PREDICTORS AND TIME TO PNEUMONIA DEVELOPMENT IN MECHANICALLY VENTILATED ADULT PATIENTS IN THE ICU AT AYDER COMPREHENSIVE SPECIALIZED HOSPITAL, MEKELLE, TIGRAY 2024

By: MASRESHA GEBRU

A THESIS SUBMITTED TO DEPARTMENT OF BIOSTATISTICS, SCHOOL OF PUBLIC HEALTH, COLLEGE OF HEALTH SCIENCES, MEKELLE UNIVERSITY IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE IN BIOSTATISTICS.

November, 2024

Mekelle, Ethiopia

MEKELLE UNIVERSITY

COLLEGE OF HEALTH SCIENCES

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Mekelle, Ethiopia

Advisor approval sheet

This is to certify that the research thesis entitled" Predictors and time to pneumonia development in mechanically ventilated adult patients in the ICU at Ayder Comprehensive Specialized Hospital, Mekelle, Tigray 2024, a Cohort Study" is submitted in partial fulfillment of the requirement for the degree of Master of Public Health in Biostatistics to the graduate program of the College of Health Sciences of Mekelle University and has been carried out by Masresha Gebru Teklehaimanot ID No CHS/PR/169494/12 under my supervision. Therefore, the student fulfilled the requirement and hence, by can submit the research thesis to the department.

_____	_____	_____
Name of Major Advisor	Signature	Date
_____	_____	_____
Name of Co-Advisor	Signature	Date

Declaration

I hereby declare this research thesis is my original work and has not been presented for a degree in any other University, and all sources of material used for this thesis have duly acknowledged.

Name: _____ Signature: _____ date: _____

This thesis had been submitted for examination with my approval as thesis advisor

Name: _____ Signature: _____ Date: _____

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List of Abbreviations and Acronyms

AICU	Adult Intensive Care Unit
ARDS	Acute Respiratory Distress Syndrome
ATS	American Thoracic Society
CDC	Center for Disease Control and Prevention
CHF	Chronic Heart Failure
COPD	Chronic Obstructive Pulmonary Disease
CVC	Central Venous Catheterization
COVID-19	Corona virus disease -19
GSC	Glasgow Coma Scale
HAP	Hospital-Acquired Pneumonia
ICU	Intensive Care Unit
IDSA	Infectious Diseases Society of America
IMV	Invasive Mechanical Ventilator
INICC	International Nosocomial Infection Control Consortium
IPPV	Intermittent positive pressure ventilation
MODS	Multiple Organ Dysfunction Syndrome
MOs	Microorganisms
MSc	Master of Sciences
NIMV	Non-Invasive Mechanical Ventilator
VAP	Ventilator Associated Pneumonia

Abstract

Introduction: Ventilator-Associated Pneumonia (VAP) is the second most common nosocomial infection in the intensive care unit (ICU). Researchers have conducted limited studies, and identifying the factors linked to the development of VAP is crucial for implementing preventive measures.

Objective: To determine predictors and time to pneumonia development in mechanically ventilated adult patients in the intensive care unit at Ayder Comprehensive Specialized Hospital, Mekelle, Tigray 2024.

Methods and Materials: A retrospective cohort study design was employed. All patients admitted to the adult intensive care unit and under mechanical ventilation from **January 1, 2018, to December 31, 2020,** were recruited consecutively. Data was collected using ODK and exported to STATA 17 for analysis. Log-rank test and multivariable lognormal regression were fitted to identify time to pneumonia development predictors. An adjusted hazard ratio with a 95% confidence interval was used to measure the association. The lognormal model best fits the data based on goodness-of-fit criteria, including the Akaike Information Criterion and Bayesian Information Criterion. The assumptions of survival times were checked using graphical methods. Models with and without interaction terms were compared, and the final model was selected based on the best fit to the data.

Result: Data from 203 patient folders were analyzed, with a median follow-up of 6 days. The overall occurrence of pneumonia among adult patients in the ICU under mechanical ventilation was 61.08%, with an incidence rate of 15.3 cases per 813 person-days. The duration of mechanical ventilation for late pneumonia (AHR=1.32, 95% CI: 1.13, 1.55), cause of admission to intensive care unit due to respiratory disease (AHR=0.72, 95% CI: 0.53, 0.93), primary indication for intubation for patient with trauma (AHR=0.72, 95% CI: 0.53, 0.98), Sex of patient female patients (AHR=0.85, 95% CI 0.73, 0.98) were significantly associated with VAP in the adult ICU patients.

