rasslan et al., 2012). Morgan et al (2010) conducted a five year study, he established that HAIs especially CLABSIs contributed to about one third of unexpected in-hospital mortality (2010, p. Morgan et al).

Soufir et al (1999) conducted a prospective, matched cohort study carried out from January 1, 1990, to December31, 1995, in two ICUs in Paris, France. Methods suggested were use of Analysis of Variance (ANOVA), Logistic model, Kaplan Meier approach and Cox PH Model. He concluded that for ICU survival rates, the risk of death was significantly increased in exposed as compared to unexposed patients, with a relative risk (RR) of 2.06 (95% CI, 1.16-3.68; p-value=0.01). However, there was no clear demonstration of utilization of all the analysis techniques outlined in methodology in relation to the results provided (Soufir et al, 1999).

In accordance to Garnacho-Montero et al (2008), in reference to a study they conducted, the median time from insertion of the catheter to the development of bacteremia was 10 days. Eighteen patients out of 66 patients who were in the study died in the ICU (27.3%). The study however did not report advanced analysis regarding the mortality. A study conducted by Blot et al (2002) concluded that nosocomial candidemia does not adversely affect the outcome in ICU patients in whom mortality is attributable to age, the severity of underlying disease and acute illness (Blot et al, 2002). The variation in the results of his study however could be attributed to the design of his study which sought to apply a ratio of 1:2 (Each ICU patient with microbiologically documented candidemia was matched with 2 other ICU patients with no candidemia (control).

De Angelis et al (2010) observed that the duration of hospitalization of a patients is increased chances of utilizing invasive catheter devices increases which predisposes a patient to the risk of HAI. In addition, he observed that many studies suffered from design aptness. Such studies that did not take into account the time-dependent nature of nosocomial infections (De Angelis et al, 2010).

Umscheid CA et al (2011) observed that majority of researchers have not been able to relate CLABSIs autonomously with increase in mortality due to multiple patient mortality causes such that exclusive impact of an infection may not be explicitly clear (Umscheid CA et al, 2011). Carrico and Ramírez (2007) observed that it may not be easy to determine the patients who die “with” CLABSI compared to those who die “because of” CLABSI (Carrico R, Ramírez J., 2007).

2.3 Conceptual framework

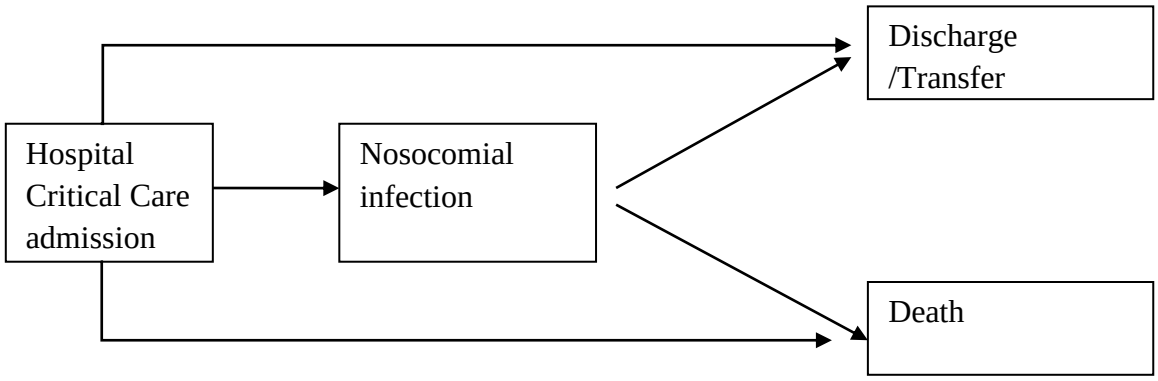


Figure 2.2: Conceptual Frame Work (De Angelis et al, 2010)

The first state; hospital critical care admission refers to the date when patients who utilized central venous catheter devices during hospitalization were admitted. The second state; Nosocomial infection, captures the date the nosocomial central line blood stream infection was detected. Discharge/transfer and death, refers to the date the admitted patients exited the hospitalization.

2.4 Pathogenesis of CLABSI

According to The Joint Commission (2012), pathogenesis refers to the origination of a disease or infection. CVCs get contaminated with microorganisms either extraluminally or intraluminally. In the former, the skin of the patient who has a central line inserted may capture the organisms migrate through the surface of the catheter device into the cutaneous tract surrounding the device which results in colonization at the tip of the catheter. On the other hand, infections acquired intraluminally, happen so through contamination of the device at along IV pathway after manipulation (The Joint Commission, 2012).

2.5 Critique of the existing literature relevant to the study

Very few studies have been carried out in developing countries thus, generalization might not be completely ideal and focused studies are needed in developing countries such as Kenya to identify survival probabilities of patients who get CVC insertion. The study shall also help in determining whether there is a significant difference in the duration of hospitalization among the infected and non-infected persons. Some of the methodologies utilised in some published studies are varied, whereas others face validity problems necessitating need for more studies. In

addition, Studies published are mostly from developed countries. Different hospitals follow distinct culture of patient safety programmes which affect outcomes of hospitalized patients.

2.6 Research gaps

The study on survival of patients in regard to central venous catheter utilization and more particularly nosocomial central line associated blood stream infections has not been adequately studied in the developing countries especially in Kenya. Various online searches did not yield any result regarding a study related to survival of Central Line Associated Bloodstream infections in Kenya, only a few studies which were not directly linked to survival modelling but mostly about neonates and or paediatrics such as Kaguongo et al (2013) on bundle implementation in a 6 bed paediatric hospital in Kenya, Blomberg et al (2007) children's antimicrobial resistance with BSI in Tanzania and O. Rasslan (2012) on catheter-associated infection rates in adult and paediatric intensive care units of hospitals in Egypt.

CHAPTER 3

METHODOLOGY

3.1 Research design

The study design was a retrospective cohort study of patients who were admitted in critical care units comprising of ICU, HDU, CT-ICU and CCU during the period running from 8th December 2012 and 30th March, 2016, being a period of about 3 years and four months. The patients included in the study were only those who utilized the Central Venous Catheters during their hospitalization. A total number of 1086 patients were included in the study. 47 patients got infected with CLABSI. The event of interest in the study was death; a total of 363 patients experienced the event during the period of study. The other patients who did not die were censored. Data was collected partly from the nursing surveillance database and partly from the hospital's electronic information management system.

3.2 Inclusion criteria

Only patients who were admitted in the Critical Care Units and utilized CVC during their hospitalization were included in the study

3.3 Exclusion Criteria

Patients who were not admitted into the critical care were not included, in addition, patients who did not utilize CVC were not included.

3.4 Population

The target population shall be Adult Critical/Intensive Care Unit admitted patients. The study population shall constitute all admitted catheterized patients with the central lines.Study period ran from January 2013 to March, 2016.

3.5 Sampling frame

Sampling frame shall consist of a list of all patients admitted in ICU who utilizedCVC devices within the period of study.

3.6 Sample and sampling technique

The study targeted data from all critical care unit admitted patients who utilized CVC devices from December 2012 to March 2016.

3.7 Instruments

Computer hardware and software shall be used to query data from the database and aggregation.

3.8 Data collection procedure

Data shall be partly obtained from an ICT database that have records of all admissions, data regarding patients who developed central line blood stream infections shall be obtained from the Unit's surveillance data. Any additional data shall be obtained from the medical files.

An Infection Control specialist nurse was involved in data collection. A blood stream infection was considered nosocomial if a recognized pathogen that is isolated from one or more per cutaneous blood cultures after 48 hrs of vascular catheterization and is unrelated to an infection at another site. The verification of the source of infection was determined by both intensivists and microbiologists by clinical evaluation.

3.9 Pilot test

A pilot test was conducted to test the appropriateness of the data collection forms and the data before final aggregation.

3.10 Analytical Methods (Data Analysis and Methods)

3.10.1 Data Quality Assurance

Once data were extracted from electronic medical records and then exported into Ms Excel. Aggregation and organization was initially carried out in Ms Excel 2010. Data were then exported into Statistical Package for the Social Sciences (SPSS v.24), R GUI (R-3.1.1) and Stata (SE 11.1) for further data management and cleaning and analysis (any additional clarification on the data was obtained from other sources of medical records). Each program was utilized to run suitable analyses as per the objectives of the study.

3.10.2 Measures utilized

Both exploratory and inferential analysis shall be undertaken. Kaplan Meier curves were used to assess the survival probabilities of exposed versus un-exposed. Log rank, Breslow, Tarone-Ware, Peto and Flemington- Harrington tests helped in testing whether the survival curves between two groups differed significantly. In addition, extended-Cox model with a time-dependent covariate and Frailty models were used. Other tests that were utilized were; Chi-Square test of association and test of equality of proportions as well as Man-Whitney test. Each of these measures has been described in detail.

3.11 Survival Analysis

3.11.1 Introduction to survival analysis

Survival analysis is a group of statistical techniques used in analysis whereby, outcome variable of interest is time it takes until an event occurs. Time could be in terms could be specified in days, months or years from the start of the follow-up of a subject until the time the specified event occurs; alternatively, survival time could also refer to age. An example of an event is death. In this study the event of interest is death, which occurred among patients who had central line devices and had been admitted in the critical care units other than paediatric or neonatal of the Aga Khan University Hospital, Nairobi between 8th December 2012 and 31st of March 2016.

In survival analysis time variable is referred to as survival time, because it gives the time that an individual has "survived" over some follow-up period. We also typically refer to the event as a failure. Hence, survival time can also be referred to as failure time or event time. Survival analyses encounter a principal analytical problem called censoring.

Censoring may be done due to:

- An individual fails to experience the event before the study ends
- An individual is lost to follow-up during the study period
- Withdrawal from the study by an individual

Censoring assumptions provide that it should be independent, random and non-informative censoring Kleinbaum et al (2011). There are at least three types of possible censoring schemes.

Right censoring is the most frequently used type of censoring. For right censored data, all that is known for some individuals is a time beyond which the subject is still alive. In the left censoring, a failure time is only known to be before a certain time while interval censoring data reflects uncertainty as to the exact time the units failed within an interval (Demissie, 2006).
In this study right censoring is the most ideal and there are three types of right censoring, i.e.

- Fixed type I censoring refers to a study ending after a given C years of follow-up.not every subject that experiences the event.
- For random type I censoring, study ends after a specified duration however subjects have different censoring times.
- In type II censoring study ends when a given number of event happens.

3.11.2 Terminology and notation

T denotes the response variable, $T \geq 0$. Let T be a random variable denoting the survival time. The distribution of survival times is characterized by any of three functions: the survival function *(S(t))*, the probability density *(f(t))* or the hazard function *(h(t))*. The survival function is defined as the probability that the survival time is greater or equal to *t* and is defined for both discrete and continuous *T* similarly; the probability density and hazard functions are easily specified for discrete and continuous *T*. Finally, we let the Greek letter delta *(δ)* denote a*(0,1)* random variable indicating either failure or censorship.