Conclusions and Recommendation: The study highlights high pneumonia incidence in mechanically ventilated patients, emphasizing prioritizing resources allocation for those who are under mechanical ventilation to minimize the incidence of pneumonia.

Key words: ventilator associated pneumonia, intensive care unit, Mechanical ventilation

1. Introduction

1.1 Background

Pneumonia is defined as inflammation of the lung parenchyma caused by infections and is usually categorized into nosocomial (hospital-acquired) and community-acquired pneumonia (1,2).

Globally, the number of patients requiring mechanical ventilation is increasing, specifically in patients with Acute Respiratory Failure (ARF). It is provided for over 20 million patients worldwide, and among intensive care unit (ICU)-admitted patients, 45% require mechanical ventilator (MV) during their admission (3,4).

According to 2016 American thoracic society (IDSA/ATS) guideline, hospital-acquired/nosocomial pneumonia (HAP) is pneumonia that occurs 48 hour or more after admission and did not appear to be incubating at time of admission. On the other hand, Ventilator-associated pneumonia (VAP) is a type of Hospital acquired pneumonia (HAP) that develops more than 48–72 hours after endotracheal intubation(5).

According to a study, more than 300,000 patients are artificially ventilated in the United States each year. These patients face a high risk of complications and poor outcomes, including death. Ventilator-associated pneumonia (VAP), acute respiratory distress syndrome, sepsis, etc. are some of the complications that may occur in patients on mechanical ventilation. Such complications may lead to increased duration of mechanical ventilation, prolonged stay in the intensive care unit and hospital, increased medical costs, and increased risk of disability and death (6,7).

1.2 Problem Statement

Despite significant advances in the treatment of ventilator-dependent patients and routine use of effective ventilator disinfection procedures, ventilator-associated pneumonia (VAP) still complicates disease progression in 8 - 28% of clients received mechanical ventilation (MV). Rates of pneumonia are considerably higher among patients hospitalized in intensive care units (ICUs) compared with those in hospital wards, and the risk of pneumonia is increased 3- to 10-fold for the intubated patient receiving MV (8).

VAP represents 80% of episodes of hospital-associated pneumonia, and is applied to episodes developed in intubated or acutely tracheotomized patients under mechanical ventilation(9).

Nosocomial infections affect more than 100 million patients globally each year. They pose a major threat to public health, leading to prolonged hospital stays, high mortality rates, and a significant economic burden on patients and healthcare systems, and globally mortality rate due to mechanical ventilator associated pneumonia it counts up to 15.6% (10–12).

The potential factors affecting the being of surgical patients in an intensive care unit (ICU) involve age, length of stay, comorbidities, type of surgery, and condition upon admission. In addition to clinical factors, the majority of the cause poor results in low resource settings lies in the unavailability of the most essential and specialized ICU components(13).

In both developing and developed nations, the disease burden and consequences of VAP have been demonstrated to decrease to a minimum level with the use of various preventive measures; however, in Ethiopia, specifically in ACSH, the prevalence and efficacy of any preventive measures remain unclear.

Growing number of tertiary and university hospitals, the numbers of ICUs are also increasing rapidly. The disease burden of VAP varies according to the patient group and hospital setting. In Ayder comprehensive specialized hospital due to limited focus activities on preventive measure to mechanical ventilated patients, there is high economic burden to their relatives/ families to buy ordered strong potency medicines like 3rd

generation drugs Cefalosporine and Vancomycine. Most of the time those drugs are not available in governmental health facilities. There was no study conducted to assess predictors and time to pneumonia development in mechanically ventilated adults in the ICU at Ayder Comprehensive Specialized Hospital.

1.3 Significance of Study

Knowledge of disease burden, proper identification, effects, risk factors, and outcomes is essential for establishing effective strategies to prevent ventilator-associated pneumonia, so this study provides a reference point on the disease burden and predictors with VAP at the Adult Intensive Care Unit (AICU) at Ayder Comprehensive Specialized Hospital (ACSH). The result of this study served as a reference line/ contribution for researchers interested in long-term functional outcome and program evaluation studies. The finding could help important guiding tools for planners, policymakers, decision-makers, and hospital administrators to prioritize problems and enhance good planning.