3.11.3 Survival functions

The survival function is expressed as follows

$$S(t) = Pr(T > t) = 1 - F(t)$$

The hazard function, *h(t)*, is the instantaneous rate at which events occur, given no previous events. The hazard function *h(t)* gives the instantaneous potential per unit time for the event to occur, given that the individual has survived up to time t. It is also known as conditional failure rate.

$$h(t) = \lim_{\Delta t \to 0} \frac{\Pr(t < T \leq t + \Delta t \mid T > t)}{\Delta t} = \frac{f(t)}{S(t)}$$

Hazard rate is used in providing information regarding conditional failures, in model identification and as a basis of expressing survival analysis math models.

The cumulative hazard describes the accumulated risk up to time *t*,

$$H(t) = \int_0^t h(u)d(u)$$

If we know any one of the functions *S(t)*, *H(t)*, or *h(t)*, we can derive the other two functions.

$$h(t) = -\frac{\partial \log(S(t))}{\partial t}$$

$$H(t) = -\log(S(t))$$

$$S(t) = \exp(-H(t))$$

Recording survival data with censoring

- T_i denotes the response for the i^{th} subject.
- Let C_i denote the censoring time for the i^{th} subject
- Let δ_i denote the event indicator

$$\delta_i = \begin{cases} 1 & \text{if the event was observed } (T_i \le C_i) \\ 0 & \text{if theresponse was censored } (T_i > C_i) \end{cases}$$

- The observed response is $Y_i = min(T_i, C_i)$.

Average hazard rate

$$\bar{h} = \frac{\#\ failures}{\sum_{j=1}^{n} t_j}$$

Average survival time (ignoring censorship status):

$$\bar{T} = \frac{\sum_{j=1}^{n} t_j}{n}$$

3.11.4 Kaplan Meier function

Kaplan Meier (KM) function enables estimation and drawing graphs of survival probabilities by utilization of the product limit formula. Failure times are usually ordered from the smallest to the largest. Kaplan Meier product limit formula is given by

$$\hat{S}\left(t_{(j)}\right)=\prod_{i=1}^{j}\hat{\Pr}\left[T>t_{(i)}\,|\,T\geq t_{(i)}\right]$$

3.11.5 Comparison of survival curves

3.11.5.1 The Log Rank Test

To compare two or more Kaplan Meier Curves we shall use Log rank test. The test is approximately Chi-Square particularly for large samples with *G-1* degrees of freedom, where G is the number of groups involved. Thefunction is expressed as follows

$$Log-rank\_Statistic=\frac{(O_i-E_i)^2}{\mathrm{var}\left(O_i-E_i\right)}\ \text{fori=1,2}$$

Fori^{th} group at time *j*, where *i* = 1 or 2:

Observed counts = m_{ij} ,

Expected counts = e_{ij} , where

Expected counts = (proportion in risk set) ×(# failures over both groups),

$$e_{ij}=\left(\frac{n_{ij}}{n_{1j}+n_{2j}}\right)\left(m_{ij}+m_{2j}\right)$$

n_{ij}= # at risk in i^{th} group at j^{th} ordered failure time

m_{ij} = observed # of failures in i^{th}group at j^{th} ordered failure time

e_{ij} = expected # of failures in i^{th} group at j^{th} ordered failure time

The null hypothesis to be tested is that there is no overall difference between the two survival curves.

Alternative test to Log –rank test will be Breslow (Wilcoxon) and the Tarone-Ware. In these test different weights are applied to i^{th} failure time.

3.11.5.2 Breslow (Wilcoxon)

This test weights the observed minus expected score at time t_i by the number at risk n_i over all the groups at time t_i. In this test the weights subjected at the earlier failure times are higher as compared to later failure times (David G. Kleinbaum, Mitchel Klein, 2012).

The test statistic is as follows

$$\frac{\left(\sum_j w(t_i)(m_{ij}-e_{ij})\right)^2}{\text{var}\left(\sum_j w(t_i)(m_{ij}-e_{ij})\right)}$$ forj=1, 2, I = i^{th} failure.

3.11.5.3 Tarone-Ware test statistic

Tarone-Ware test statistic also applies more weight to the early failure times by weighting the observed minus expected score at time t(i) by the square root of the number at risk $\sqrt{n_i}$.

$$\chi_{tw}{}^2 = \frac{\left[\sum_{j=1}^{k} w_j(d_{j1}-r_{j1}*d_j/r_j)\right]^2}{\sum_{j=1}^{k}\frac{w_j^2 r_{1j} r_{0j} d_j(r_j-d_j)}{r_j^2(r_j-1)}}$$

3.11.5.4 Flemington-Harrington test

This test uses the Kaplan-Meier survival estimate $\hat{S}(t)$ over all groups to calculate its weights for the i^{th} failure time. This test provides flexibility since the researcher can provide different values of p and q.

Weights are computed as below;

$$w(t) = \hat{S}(t_{(i-1)})^p[1-\hat{S}(t_{(i-1)})]^q$$

Test statistic

$$\frac{\left(\sum_j w(t_i)(m_{ij}-e_{ij})\right)^2}{\mathrm{var}\left(\sum_j w(t_i)(m_{ij}-e_{ij})\right)}$$

3.11.6 Cox Proportional Hazards (PH) Model

The Cox PH Model takes the form below. It is normally written in terms of the hazard model formula

$$h(t,\mathbf{X}) = h_0(t)e^{\sum_{i=1}^{p} B_i X_i}$$

Where *x* represents the explanatory/independent variables and $h_0(t)$, is called the baseline hazard function. The Cox model is expressed as hazard at time *t* is the product of two quantities. The first quantity, $h_0(t)$, is called the baseline hazard function whereas the second quantity is the exponent *(e)* to the linear sum of $\beta_i X_i$. The assumption is that the baseline hazard does not involve the X's and that the $h_0(t)$ is an unspecified function which leads to the Cox PH model being referred to as *semi-parametric model;* the property that makes it a popular model. Kleinbaum et al (2011) indicated that the principal basis regarding popularity of this model is because, though the baseline hazard is not specified, good estimates can be obtained.

β_i's are approximately by use of Maximum Likelihood (ML) estimates, these estimates are derived by maximizing a likelihood function (L), more specifically $L(\beta)$. However the Likelihood function is accurately referred to as partial since it considers only those subjects that experience the event of interest.

$$L = L_1.L_2.L_3...L_k = \prod_{j=1}^{k} L_j$$

Then maximize

$\frac{\partial \ln L}{\partial \beta_i} = 0$ for i=1,2,3,…,p (number of parameters)

Hazard Ratio is computed as follows;

$HR = \frac{\hat{h}(t, X^*)}{\hat{h}(t, X)}$, which is further expressed as;

$$HR = \frac{\hat{h}_0(t)e^{\sum_{i=1}^{p}\hat{\beta}_i X_i^*}}{\hat{h}_0(t)e^{\sum_{i=1}^{p}\hat{\beta}_i X_i}} = e^{\sum_{i=1}^{p}\hat{\beta}_i (X_i^* - X_i)}$$

PH assumption is that the Hazard Ratio (HR) is constant over time, or more particularly; the hazard of one individual is proportional to the hazard of any other variable being independent of time. PH assumption is evaluated by use of three approaches namely; graphical, goodness-of-fit (GOF) and time dependent approach.

3.11.7 Adjusted Survival Curves Using the Cox PH Model

Using the Cox to fit survival data, we obtain a step function just like with the Kaplan Meier curves; the difference is that the curves are as a result of adjustment for the explanatory variables.

The formula used for exposed subject survival curves is

$$\hat{S}(t, X_1) = [\hat{S}_0(t)]e^{[\hat{\beta}_1(1) + \sum_{i\neq 1}\hat{\beta}_i \bar{X}_i]}$$

And for the un-exposed subjects is;

$$\hat{S}(t, X_0) = [\hat{S}_0(t)]e^{[\hat{\beta}_1(0) + \sum_{i\neq 1}\hat{\beta}_i \bar{X}_i]}$$

A key assumption about Cox PH model is that the *hazard ratio* is constant over time. Cases where hazards curves cross, PH model becomes inappropriate.

The Cox PH Cause Specific Model is of the form

$$h_c(t, X) = h_{0c}(t)\exp\left[\sum_{i=1}^{p}\beta_{ic}X_i\right]$$

3.10.8 Extended Cox Model for Time-Dependent Covariates

A time-dependent variable is any variable whose value for a given subject may change over time.

$$h(t, X(t)) = h_0(t)\exp\left[\sum_{i=1}^{p1}\beta_i X_i + \sum_{j=1}^{p2}\delta_j X_j(t)\right]$$

X(t) = (X_1,X_2,…,X_{p1}>Time – independent, $X_1(t)$,$X_2(t)$,$X_3(t)$,…$X_{p2}(t)$> time-dependent.

3.11.9 Parametric Survival Models

In parametric survival models, survival time is assumed to follow a known distribution. The following distributions are commonly utilized in models of the survival data; Exponential, Weibull, Lognormal, Log- logistic and Generalized gamma. An Accelerated Failure Time (AFT) model is applied in comparing hazards which assumes that the effect of covariates is multiplicative with respect to the survival time.

Exponential model;

Survival function is given by; $S(t) = e^{-\lambda t}$

Hazard function is $h(t) = \lambda$

Weibull model;

The survival function is provided as follows,

$S(t) = e^{-\lambda t^p}$ where P>1, λ>1 and

The hazard function

$h(t) = \lambda p t^{p-1}$ where $\lambda = e^{\sum_{i=0}\beta_i X_i}$

Acceleration Factor Model usually describes stretching out or contraction of the survival time when comparing one group from another it is denoted by γ. We illustrate by expressing t in terms of other variables using the exponential function.

$$t = \left[-\ln\left(S\left(t\right)\right)\right] * \frac{1}{\lambda}$$

We let $\frac{1}{\lambda} = e^{(\alpha_0 + \alpha_1 X)}$, where X is a binary variable.

By letting S(t)=q and the Acceleration factor γ(X=1 vs X=0), we get

$$\gamma = \frac{\left[-\ln(q)\right] e^{(\alpha_0 + \alpha_1)}}{\left[-\ln(q)\right] e^{(\alpha_0)}} = e^{\alpha_1}$$

AFT assumption is that $S_2\left(t\right) = S_1\left(\gamma t\right)$ and the Weibull distribution, which the commonest distribution used in parametric models, has an important property which follows that if the AFT assumption holds then the Proportion Hazards (PH) assumption also holds. In cases where the KM plot of the log – log survival function against the plot of log of time is approximately linear (straight lines and parallel) then the Weibull assumption is reasonable.

3.11.10 Parametric Approach using Frailty models

Frailty is a random component that accounts for extra variability due to unobserved factors in the model. The frailty component is denoted by α which is unobserved multiplicative effect on the hazard function. The α follows a distribution g(α) with α>0 and E(α)=1. The Var (α)=θ, usually estimated from the data. Stata provides procedures for running frailty models using gamma and inverse – Gaussian.

Hazard accustomed on frailty, $h(t \mid \alpha) = \alpha h(t)$

Survival accustomed on frailty, $S(t \mid \alpha) = S(t)^{\alpha}$

The unconditional survival with gamma frailty is provided below

$$S_U(t) = \int_0^{\infty} S(t \mid \alpha) g\{\alpha\} dx$$

And the corresponding hazard

$$h_U(t) = \frac{-d[S_U(t)]/dt}{S_U(t)}$$

The unconditional hazard with gamma frailty can be expressed as;

$h_U(t) = \frac{h(t)}{1-\theta \ln[S_U(t)]}$ if θ=0, then $h_U(t)$=h(t) indicating no frailty.

3.12 Test of equality of proportions

We consider the difference in the two proportions to be given by

$d = \frac{x_1}{n_1} - \frac{x_2}{n_2}$, which will be approximately normally distributed with mean zero and

Variance $V_p(d) = \left(\frac{1}{n_1} + \frac{1}{n_2}\right) * P(1-p)$ if the counts are binomially distributed with the same

*p*arameter.

So to test the hypothesis that $p_1 = p_2$,

The common estimate $\hat{p} = \frac{x_1 + x_2}{n_1 + n_2}$ into the variance formula

We can then use $u = \frac{d}{\sqrt{v_{\hat{p}}(d)}}$ which approximately follows normal distribution or U^2 which

follows Chi-square distribution.

3.13 Chi Square test of Independence

The chi square test of independence is a test used to determine whether there is a significant association between two categorical variables. Chi square statistic is given by

$\chi^2 = \frac{\sum_i (O-E)^2}{E}$ with (r-1)(c-1) df

And $E_{ij} = \frac{n_{i.} * n_{.j}}{n_{..}}$

3.14 Ethical Consideration

Authority to conduct the study was sought from the Aga Khan University Hospital, Nairobi, a submission of research proposal was done to the Kenyatta National Hospital/ University of Nairobi Ethical and Research committee to review the proposal and thereafter issue a letter of affiliation. An affiliation letter will then be sent to the Ethics and Research Committee of Aga Khan University Hospital, Nairobi for authorization. In addition the head of department the Critical Care was involved. Privacy and confidentiality will be maintained by ensuring the information gathered is not relayed to anyone, but used for this study only. Patients' names will not include in the data collected and only an identification number. No risks will be subjected to the patients. Direct benefit is not intended to the study population; however the results will be useful in terms of adding knowledge to the existing research.

3.15 Protection of data and health records

Raw data will be utilized electronically and the computer used in data analysis is personalized with locked folders with password for access. No public computer shall be utilized in data aggregation or analysis.

3.16 Dissemination Plan

For the study results will be done through the School of Mathematics, University of Nairobi as well as Research Support Unit, Aga Khan University.

3.17 Study Limitations

The data having two subgroups of which one group (with the nosocomial CLABSI) had a very small proportion of 4.3% of the total number patients who fit the criteria of inclusion, this small proportion may not yield desired results in model fitting. Getting enough data that can be used to provide data for stratification analysis by discharge diagnosis specific survival and hazard rates would require a longer period of data collection. Getting published journals from studies carried out in Kenya as a country and African continent especially in regard to survival analysis modelling in relation use of CVC devices were not available.

CHAPTER 4

RESULTS AND ANALYSIS

4.0 Introduction

This chapter provides the results obtained from the survival dataset of the study. The event of interest was death after hospitalization for the patients who were admitted in the Critical Care units (ICU, HDU, CT-ICU and CCU) and utilized Central Venous Catheters during their hospitalization.

4.1 Study participants profile

A total of 1086 patients were included in the study. Patient's inclusion into the study was based on admission into the critical care units and utilization of the Central Venous Catheter (CVC) devices during the period of hospitalization and having been on admission for at least 48 hours. In terms of gender, the number of males were 648 (59.7%) and females 438(40.3%) who fit the criteria for inclusion into the study.363 patients experienced the event of interest (death). 47 patients developed nosocomial central line associated blood stream infection during their hospitalization, Interventists and microbiologists were involved in determination of Central Line Associated Blood Stream Infection (CLABSI) occurrence. CLABSI was classified as nosocomial if it occurred after 48 hours of admission and upon utilization of CVC as an access device.

Table 1: Summary of study participant's demographics

Variable	Values	Frequency (F)	Proportion (%)
Event Status	Censored	723	66.6%
	Event	363	33.4%
Gender	Male	648	59.7%
	Female	438	40.3%
Infection status	Yes	47	4.3%
	No	1039	95.7%

4.2 Exploratory data analysis.

4.2.1 Summary statistics by infection status and length of stay

The table below demonstrates survival time summary statistics disaggregated by infection status. Time was measured in terms of days. The average duration of 18.19 days (s.e 0.611)was taken by patients who did not develop a nosocomial CLABSI compared to an average of 56.79 days (s.e of 5.171) taken by those who got an infection. Median days taken by the infected group were 51 days whereas those taken by non-infected group were 12 days.

Table 2: Summary Statistics by infection status

	Length of stay						
Infection Status	Mean	N	Std. Deviation	Std. Error of Mean	Median	Minimum	Maximum
No	18.19	1039	19.701	.611	12.00	3	202
Yes	56.79	47	35.450	5.171	51.00	6	149
Total	19.86	1086	22.054	.669	12.00	3	202

4.2.2 Summary statistics based on age distribution

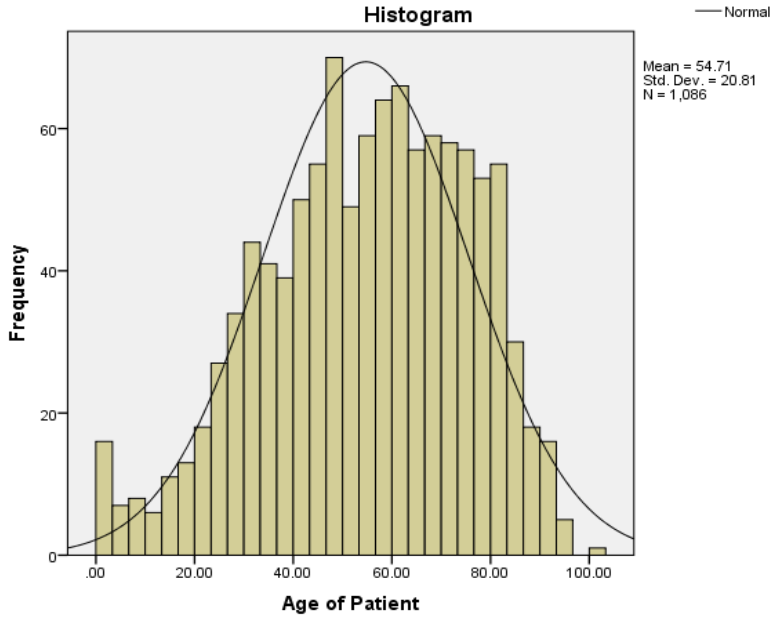
The average age of patients included in the study was 54.7 years (s.e 0.631 years), median of 56.5 years and a mode of 64 years.

Table 3: Summary statistics by age of patients

Patients total	1086
Mean	54.7124
Std. Error of Mean	.63148
Median	56.4819
Mode	64.00
Std. Deviation	20.81021
Variance	433.065

The Figure 1 below shows patient's age distribution, which depict that age data deviate from normal distribution.

Figure 1: Histogram of Patient's age distribution



A Shapiro Wilk and Kolmorgorov Smirnov tests conducted on the data indicate that data are not normally distributed (see **Error! Reference source not found.**).

Table 4: Tests of Normality for the age variable

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Age of Patient	.044	1086	.000	.981	1086	.000

a. Lilliefors Significance Correction

4.2.3 Summary statistics based on the number of CVC devices utilized

The number of CVC devices utilized during hospitalization was captured. A summary of the results is given in Table 5. The average number of devices used was 2.08. Majority of patients used only a single CVC device during their admission, depicted by a mode of one CVC device.

Table 5: Number of CVC utilized

Patients total	1086
Mean	2.08
Std. Error of Mean	.067
Median	1.00
Mode	1
Std. Deviation	2.221
Variance	4.934

4.3 Tests of association

4.3.1 Test of association between infection status and event (discharge) status

Test of association was conducted to find out if there was a significant association between infection and discharge status, where discharge status referred to either the patient was discharged alive or died (experienced the event of interest). Chi-square test of independence was used.

The null and alternative hypotheses were as follows;

H_0: There is no significant association between the discharge status and the infection status

H_1: There is a significant association between the discharge status and infection status.

The tests were carried out at 5% level of significance.

Table 6: Test of association between discharge and infection status

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)
Pearson Chi-Square	6.868	1	.009	
Continuity Correction	6.065	1	.014	
Likelihood Ratio	6.480	1	.011	
Fisher's Exact Test				.011
Linear-by-Linear Association	6.862	1	.009	
N of Valid Cases	1086			

The results depict a chi-square statistic of 6.868 at 1 df. The p-value was 0.009 which is significant at 5% level. We therefore conclude that there is a significant statistical association between the infection status and the event (discharge) status at 5% level.

4.3.2 Test of association between gender and event (discharge) status

Test of association was conducted to find out if there was a significant association between the gender of the patient and the discharge status. Chi Square test of independence was used.

The null and alternative hypotheses were as follows;

Ho: There is no significant association between the gender of the patient and the discharge status

H_1: There is a significant association between the gender of the patient and the discharge status.

The tests were carried out at 5% level of significance.

Table 7: Test of association between gender of the patient and discharge status

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)
Pearson Chi-Square	.705	1	.401	
Continuity Correction	.599	1	.439	
Likelihood Ratio	.707	1	.401	
Fisher's Exact Test				.431
Linear-by-Linear Association	.704	1	.401	
N of Valid Cases	1086			

The results depict a chi-square statistic of 0.705 at 1 df. The p-value was 0.401 which is not significant at 5% level. We therefore conclude that there is no significant association between the gender of the patient and the discharge status at 5% level.

4.3.3 Test of association between the gender of the patient and the infection status

Test of association was conducted to find out if there was a significant association between the gender of the patient and the infection status. Chi-square test of independence was used.

The null and alternative hypotheses were as follows;

H_o: There is no significant association between the gender of the patient and the infection status

H_1: There is a significant association between the gender of the patient and the infection status.

The tests were carried out at 5% level of significance.