2 Literature Review

2.1 Overview of Ventilator-Associated Pneumonia

Ventilator-associated pneumonia (VAP) is estimated to affect 5% to 40% of patients receiving invasive mechanical ventilation, depending on the country, type of ICU, and the criteria used to identify VAP. The incidence of VAP in North American hospitals has been reported to be as low as 1 to 2.5 cases per 1000 ventilator-days. However, European centers have reported much higher rates, with an incidence density of 18.3 VAP episodes per 1000 ventilator-days. Rates are also higher in low- and middle-income countries compared to U.S. hospitals, particularly in high-income countries, at 18.5 and 9.0 per 1000 ventilator-days, respectively (14).

According to a report on endotracheal device-associated infections in 173 ICUs from 25 countries in Latin America, Asia, Africa, and Europe, crude excess mortality in adult patients was 29.3%. And the risk of development of nosocomial Pneumonia is increased 4- to 21-fold for intubated patients and increases with the duration of mechanical ventilation. Similarly it showed that VAP increase in mortality rate by 2- to 10-fold and a two- to three-fold increase in hospital stay (12,15,16).

2.2 Time to develop pneumonia

A retrospective cohort study in Southern Taiwan (2020) examined ventilator-associated pneumonia, finding an occurrence rate of 26%. Patients typically developed these events in a median of 13 days, with early events occurring in a median of 5 days and late events in 17 days. Outcomes for the late event group were worse than for early events, particularly regarding ventilator dependence and total ventilation days. Additionally, early ventilator-associated pneumonia was strong predictors of poorer outcomes at 7, 14, and 28 days. (17).

A retrospective study conducted at Helen Joseph Hospital ICU in Johannesburg showed that tracheostomy was more likely to develop VAP and was 2.36 times higher to develop late-onset VAP. (18).

2.3 Incidence of VAP

A retrospective observational study conducted in liver/general adult ICU in Adden Brooke's Hospital, Cambridge, UK shows that COVID-19 patients were Ventilator-associated pneumonia occurs in 28% of patients who receive mechanical ventilation, where its rate of occurrence varies with the duration of mechanical ventilation. Estimated rates are 3% per day for the first 5 days, 2% per day for days 6–10, and 1% per day after day 10 (19).

A cohort study conducted in Portuguese shows that hospital-acquired pneumonia was 58.3% had an ICU-acquired hospital-acquired pneumonia /HAP/, and based on the onset of early-onset VAP was present in 43.3% and late-onset VAP in the remainder 56.7% (20)**.**

In a retrospective cohort study conducted in China General Army Hospital, among 901 enrolled clients under mechanical ventilators 17.3% were diagnosed with VAP and the incidence density of VAP was 4.25 ventilator day (21).

A prospective cross-sectional study conducted in 2020 at Zewuditu Memorial Hospital in Addis Ababa showed that approximately 20% of patients experienced hospital-acquired infections. Additionally, 27.2% of patients had more than one type of hospital-acquired infection. Most infections included pneumonia, accounting for 24.7%.(22).

In a facility based cross sectional study conducted at ACSH the probability of respiratory infection among ICU patients with mechanical ventilation was 52.81%(23)

2.4 Predictors of Ventilation Related Pneumonia

Socio-demographic Factors

In a retrospective study conducted in China on 2019 risk factors for VAP, age was more likely associated with the development of VAP. Advanced age (≥60 years) was considered as a risk factor for VAP. Similarly, gender was declared an independent risk factor for VAP with males having 1.3-fold higher than females (24).

A post hoc study conducted in Poitiers France revealed that males were more likely to be admitted to ICU by different causes compared to females and the reintubation rate was

higher in males than in females (25). A prospective observational clinical trial study performed at Charité University Hospital in Berlin showed that male patients were more likely to develop VAP than female (26).

Clinical Factors for Ventilator-Associated Pneumonia

A Facility based cross-sectional Study conducted at Ayder hospital shows that MV use and length of ICU stay were more likely associated with the acquisition of nosocomial sepsis(23).

A retrospective study conducted at Bahardar Felege Hiwot Hospital shows that Trauma is the independent predictor of mechanical ventilation use, sedation status, NGT insertion, and head injury type to develop aspiration pneumonia among patients in the ICU(27).

A retrospective observational study conducted in adult ICU in Adden Brooke's Hospital, Cambridge, UK showed that COVID-19 patients were more likely to develop VAP than patients without COVID (19).