Table 7: Test of association between gender of the patient and the infection status

Chi-Square Tests

	Value	Df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)
Pearson Chi-Square	1.446[a]	1	.229	
Continuity Correction[b]	1.104	1	.293	
Likelihood Ratio	1.486	1	.223	
Fisher's Exact Test				.287
Linear-by-Linear Association	1.445	1	.229	
N of Valid Cases	1086			

The results depict a Chi-square statistic of 1.446 at 1 df. The p-value was 0.229 which is not significant at 5% level. We therefore conclude that there is no significant association between the gender of the patient and the infection status at 5% level.

4.4 Test of equality of proportions of death between CLABSI infected and group not infected by CLABSI

A test of equality of proportions was conducted by comparing the proportion of patients who died after developing the nosocomial CLABSI against the proportion of patients who died having not developed the nosocomial CLABSI. The null hypothesis was that the proportions of experiencing the event (death) of interest between the two groups were equal. The alternative hypothesis was that the proportions were significantly different. The measure was at 5% level of significance.

We denote P1 as the estimate for the proportion of patients who die after developing a nosocomial CLABSI and P2 as an estimate of the proportion of patients who die having not developed the nosocomial CLABSI.

H_o: $P_1=P_2$

H_1: $P_1 \neq P_2$

The results were as follows;

	Value of proportions	**Chi-square value**	**P-Value**	**95% CI**	
Prop 1	0.5106383	6.0647	0.01379	0.02751508	0.34121099
Prop 2	0.3262753				

Chi-square statistic was 6.0647 at 1 df the p-value was 0.01379 which is less than 0.05. This indicates that we do reject H_o and conclude that the proportions between the two groups are significantly different at 5% level. This indicates that CLABSI subjects a patient to a higher mortality rate as compared to patients who do not get the infection.

4.5 Survival Probabilities using Kaplan Meier method

We explored the following assumptions of Kaplan Meier

i. The event status consisted of two mutually exclusive events (death or being discharged alive)
ii. The survival time was clearly defined and precisely measured in terms of days.
iii. Data only comprised of right censored observations.
iv. Censoring was independent.

v. There were no secular trends, the patient's entered into the study were those admitted in critical care units and utilized CVC devices and were followed until their time of discharge.

vi. There was censorship in both groups, namely; infected and non-infected group. As shown in Table 8 below, both groups had censored subjects, infected had 48.9% censorship whereas non-infected had 67.4% censorship.

Table 8: Crosstabulation between infection status and discharge (event) status

Infection Status	Discharge (Event) status		Total	Censorship (%)
	Event	Censored		
No	339	700	1039	67.4%
Yes	24	23	47	48.9%
Overall	363	723	1086	66.6%

4.5.1 Exploring Survival probabilities plots

Assessing Kaplan Meier (KM) curve for all subjects (see **Error! Reference source not found.**), in the initial period of about 50 days after admission, survival probabilities decline at relatively more close ranges as compared the period after 50 days. The overall mean time estimate was 70.72 days (95% CI; 60.362, 81.084) and the overall median time estimate was 44 days (95% CI; 36.49, 51.51).

Figure 2: Survival Probabilities for all patients who used CVC in Critical Care

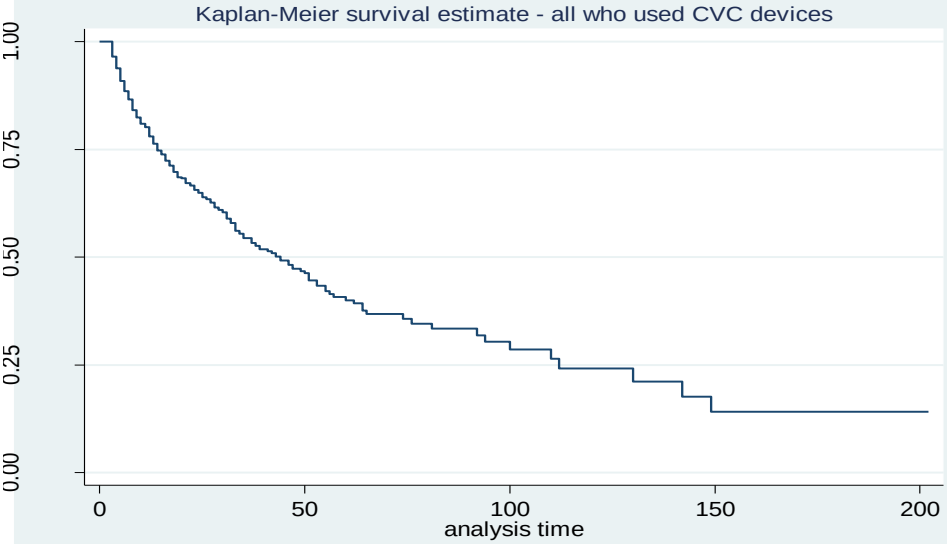


Table 9: Means and Medians for Survival Time

Infection Status	Mean[a]				Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
No	76.376	6.513	63.610	89.141	43.000	4.127	34.911	51.089
Yes	83.807	8.380	67.382	100.232	76.000	19.982	36.836	115.164
Overall	70.723	5.286	60.362	81.084	44.000	3.832	36.490	51.510

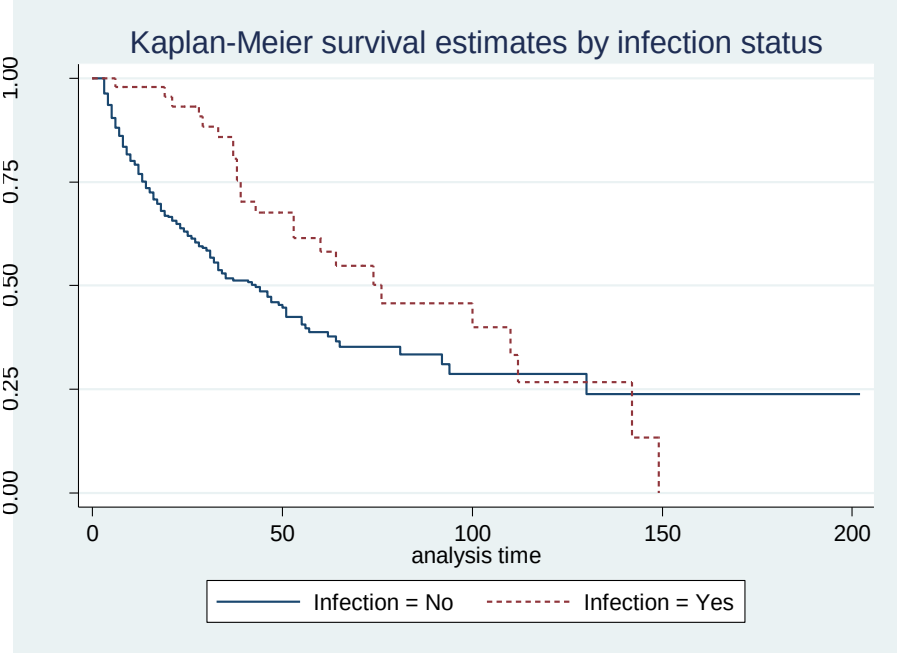
a. Estimation is limited to the largest survival time if it is censored.

The Kaplan Meier curves shown in Figure 3 depict that at the initial stages, there are higher probabilities of survival among the patients with CLABSI as compared to the group of patients with no CLABSI. However, this trend changes after about 113 days where the survival probabilities of the group not infected are higher. At about 140 days of admission, the survival probabilities of infected group decline sharply. The small sample of the patients with nosocomial CLABSI compared to the rest (with no CLABSI) may have contributed to this pattern.

The median number of days estimates for the group which did not have nosocomial CLABSI were43 days (95% CI; 34.911, 51.089) and whereas for the group which developed a nosocomial CLABSI was 76 days (95% CI; 36.836, 115.164) (see

Table 9). On the other hand, the average number of days estimates were76.376days (95% CI; 63.610, 89.141) and 83.807days (95% CI; 67.382, 100.232) for non-infected and infected groups respectively.

Figure 3: Survival Curves by Infection status



4.5.2 Tests on the survival curves

We used five tests to test whether the survival curves were the same in relation to the two infection statuses. The tests are Log Rank (Mantel-Cox), Breslow (Generalized Wilcoxon),Tarone-Ware, Peto and Fleming-Harrington. The null hypothesis was that all survival curves are the same versus an alternative hypothesis that all the survival curves are different. The tests were performed at 5% level of significance. Results from all the five tests show that the survival curves are significantly different as depicted in Table 11 below.

Table 11: Tests on Survival Curves

Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	6.364	1	0.0116
Breslow (Generalized Wilcoxon)	13.954	1	0.0002
Tarone-Ware	13.326	1	0.0003
Peto-peto	11.47	1	0.0007
Fleming-Harrington*	11.23	1	0.0008

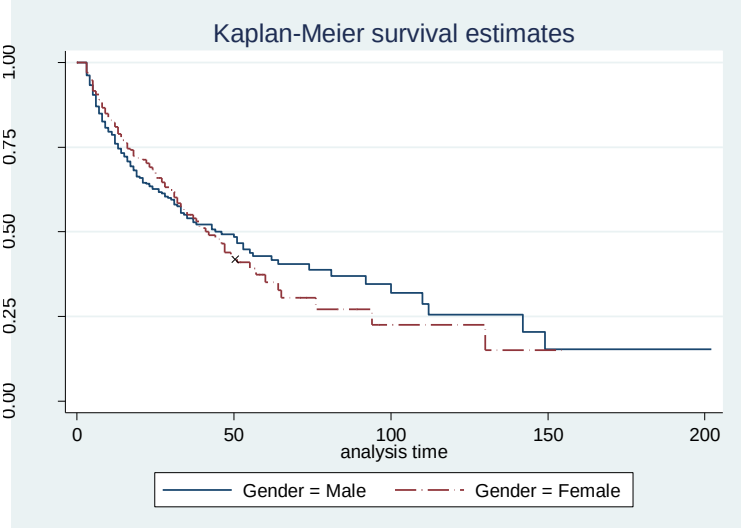
Tests on survival curves were based on; Log Rank statistic (χ^2_1) which obtained a chi square value of 6.364 p-value(0.0116),Breslow (Generalized Wilcoxon) had a χ^2_1=13.95 (p-value =0.0002),Tarone-Ware had a χ^2_1=13.326(0.0003), Peto had χ^2_1=11.47 (0.0007) and Fleming-Harrington had a χ^2_1=11.47 (0.0008)all of which are significant at 5% level depicting that the two survival curves based on the infection status are different.

Test on survival time in relation to the infection status was conducted using a two sample Wilcox on rank sum test (Mann–Whitney test) which is a distribution free/non parametric method. The v alue of test statistic was 6112.5anda corresponding-value < 2.2e-16, which is indicates that it is si gnificant at 5% level. We can hence deduce that there is a significant difference between the leng th of stay by the patients who develop nosocomial CLABSI compared to the patients who do not develop the infection.