A retrospective study conducted at army hospital in china showed that based on patient transfer from medical side and emergency were more likely to develop VAP while comparing with other patient origin(21).

A retrospective follow-up study conducted at Bahar Dar hospital showed that patients who used corticosteroid drugs had 2.1 times higher risk of developing VAP than who were not used corticosteroids(28) .

A prospective cohort study conducted on three teaching and referral hospital ICUs in Southern Ethiopia showed that patient admission due to respiratory diseases was the commonest diagnosis followed by neurologic diseases (stroke) high likely to develop pneumonia than other admission causes (29).

A institutional-based cross-sectional study conducted on private and governmental hospitals in Addis Ababa revealed that reason for admission, (31.1%) had respiratory problems, followed by neurologic (18.4%), and cardiac (11%)(30).

A retrospective single center study in the University Hospital of Lille, France revealed that use of paralytic agents were more likely associated with the occurrence of VAP than none used (31).

Observational longitudinal study conducted in European intensive care unit showed that trauma increases risk of developing VAP. Similarly, multicenter retrospective cohort study conducted in Addis Ababa indicated that patients with traumatic injury (surgery patients) had a more likely to have hazard or develop the morbidity than those without traumatic injury. (4,13)

Comorbidity and Ventilation associate with Pneumonia

A retrospective cohort study conducted in 2020 at Krakow the most common co-morbidities occurring among the studied patients were arterial hypertension (65%), diabetes (38%), obesity (15%), atherosclerosis (11%), alcoholism (11%), thromboembolism (9%), and COPD (4%) (32).

A systematic review study conducted in 2019, from the United States shows that the most common risk factors for VAP are older age, male sex, prolonged mechanical ventilation, patients with an altered level of consciousness, burns, chronic diseases such as chronic renal failure, previous antibiotic therapy, invasive. Procedures such as tracheotomy, fiber optic bronchoscopy, indwelling gastric tubes and chest tubes.(24)

The conceptual framework was adopted after reviewing different literature. Explanatory variables that were assumed to influence the development of pneumonia are given below:

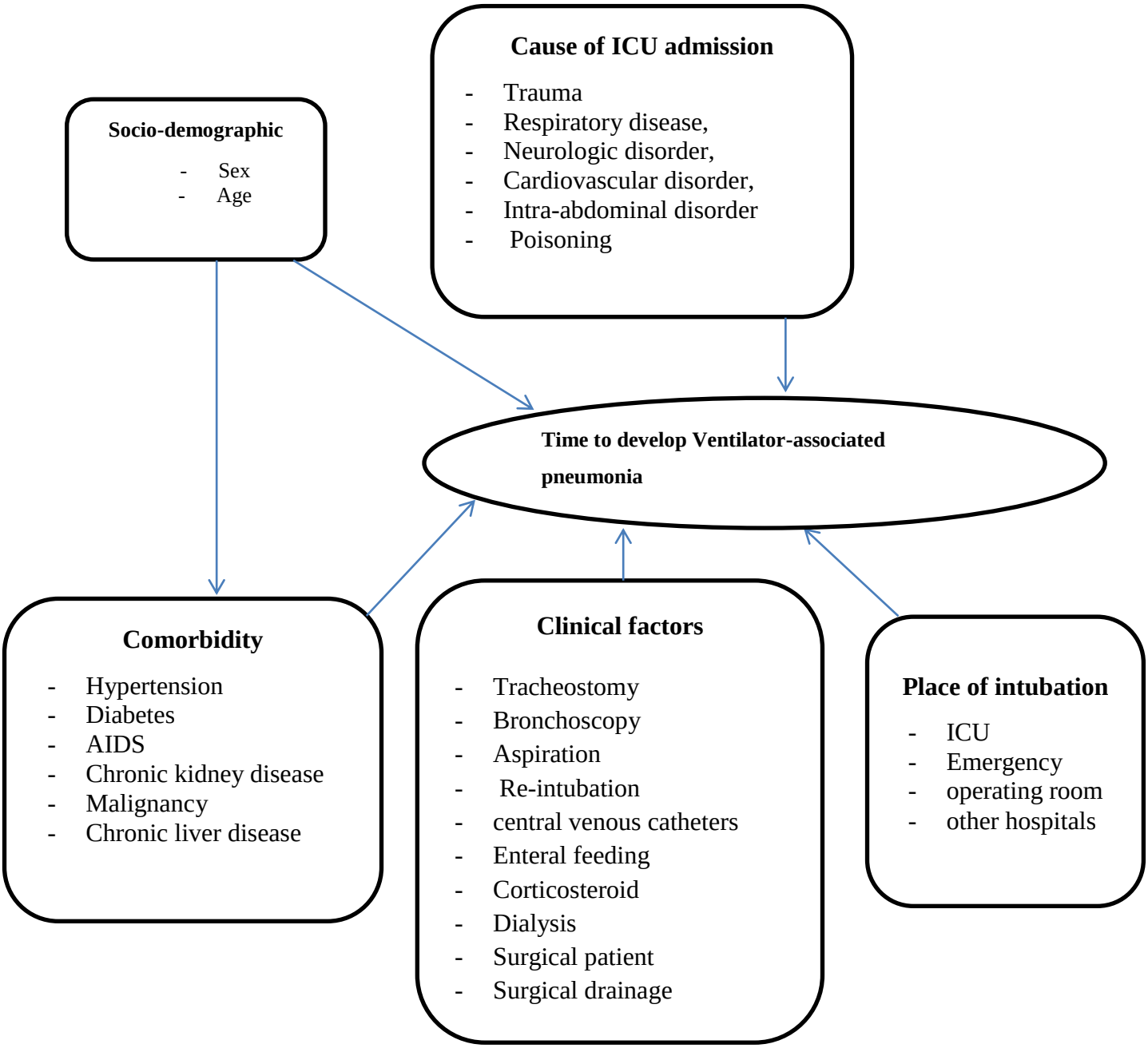

Figure 1: Conceptual frame work for Predictors of time to pneumonia development in mechanically ventilated adult patients admitted in the ICU (4,13,15,23,27,28,32,33)**.**

3 Objective

3.1 General Objective

To assess predictors and time to pneumonia development in mechanically ventilated adult patients in the ICU at Ayder Comprehensive Specialized Hospital, Mekelle, Tigray 2024.

3.2 Specific Objectives

- To determine the incidence of ventilator associated pneumonia among adult patients admitted in intensive care unit of Ayder comprehensive specialized hospital, Mekelle, Tigray 2024.
- To determine time to pneumonia development in mechanical ventilated adult patients admitted in intensive care unit of Ayder comprehensive specialized hospital, Mekelle, Tigray 2024.
- To identify predictors of development of ventilator associated pneumonia among mechanical ventilated adult patients admitted in intensive care unit of Ayder comprehensive specialized hospital, Mekelle, Tigray 2024.

4 Materials and Methods

4.1 Study Area

This study was conducted at Ayder Comprehensive Specialized Hospital (ACSH). This is a public hospital and is found in Mekelle capital city of Tigray, Ethiopia. Ayder Comprehensive Specialized Hospital started its referral and non-referral services in 2008 to reach the 9 million populations in its catchment areas of the Tigray and neighborhood countries. Ayder Comprehensive Specialized Hospital has over 170,000 total patient visits a year. It is a main referral center in the region with daily estimated average patients visit over 465. ACSH provides continuous, uninterrupted availability specialty services in outpatient and inpatient services, emergency medicine, critical care, trauma and acute care surgery, orthopedics, neurosurgery, and forensic medicine Ayder comprehensive specialized hospital has four intensive care units: neonatal ICU, pediatric ICU, medical ICU and Surgical ICU. Medical and surgical ICU has a bed capacity of sixteen. Those intensive care units has equipped with mechanical ventilators, defibrillators, perfusers, echocardiography and portable chest x-ray machines. All intensive care units provide medical, surgical, obstetric and emergency services.

During the genocidal war in Tigray in 2020, hospital staff struggled to keep up with the flow of trauma, medical patients and had limited surgical equipment. After the war, many customers died due to lack of medical supplies and medical oxygen, health provider turnover is high and patient to health provider ratio also varies depending on follow of patients(34).

4.2 Study Period

The data collection was conducted from May 20 to May 30, 2023.

4.3 Study Design

Institutional based retrospective cohort study was employed.

4.4 Population

4.4.1 Source Population

All patients were admitted to AICU and were under a mechanical ventilator in Ayder comprehensive specialized hospital.

4.4.2 Study Population

All patients were admitted to AICU and were under a mechanical ventilator in Ayder comprehensive specialized hospital from Jan 1, 2018, to December 31, 2020.