4.5.3 Stratification by gender

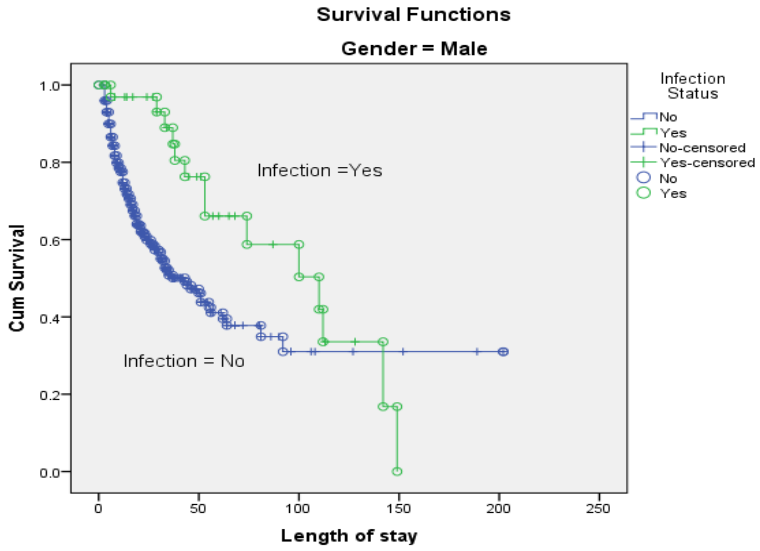
Stratification by gender yielded the following survival curves for male and female. The survival probabilities for the female subgroup were higher at the initial phase of about 40 days after admission after which the male's survival rates remained higher until the end.

Figure 4: Survival curves comparison by gender



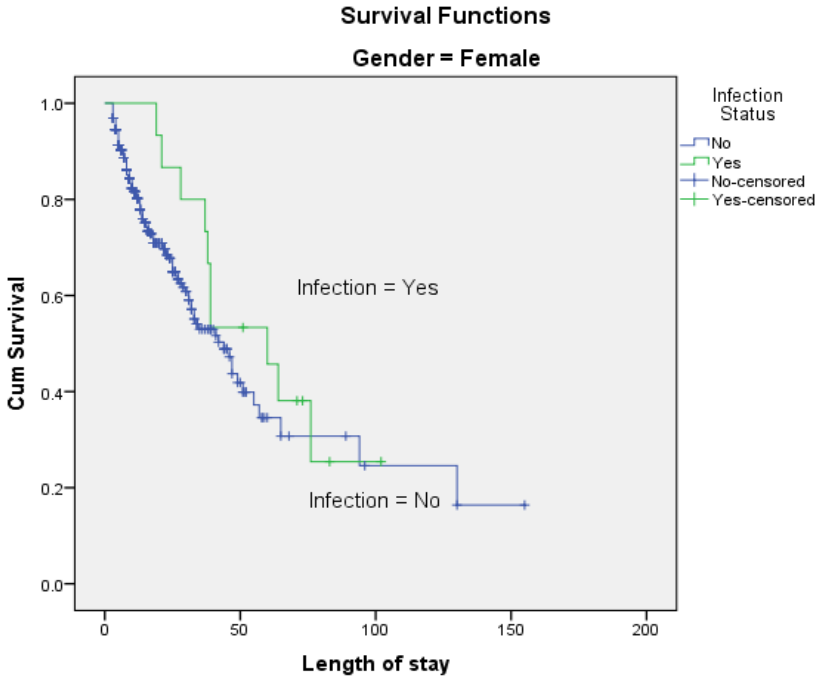
Assessing the male curve separately, higher survival ratesfor the CLABSI infected group are evident at the initial phases as compared the group not infected, then at about 140 days the infected group survival probabilities decrease sharply as compared to the group not infected.

Figure 5: KM Curve - Male stratum



Female stratum (seeFigure 6) similarly indicates higher survival rates of patients in the group that had nosocomial CLABSI at the initial stages up to about 80 days where the group without nosocomial blood stream infection surpassed infected group. It is however noted the small sample size of the infected group could have led to the existing plot.

Figure 6: KM curve - Female stratum



Stratification by gender further provided the below summary statistics for the proportion of censored patients. In both strata, the group not infected produced a higher proportion of censored events; this is indicative that a higher proportion of patients who developed an infection ended up experiencing the event of interest (death).

Table 10: Stratification by gender frequencies summary

Gender of the patient	Infection Status	Total N	N of Events	Censored	
				N	Percent
Male	No	616	209	407	66.1%
	Yes	32	14	18	56.2%
	Overall	648	223	425	65.6%
Female	No	423	130	293	69.3%
	Yes	15	10	5	33.3%
	Overall	438	140	298	68.0%
Overall	Overall	1086	363	723	66.6%

The overall average duration by male patients was 73.69 days (95% CI; 60.970, 86.958) whereas that of female patients was 59.9 (95% CI, 60.970, 86.958). The average duration taken by the male patients who got infected by CLABSI was 94.324 days (95% CI; 73.6, 115.0) whereas that of female patients was 59.904 days (95% CI; 48.7, 71.1). Median on the other hand was 46 days (95% CI; 34.8, 57.2) for male patients and 42 days (95% CI; 33.5, 50.5) for female patients.

Table 11: Means and Medians for Survival Time

Gender of the patient	Infection Status	Mean[a]				Median			
		Estimate	Std. Error	95% CI		Estimate	Std. Error	95% CI	
Male	No	82.564	7.793	67.289	97.838	43.0	5.580	32.063	53.937
	Yes	94.324	10.570	73.607	115.040	110.0	27.575	55.953	164.047
	Overall	73.964	6.630	60.970	86.958	46.0	5.709	34.811	57.189
Female	No	61.274	6.514	48.507	74.042	44.0	5.260	33.690	54.310
	Yes	59.737	7.987	44.082	75.391	60.0	11.923	36.631	83.369
	Overall	59.904	5.708	48.716	71.092	42.0	4.330	33.514	50.486
Overall	Overall	70.723	5.286	60.362	81.084	44.0	3.832	36.490	51.510

a. Estimation is limited to the largest survival time if it is censored.

4.5.4 Tests on the survival curves with respect to infection status adjusted for gender

Tests on survival curves by infection status after adjusting for gender using the three tests displayed on Table 12below indicate that the survival curves were all significantly different at 5% level. The null hypotheses are that all the survival curves are the same.

The tests on curves with respect to infection status after adjusting for the gender Log Rank (Mantel-Cox) χ^2_1 =6.499 (p-value =0.011),Breslow (Generalized Wilcoxon) χ^2_1 =13.995 (p-value=0.000[3dp]) and Tarone-Ware χ^2_1 =13.607(0.000[3dp]). Hence all the survival curves were different.

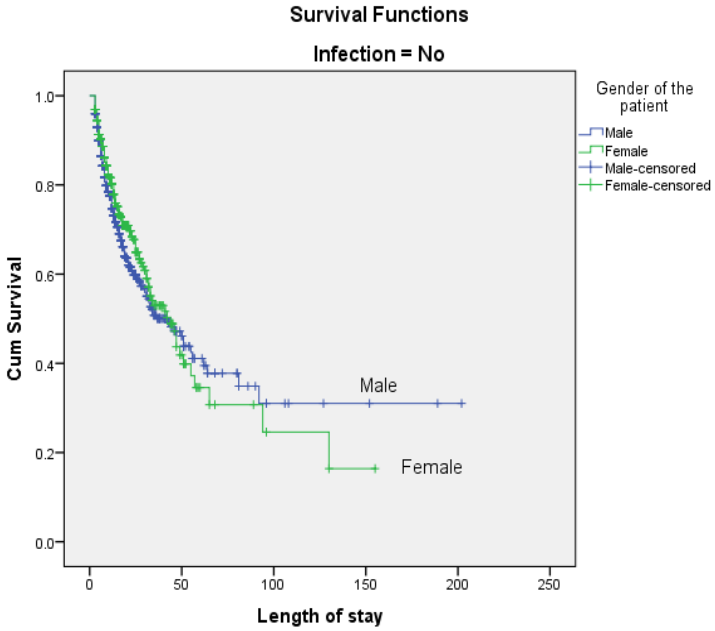
Table 12: Gender adjusted survival curves tests

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	6.499	1	.011
Breslow (Generalized Wilcoxon)	13.995	1	.000
Tarone-Ware	13.607	1	.000

4.5.6 Tests on the survival curves with respect to gender adjusted for infection status

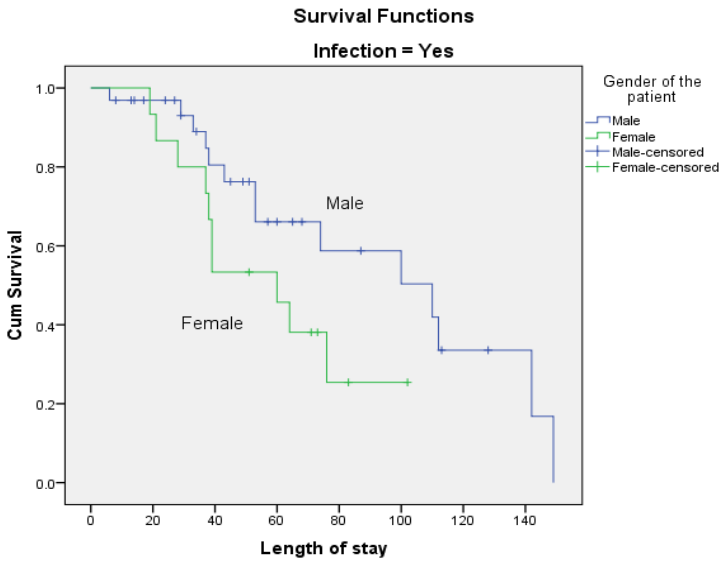
We assess first the group with no infection; initially both male and female patients indicate similar survival rates from the beginning of the admission period up to about the tenth day of admission. After approximately the tenth day the female subgroup seem to portray higher survival rates as compared to the male gender up to about 45th day of admission. After 45days the female's survival rate decreases as compared to the male's subgroup (see Figure 7).

Figure 7: Survival curves with respect to gender stratified by infection status (infection = no)



Stratification by patients who developed nosocomial CLABSI indicates that initially both male and female experienced similar survival rates up to approximately 6 days where the survival rates for male remain higher as compared to that of female subgroup (see Figure 8). This indicates that among the individuals who become infected by CLABSI, the male patients generally have higher survival rates as compared to the female patients.

Figure 8: Survival curves with respect to gender stratified by infection status (infection = yes)



Three pair wise tests were conducted on survival curves with respect to gender after adjusting for infection status. The null hypothesis was that the survival curves were the same measured at 5% level of significance. Results indicate that all the three tests were not significant at 5% level (see Table 13). Log Rank (Mantel-Cox), Breslow (Generalized Wilcoxon) and Tarone-Ware provided respective Chi Square statistics of 0.429, 3.146 and 2.408 each at 1 d.f with the p-values of 0.512, 0.076 and 0.121 respectively.

Table 13: Survival curves comparisons by gender after adjusting for infection status

Pairwise Comparisons[a]					
Test	Gender of the patient	Male		Female	
		Chi-Square	Sig.	Chi-Square	Sig.
Log Rank (Mantel-Cox)	Male			.429	.512
	Female	.429	.512		
Breslow (Generalized Wilcoxon)	Male			3.146	.076
	Female	3.146	.076		
Tarone-Ware	Male			2.408	.121
	Female	2.408	.121		

4.6 Survival Probabilities

This section portrays the survival tables for all the patients studied as well as for specific subgroups

4.6.1 Survival Probabilities tables

The survival table for all the patients who got admitted into the critical care units and utilized the CVC device is as provided in Table 14 below.

Table 14: Survival Table for Patients who utilized the CVC devices during hospitalization

Time	Beg. Total	Fail	Survivor Function	Std. Error	[95% Conf. Int.]	
0	0	0	1.0000	.	.	.
5	975	97	0.9090	0.0088	0.8901	0.9248
10	659	91	0.8091	0.0127	0.7828	0.8325
15	472	49	0.7384	0.0151	0.7076	0.7666
20	340	31	0.6829	0.0169	0.6484	0.7148
25	265	19	0.6396	0.0186	0.6020	0.6747
30	210	13	0.6038	0.0200	0.5633	0.6417
35	161	19	0.5439	0.0223	0.4992	0.5864
40	129	7	0.5179	0.0233	0.4714	0.5624
45	108	6	0.4922	0.0244	0.4436	0.5389
50	89	6	0.4624	0.0258	0.4113	0.5120
55	67	7	0.4206	0.0279	0.3656	0.4746
60	56	3	0.4002	0.0289	0.3433	0.4563
65	45	4	0.3681	0.0308	0.3081	0.4281
70	42	0	0.3681	0.0308	0.3081	0.4281
75	33	1	0.3569	0.0318	0.2951	0.4191
80	31	1	0.3458	0.0327	0.2824	0.4099
85	27	1	0.3339	0.0337	0.2689	0.4000
90	23	0	0.3339	0.0337	0.2689	0.4000
95	21	2	0.3035	0.0368	0.2333	0.3765
100	17	1	0.2857	0.0387	0.2125	0.3630
105	16	0	0.2857	0.0387	0.2125	0.3630
110	13	1	0.2637	0.0415	0.1863	0.3473
115	11	1	0.2417	0.0435	0.1620	0.3303
120	11	0	0.2417	0.0435	0.1620	0.3303
125	11	0	0.2417	0.0435	0.1620	0.3303
130	8	1	0.2115	0.0474	0.1273	0.3101
135	8	0	0.2115	0.0474	0.1273	0.3101
140	8	0	0.2115	0.0474	0.1273	0.3101
145	6	1	0.1763	0.0509	0.0902	0.2858
150	5	1	0.1410	0.0515	0.0594	0.2569
155	3	0	0.1410	0.0515	0.0594	0.2569
160	3	0	0.1410	0.0515	0.0594	0.2569
165	3	0	0.1410	0.0515	0.0594	0.2569
170	3	0	0.1410	0.0515	0.0594	0.2569
175	3	0	0.1410	0.0515	0.0594	0.2569
180	3	0	0.1410	0.0515	0.0594	0.2569
185	3	0	0.1410	0.0515	0.0594	0.2569
190	2	0	0.1410	0.0515	0.0594	0.2569
195	2	0	0.1410	0.0515	0.0594	0.2569
200	2	0	0.1410	0.0515	0.0594	0.2569

Note: survivor function is calculated over full data and evaluated at indicated times; it is not calculated from aggregates shown at left.

Survival table for the group which got infected by CLABSI is as provided in

Table 15.

Table 15: Survival Table for the infected group

Time	Beg.Total	Fail	Survivor Function	Std. Error	[95% Conf. Int.]	
0	0	0	1.0000	.	.	.
5	0	0	1.0000	.	.	.
10	46	1	0.9787	0.0210	0.8584	0.9970
15	44	0	0.9787	0.0210	0.8584	0.9970
20	42	1	0.9554	0.0309	0.8330	0.9887
25	40	1	0.9321	0.0379	0.8038	0.9776
30	37	2	0.8831	0.0493	0.7410	0.9497
35	34	1	0.8578	0.0540	0.7099	0.9337
40	29	6	0.7019	0.0726	0.5339	0.8190
45	26	1	0.6759	0.0744	0.5069	0.7978
50	25	0	0.6759	0.0744	0.5069	0.7978
55	22	2	0.6144	0.0793	0.4410	0.7484
60	19	1	0.5821	0.0815	0.4073	0.7218
65	16	1	0.5478	0.0836	0.3720	0.6934
70	15	0	0.5478	0.0836	0.3720	0.6934
75	12	1	0.5022	0.0882	0.3213	0.6584
80	11	1	0.4565	0.0912	0.2747	0.6214
85	10	0	0.4565	0.0912	0.2747	0.6214
90	9	0	0.4565	0.0912	0.2747	0.6214
95	9	0	0.4565	0.0912	0.2747	0.6214
100	8	1	0.3995	0.0960	0.2158	0.5775
105	7	0	0.3995	0.0960	0.2158	0.5775
110	6	1	0.3329	0.1005	0.1521	0.5261
115	4	1	0.2663	0.1000	0.0994	0.4684
120	4	0	0.2663	0.1000	0.0994	0.4684
125	4	0	0.2663	0.1000	0.0994	0.4684
130	3	0	0.2663	0.1000	0.0994	0.4684
135	3	0	0.2663	0.1000	0.0994	0.4684
140	3	0	0.2663	0.1000	0.0994	0.4684
145	2	1	0.1332	0.1066	0.0124	0.3962
150	1	1	.	.	.	.
155	1	0	.	.	.	.

Note: survivor function is calculated over full data and evaluated at indicated times; it is not calculated from aggregates shown at left.

The survival table for the patient group who did not get infected by CLABSI is as shown in Table 16.

Table 16: Survival table for patient with no CLABSI

Time	Beg.Total	Fail	Survivor Function	Std. Error	[95% Conf. Int.]	
0	0	0	1.0000	.	.	.
5	928	97	0.9048	0.0092	0.8851	0.9213
10	614	90	0.8004	0.0132	0.7730	0.8249
15	429	49	0.7245	0.0158	0.6921	0.7541
20	299	30	0.6658	0.0178	0.6295	0.6994
25	226	18	0.6193	0.0197	0.5795	0.6566
30	175	11	0.5843	0.0212	0.5415	0.6246
35	128	18	0.5172	0.0240	0.4692	0.5631
40	102	1	0.5128	0.0242	0.4644	0.5591
45	82	5	0.4855	0.0258	0.4340	0.5350
50	65	6	0.4463	0.0283	0.3903	0.5007
55	47	5	0.4063	0.0310	0.3454	0.4663
60	37	2	0.3878	0.0322	0.3248	0.4504
65	29	3	0.3524	0.0352	0.2841	0.4212
70	27	0	0.3524	0.0352	0.2841	0.4212
75	22	0	0.3524	0.0352	0.2841	0.4212
80	21	0	0.3524	0.0352	0.2841	0.4212
85	19	1	0.3338	0.0379	0.2609	0.4083
90	15	0	0.3338	0.0379	0.2609	0.4083
95	13	2	0.2862	0.0451	0.2016	0.3762
100	12	0	0.2862	0.0451	0.2016	0.3762
105	12	0	0.2862	0.0451	0.2016	0.3762
110	8	0	0.2862	0.0451	0.2016	0.3762
115	8	0	0.2862	0.0451	0.2016	0.3762
120	8	0	0.2862	0.0451	0.2016	0.3762
125	8	0	0.2862	0.0451	0.2016	0.3762
130	6	1	0.2385	0.0575	0.1362	0.3567
135	6	0	0.2385	0.0575	0.1362	0.3567
140	6	0	0.2385	0.0575	0.1362	0.3567
145	6	0	0.2385	0.0575	0.1362	0.3567
150	6	0	0.2385	0.0575	0.1362	0.3567
155	3	0	0.2385	0.0575	0.1362	0.3567
160	3	0	0.2385	0.0575	0.1362	0.3567
165	3	0	0.2385	0.0575	0.1362	0.3567
170	3	0	0.2385	0.0575	0.1362	0.3567
175	3	0	0.2385	0.0575	0.1362	0.3567
180	3	0	0.2385	0.0575	0.1362	0.3567
185	3	0	0.2385	0.0575	0.1362	0.3567
190	2	0	0.2385	0.0575	0.1362	0.3567
195	2	0	0.2385	0.0575	0.1362	0.3567
200	2	0	0.2385	0.0575	0.1362	0.3567

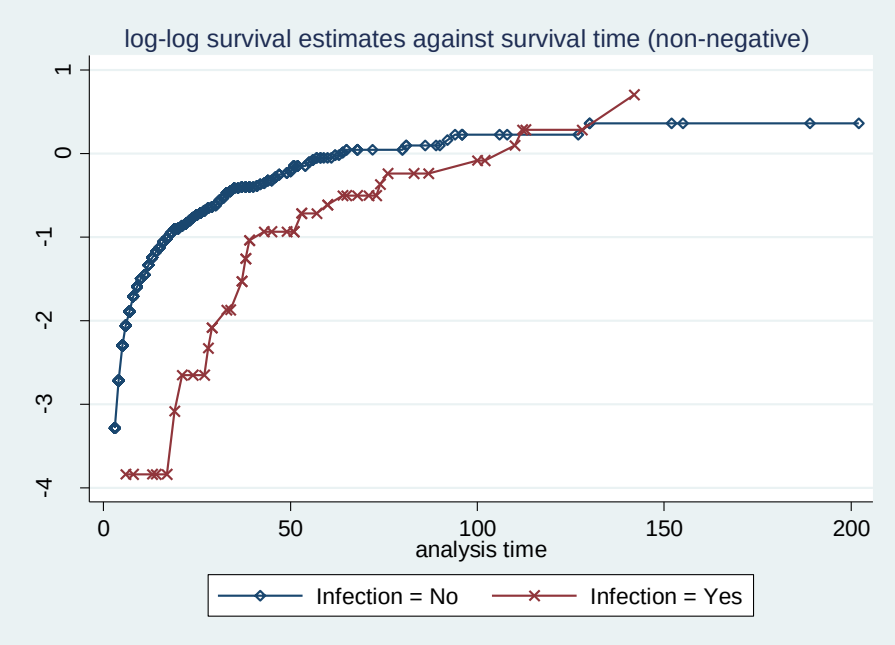
Note: survivor function is calculated over full data and evaluated at indicated times; it is not calculated from aggregates shown at left.