4.4.3 Study Unit

A patient was admitted to AICU and who was under mechanical ventilator in Ayder comprehensive specialized hospital from Jan 1, 2018, to December 31, 2020.

4.5 Inclusion and Exclusion Criteria

4.5.1 Inclusion Criteria

- All adult patients who were under mechanical ventilation for more than 48 hours during the study period.

4.5.2 Exclusion Criteria

- Previous diagnosis of pneumonia before 48 hours of mechanical ventilation
- Patients with incomplete medical records
- Patients on mechanical ventilation who received/ taken prior medication for pneumonia

4.6 Sample Size and Sampling Procedure

The sample size was determined by using survival analysis formula based on the following assumptions: 95% confidence interval, 80% of power, probability of event 0.177, and hazard ratio of 3.02 from previous study. Sample size was computed using STATA V. 17. The parameters HR and Event probability were taken from study done in Behardar Felege Hiwot Hospital. Using the above assumptions, the sample size was calculated taking into account the following independent predictors: nasogastric tube insertion with hazard ratio of 3.02(27).

The calculation was used STATA V.17: **power cox, hratio (3.02) alpha (0.05) power (0.8) eventprob (0.18)**

Where; $\mathbf{E} = \frac{(\mathbf{Z1}-\frac{\alpha}{2}+\mathbf{Z_\beta})^2}{\pi_1\pi_2\ (\ln \mathbf{HR})^2}$ …….. (35)

$$n = \frac{E}{PE}$$

- **Hratio (HR)** is the hazard ratio for predictors, 3.02 (27)
- **Alpha (α)** is the significance level, which is set to be 0.05,
- **Power (1-β)** is the probability of not committing type II error which is set to 0.8
- **Eventprob (PE)** is the overall probability of the event of interest 0.177~0.18 (27)

By considering the above assumptions the cohort had a sample of 143 study subjects.
And finally, adding 10 % for incomplete and voided patient folder rate, the final sample size was 157.

- But this study included all the 203 eligible patients' record in the AICU who were ventilated mechanically.

4.7 Study Variables

4.7.1 Dependent Variable

Event

- Ventilator-associated pneumonia

VAP was evaluated using:

Clinical criteria: MV time ≥ 48 h, new or progressive radiographic consolidation or infiltrate and presence of two or more clinical criteria: fever (≥ 38.5°C) or hypothermia (< 36.5°C), Leukocytosis (white blood cell count ≥ 12,000 cells/mm^3) or leukopenia (white blood cell count < 4,000 cells/mm^3), and purulent tracheal secretions.(36).

Time

- Length of stay or follow-up time in days calculated from the time of ICU admission to development of VAP or Discharge

Categories of Censoring and Truncation

Definition of categories of censoring and Truncation (37).

- **Censoring** - incomplete observation of survival times; subjects with an incomplete observation are referred to as censored. Or if the mechanical ventilated patient didn't develop pneumonia from admission until discharge, recovered or died.
- **Left censoring** - The patient is known to have experienced the event before the start of the observation period, so the actual time-to-event is shorter than the interval between the origin and start of observation, but it is unknown by how much.
- **Right censoring** - Observation of the patient is terminated before the event occurs, so the actual time-to-event, if it were to occur, is longer than the observation time, but it is unknown by how much.
- **Truncation** - Subject selection depending on whether the event has occurred.
- **Left truncation** - Selective inclusion of patients in whom the event has not occurred early; patients who have already experienced the event before the time point of patient identification are not identified and often may not even be known to exist.
- **Right truncation** - Selective inclusion of patients in whom the event has occurred.

4.7.2 Independent Variable

- Socio-demographic (age, sex)
- Presence of co-morbidity (Hypertension, Diabetes, AIDS, Chronic kidney disease, Presence of malignancy (cancer), Chronic liver disease)
- Indication of Mechanical ventilation (ARDS, Acute pulmonary edema/CHF, Aspiration, Trauma, Coma or impaired consciousness, Neuro-muscular diseases (GBS, myasthenia gravis)
- Cause of ICU admission (Trauma, Respiratory disease, Neurologic disorder, Cardiovascular disorder, Intra-abdominal disorder (GI), Poisoning (usually attempted suicide), or intoxications, Metabolic or renal.)
- Place of intubation (ICU, emergency, operating room, other hospitals)
- Other clinical exposed factors (Tracheostomy, Bronchoscopy, Aspiration of gastric content, Re-intubation, Presence and duration of central venous and arterial catheters,

NGT and enteral feeding, Prior use of antibiotics, Corticosteroid, Transportation out of the hospital (ICU) after intubation, Surgery, Surgical drainage (mainly thoracic) or thoraco-abdominal surgery, Paralytic agents, continuous intravenous sedation, Traumatic intubation (Emergency intubation), Dialysis, Ionotropic medication)

4.8 Operational Definitions

Ventilator associated pneumonia - A pneumonia where the patient is on mechanical ventilation for > 2 calendar days on the date of event, with day of ventilator placement being Day 1, (18).