4.7 Assessment of the PH Assumptions

4.7.1 Graphical techniques – Log minus log plots

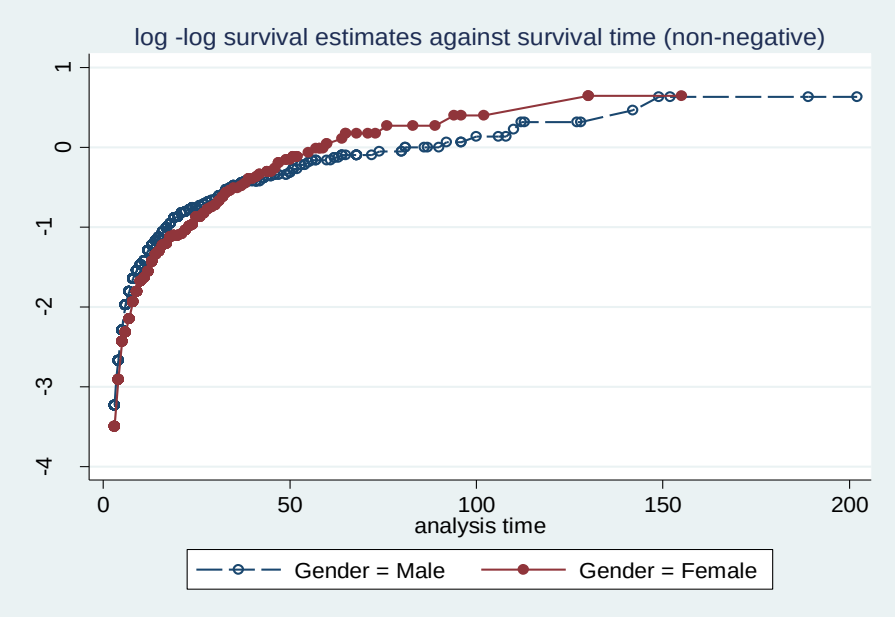
The log minus log graph of survival estimates against survival time was fit since it is more informative as compared to log –log curve against log (survival time). Assessment of the log minus log curves by infection status indicates that they are not parallel. The two curves cross at about110th day and 130th day. Hence, we conclude that the PH assumption is violated.

Figure 9: Log minus Log graph for stratification by infection status



In addition, stratifying by gender shows that the two curves are not parallel and cross at various points, thus violating the PH assumption (Figure 10).

Figure 10: Log minus Log graph for stratification by infection status

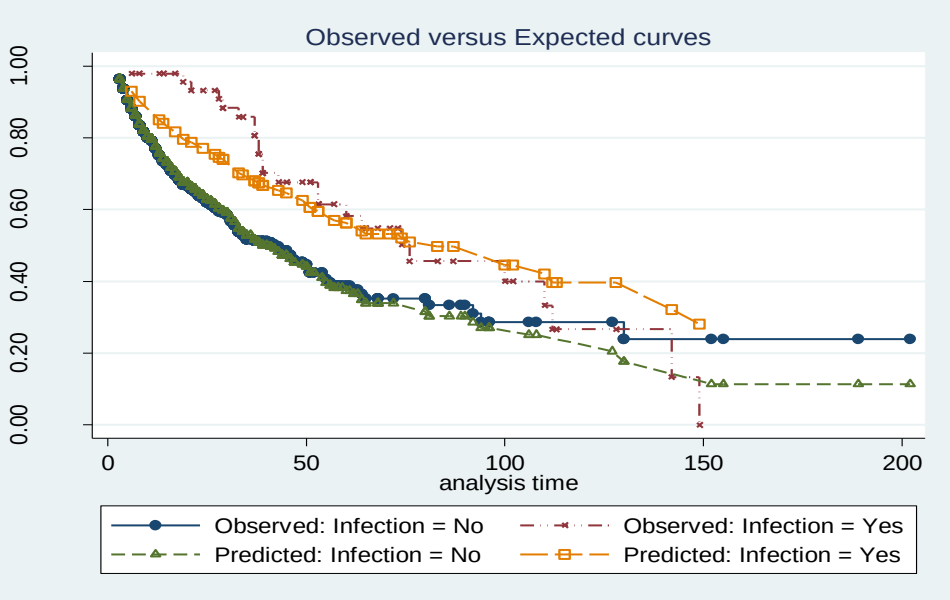


4.7.2 Graphical techniques – Observed versus Expected plots

This assumption is evaluated by comparing observed (Kaplan-Meier survival estimates)versus expected (Cox adjusted)survival curve estimates plotted on the same graph with an anticipation that they would be as close to each other as possible.

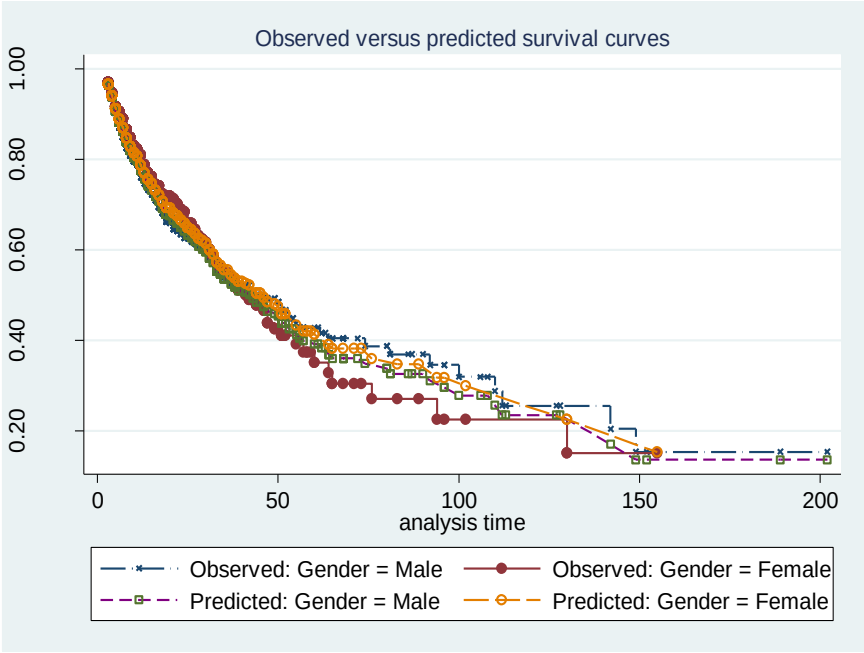
First considering stratification by infection status, results indicate that both sets of curves diverge from each other. The observed and predicted curves for the non-infected group are close to each other from the beginning to about the 60thday where they diverge from each other up to the end. The infected (CLABSI) group depicts a clear violation of the Cox PH assumption from the beginning of the plots to the end, where the predicted and observed curves are wide apart. The Figure 11portrays the results.

Figure 11: KM Curves vs Cox adjusted Survival estimates by infection status



A similar plot by gender is as portrayed in Figure 12. For each gender category, the plots for observed and expected estimates are close to each other from the beginning to about the 40th day, and thereafter they diverge indicating violation of PH assumption.

Figure 12: KM Curves vs Cox adjusted Survival estimates by gender



4.7.3 Using Goodness of fit (GOF) test

GOF test provides a more objective technique of assessing the PH assumption. The results indicate that only the infection status doesn't violate the PH assumption. Age, gender and number of the devices used have p-values less 0.05 indicating that violation of the PH assumption.

Table 17: GOF PH Assumption test results

	Rho	chi^2	df	Prob>chi^2
Infection status	0.10671	3.74	1	0.0530
Gender	0.11674	5.03	1	0.0250
Age	0.14845	9.09	1	0.0026
Count of devices	0.16444	6.43	1	0.0112
global test		32.81	4	0.0000

4.8 Extended Cox Model- regression model with a time-dependent covariate

The time dependent Cox model was fit as a result of the PH assumptions violation by the data.

4.8.1 Cox regression with time dependent model results

The LR statistic obtained a chi square value of 23.25 and P-value<0.001 which is less than 0.05 indicating significance at 5% level. This was under the null hypothesis of no interaction effect; the test statistic has a chi-square distributionwith5 degrees of freedom, where 5denote the number of predictors being assessed.

Table 18: Likelihood Ratio (LR) Statistic for Time dependent model

Omnibus Tests of Model Coefficients[a]

-2 Log Likelihood	Overall (score)			Change From Previous Step			Change From Previous Block		
	Chi-square	Df	Sig.	Chi-square	df	Sig.	Chi-square	Df	Sig.
4439.442	23.249	5	.000	24.634	5	.000	24.634	5	.000

The model was fitted using the following covariates: the time dependent covariate which was a product of the age, number of the CVCs used, age of the patients, gender of the patients and infection status.

The level of significance chosen was 5% level.

Under the null hypothesis the model without time dependent variable is the better fit compared to the model with the interaction term. Among the covariates tested, The time dependent covariate (ln(_t*age) obtained a hazard ratio of 1.01 [95% CI; 1.005, 1.016], which indicates that an increase by one unit leads to an increase in the hazard ratio by 1.06%.

Table 19: Cox regression time dependent model results

_t	Haz. Ratio	Std. Err.	Z	P>|z|	[95% Conf.	Interval]
Main						
Infection	0.657586	0.154869	-1.78	0.075	0.414462	1.043326
Gender	0.912228	0.098973	-0.85	0.397	0.737483	1.128379
Age	0.976083	0.006966	-3.39	0.001	0.962524	0.989832
Count	0.961659	0.02034	-1.85	0.065	0.922609	1.002362
Tvc						
Age	1.010603	0.00288	3.7	0.000	1.004974	1.016264

Note: variables in tvc equation interacted with ln(_t) (Stata Output)

4.9 Parametric Approach using Gamma Frailty Model

Frailty is a random component that accounts for extra variability due to unobserved factors in the survival model.

Table 20: Gamma Frailty model

No. of subjects =	1086	Number of obs =	1086
No. of failures =	363	LR $chi^2(4)$ =	50.04
Log likelihood =	-905.37388	Prob> chi^2 =	0.0000

__t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Infection status	0.097059	0.093554	-2.42	0.016	0.014675	0.641948
Gender	0.627344	0.182802	-1.6	0.110	0.354384	1.110549
Age	0.994418	0.006786	-0.82	0.412	0.981207	1.007806
Count (devices)	0.691274	0.070377	-3.63	0.000	0.566229	0.843934
/ln_p	1.172823	0.160542	7.31	0.000	0.858166	1.48748
/ln_the	2.222404	0.258196	8.61	0.000	1.71635	2.728458
p	3.231101	0.518729			2.35883	4.425929
1/p	0.309492	0.049687			0.225941	0.423939
theta	9.22949	2.383014			5.564181	15.30926

Likelihood-ratio test of theta=0: $chibar^2(01)$ = 104.23 Prob>$chibar^2$ = 0.000

Results indicate variance(theta) of the frailty =9.229 (95% CI;5.564, 15.309). The likelihood ratio test for theta, which has a Chi-square value of 104.23 and a p-value less than 0.001 indicates that it is highly significant at 5% as well as at 1% level. The shape parameter p has a

hazard ratio of 3.231(s.e 0.519) indicating an increasing hazard over time.Twoout of the four predictors were significant at 5% level of significance after adjusting for other covariates, the p-values for Infection status and number of the CVC devices used were; 0.016 and <0.001 respectively.

The hazard ratio for the infection status after adjusting for the other factors is 0.097(95% CI;0.0147, 0.642) indicating that CLABSI infection reduced likelihood of dying by 90.3% compared to the group with no infection. This could however be attributed to the sample sizes, only 4.3% of the total sample developed the infection.

The hazard ratio for the number of CVC devices used after adjusting other factors is 0.691(95% CI; 0.566, 0.844). This indicates that an increase in utilization of one CVC device leads to a decrease by 30.9% of hazard, holding other factors constant.

CHAPTER 5

DISCUSSION

The study was based on patients, who were admitted in the Critical Care units (ICU, HDU, CT-ICU and CCU) and utilized Central Venous Catheters during their hospitalization during the period of study (8th Dec, 2012 and 31st Mar, 2016). Patient's inclusion into the study was based on admission into the critical care units and utilization of the Central Venous Catheter (CVC) devices during the period of hospitalization and having been on admission for at least 48 hours. CVCs also referred to as central lines are useful devices in delivery of care to the patients, they help in administration of Intravenous (IV) fluids, blood products, medications, parenteral nutrition, providing access for hemodialysis and hemodynamic monitoring(The Joint Commission, 2012). There is however a risk associated with the use of the CVC devices which is development of an infection referred to as Central Line Associated Blood Stream Infections (CLABSI). A total of 1086 patients (males were 648 [59.7%] and females 438 [40.3%]) were included in the study. 363 patients experienced the event of interest (death). 47 patients (4.3% of the total number of patients included in the study) developed nosocomial central line associated blood stream infection during their hospitalization, Interventists and microbiologists were involved in determination of CLABSI occurrence.

The average duration of 18.19 days (s.e 0.611) and median of 12 days was taken by patients who did not develop a nosocomial CLABSI compared to an average of 56.79 days (s.e of 5.171) and a median of 51 days. There was a significant association between infection status and discharge status at 5% level which depicted a chi-square statistic of 6.868 (p-value of 0.009). The average age of patients included in the study was 54.7 years (s.e 0.631 years), median of 56.5 years and a mode of 64 years. An average of 2.08 CVC devices, were used on the patients. Majority of patients used only one CVC device during their admission. De Angelis et al (2010) deduced that the longer the patient is hospitalized, the greater the opportunity for the patient to experience the use of invasive medical devices such as CVCs that may cause HAI, therefore predisposing a patient to a higher probability of occurrence of a nosocomial infection(De Angelis et al, 2010).

A test comparing the proportion of patients who died after developing the nosocomial CLABSI and the proportion of the group of patients who died having not developed CLABSI revealed that

there is a significant difference in the two proportions at 5% level. The chi-square statistic was 6.0647 at 1 df with a p-value of 0.01379. We therefore deduce that mortality as well as morbidity is significantly increased when a patient develops a nosocomial CLABSI, the studies by (Smith et al, 1991), (Martin et al, 1989),Soufir et al (1999), (Harley et al, 1980) and (Pittet et al, 1994) obtained similar results. In a previous study however, Carrico and Ramírez highlighted that it may be challenging to differentiate between patients who die "with" an infection and those who die "because of" an infection (Carrico R, Ramírez J., 2007)

There was censorship of subjects in both groups, infected had 74.5% whereas non-infected had 74.5%.The initial period of about 50 days after admission, survival probabilities declined at relatively more close ranges as compared the period after 50 days. The overall average duration taken by the patients was 70.72 days (95% CI; 60.362, 81.084) and the overall median time estimate was 44 days (95% CI; 36.49, 51.51). There are higher probabilities of survival among the patients with nosocomial CLABSI as compared to the group of patients with no CLABSI. However, this trend changes after about 113 days where the survival probabilities of the group not infected are higher. At about 140 days of admission, the survival probabilities of infected group (CLABSI) decline sharply. The small proportion of patients with CLABSI in the study (4.3%) may have contributed to this pattern which may not represent the real situation.

Tests on survival curves were based on; Log Rank statistic (χ^2_1) which obtained a chi square value of 6.364 p-value (0.0116), Breslow (Generalized Wilcoxon) had a χ^2_1 =13.95 (p-value =0.0002), Tarone-Ware had a χ^2_1 =13.326(0.0003), Peto-peto had χ^2_1 =11.47 (0.0007) and Fleming-Harrington had a χ^2_1 =11.47 (0.0008) all of which are significant at 5% level depicting that the two survival curves based on the infection status are different.

Test on survival time in relation to the infection status was conducted using a two sample Wilcox on rank sum test (Mann–Whitney test). The test's statistic W=6112.5 and p-value < 2.2e-16, whi ch is indicates that it is significant at 5% level. We can hence deduce that there is a significant dif ference between the length of stay by the patients who develop nosocomial CLABSI compared t o the patients who do not develop the infection.

The overall average duration by male patients was 73.69 days (95% CI; 60.970, 86.958) whereas that of female patients was 59.9 (95% CI, 60.970, 86.958). Median on the other hand was 46 days (95% CI; 34.8, 57.2) for male patients and 42 days (95% CI; 33.5, 50.5) for female patients

The tests on curves with respect to infection status after adjusting for the gender Log Rank (Mantel-Cox) χ^2_1=6.499 (p-value =0.011), Breslow (Generalized Wilcoxon) χ^2_1=13.995 (p-value=0.000[3dp]) and Tarone-Ware χ^2_1=13.607(0.000[3dp]). Hence all the survival curves were different.

Pair wise tests were conducted on survival curves with respect to gender after adjusting for infection status indicated that they were not significant at 5% level. Log Rank (Mantel-Cox), Breslow (Generalized Wilcoxon) and Tarone-Ware provided respective Chi-square statistics of 0.429, 3.146 and 2.408 each at 1 df with the p-values of 0.512, 0.076 and 0.121 respectively.

There was a significant association between infection status and discharge status; the results depict a chi-square statistic of 6.868 at 1 df and a p-value of 0.009 which is significant at 5% level. There was however no significant association for the gender of the patient and the discharge status at 5% level; which obtained a chi-square statistic value of 0.705 at 1 df with a p-value of 0.401. Similarly, there was no significant association between the gender of the patient and the infection status at 5% level; chi-square statistic was 1.446 at 1 df and a p-value of 0.229.

Data was found to have violated the assumption of Cox PH model hence the extend Cox model and Gamma Frailty model was fit to the data. The Extended Cox model for time-dependent variables produced an LR statistic with a chi-square value of 23.25 and p-value=0.000(3dp) which is less than 0.05 indicating significance at 5% level. This was under the null hypothesis of no interaction effect; the test statistic has a chi-square distribution with 5 degrees of freedom, where 5 denote the number of predictors being assessed. Among the covariates tested, two of them, viz; age of the patients and the time dependent covariate were significant at 5% level with a p-values of 0.001 and 0.000 (3dp) respectively. The hazard ratio for the age of patients was HR=0.976 (95% CI; 0.963, 0.989) indicating that an increase in age of patients by one year leads to a reduction of hazard of death by 2.4%. The time dependent variable covariate (ln(_t*age)

obtained a hazard ratio of 1.01 [95% CI; 1.005, 1.016], which indicates that an increase by one unit leads to an increase in the hazard ratio by 1.06%.

Gamma Frailty model was fit to the data, frailty is a random component that accounts for extra variability due to unobserved factors in the survival model. Results indicate variance (theta) of the frailty = 9.229 (95% CI; 5.564, 15.309). The likelihood ratio test for theta, which has a chi-square value of 104.23 and a p-value less than 0.001 indicates that it is highly significant at 5%. The shape parameter p has a hazard ratio of 3.231(s.e 0.519) indicating an increasing hazard over time. Two out of the four predictors were significant at 5% level of significance after adjusting for other covariates, the p-values for Infection status and number of the CVC devices used were; 0.016 and 0.000 (3dp.) respectively. The hazard ratio for the infection status after adjusting for the other factors was 0.097 (95% CI; 0.0147, 0.642) indicating that CLABSI infection reduced likelihood of dying by 90.3% compared to the group with no infection. This could however be attributed to the sample sizes, only 4.3% of the total sample developed the infection. The hazard ratio for the number of CVC devices used after adjusting other factors is 0.691 (95% CI; 0.566, 0.844). This indicates that an increase in utilization of one CVC device leads to a decrease by 30.9% of hazard, holding other factors constant.

CHAPTER 6

CONCLUSION AND RECOMMENDATIONS

6.1 Conclusions

The results indicate that there was a significant association between infection status and the event status. In addition, there is a difference between the survival rates of the patients who developed nosocomial CLABSI as compared to those who did not develop the nosocomial CLABSI. The proportions of death by the patients who developed the nosocomial CLABSI was higher as compared to the proportion of death of the patients who did not develop CLABSI, hence mortality is significantly increased when a patient develops a nosocomial blood stream infection. The duration of hospitalization (length of stay) by the patients who developed CLABSI was significantly higher compared with the duration taken (length of stay) by patients who did not develop CLABSI this has a great impact on the financial burden the patients are subjected to due to added hospital bed days as well as medication administered.

6.2 Recommendations

Since CLABSI infections have been found to elongate patient's length of stay, appropriate strategies such as implementation of and adherence to the Central Venous Catheter insertion and maintenance bundles would be ideal in order to reduce the infection rates. Appropriate matched study in relation to Central Venous Catheter utilization along specific age groups and in specific diagnoses. More research is needed in developing countries in regard to Central Line Blood Stream Infections as well as utilization of the CVCs in order to provide further results for meta-analysis.

APPENDIX

7.1 Data Collection tool

Data shall be retrieved electronically from a database except for the variables regarding date of infection, the below fields will be considered;

1. Medical Record Number_____
2. Gender ☐Male ☐Female
3. Age _____
4. Duration of CVC insertion (days) _____
5. Admission date _____
6. Discharge/transfer date _____
7. Date of infection (CLABSI) _____
8. Infection status (CLABSI) ☐ Yes ☐No
9. Discharge Diagnosis_____
10. Co morbidities_____
11. Event Status (Death) ☐ Yes ☐No
12. Type of CVC used
13. Number of CVC devices inserted during hospitalization _____

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