Early pneumonia –After Mechanical ventilation develops pneumonia < 5 days.

Late pneumonia - After Mechanical ventilation develops pneumonia >= 5 days (18).

4.9 Data collection Instrument and Process

4.9.1 Data Collection Instrument

Structured English version checklist was entered to ODK tool and the format contains closed-ended type of statements i.e. Age, sex, admission diagnosis, indication for mechanical ventilation, admitting ward, source of admission, length of stay in the ICU, the primary indication for mechanical ventilation, length of mechanical ventilation, onset of VAP, presence of co-morbidity, and place of intubation, Tracheostomy, bronchoscopy, aspiration of gastric contents, reintubation, NGT central catheter, surgical drainage, surgical patient dialysis traumatic intubation and inotropic medications.

4.9.2 Data Collection Process

Patient records were reviewed from January 2018 to December 2020. This was a retrospective chart review. The patient folder was reviewed and checked by two adult intensive care unit nurses, who were trained for 2 days with practice using an electronic data collection format.

4.10 Data Quality Control

To ensure the quality of data, close supervision was maintained by the principal investigator. The pretest was done with 10 patient folders using the structured electronic

checklist. Any ambiguities during the review process were resolved by discussion with record reviewers, the principal investigator and feedback was given daily. Then the recorded data was checked for completeness daily. The data was cleaned, coded, and entered the ODK tool.

4.11 Plan for Data Analysis and Presentation

I. Data Description

After the completion of the data collection, the collected data was exported using ODK briefcase in the form of csv file then imported to STATA version 17. Data was declared into survival data. Descriptive statistics of numeric variables presented in medians, categorical variables were presented using frequency and percentages, and the outcomes of each patient dichotomized into censored or ventilator-associated pneumonia. The person-days of follow-up computed from Admission to ventilator-associated pneumonia, loss to follow-up, or the end of the study. The cumulative survival rate was estimated using the Kaplan Meier survival curve. The observed difference in survival time between different categorical variables was compared using the Log-rank test.

II. Variable Selection Procedure

For those categorical covariates which are found to be significant in the log rank test and univariate analysis respectively were checked simultaneously with an alpha value of 0.25 using the forward, stepwise approach. Interaction between predicators was checked and only significant interaction terms were included in the model development.

III. Multi-Variable Model Building Strategies

Multivariable regression analysis was performed using several survival modeling methods and results were compared. In this study first built a Cox-proportional hazard model and evaluated the proportional hazards assumption. Then parametric models were also built using Weibull, exponential, Gompertz, log logistic, and lognormal.

Cox-Proportional Hazard Model

To determine the association among variables and time to develop pneumonia multivariable Cox proportional hazards regression model was applied. The assumptions of the Cox proportional hazard regression model checked by the following procedures: Log (-log (St) plots, Schoenfeld residual plots, and by regressing Schoenfeld residuals against time to test for independence between time and residuals. Interaction for the main effect model was also checked (P-value > 0.05). Breslow test was used to handle those tied failures, the summary measures of estimated Adjusted Hazard Ratio (AHR) with a 95% confidence interval for the survival rate among the patients estimated. P-value < 0.05 used to declare statistical significance the final model was modeled as

$$h_i(t) = h_0(t) \exp(\beta_1 x_1 + \beta_2 x_2 + \ldots \beta_p x_p)$$

Where $h_i(t)$ is the expected hazard at time t, $h_0(t)$ is the baseline hazard and represents the hazard when all the predictors (or independent variables) X_1, X_2, X_p are equal to zero. Notice that the predicted hazard (i.e., $h_i(t)$), or the rate of getting the event of interest in the next instant, is the product of the baseline hazard ($h_0(t)$) and the exponential function of the linear combination of the predictors. Thus, the predictors have a multiplicative or proportional effect on the predicted hazard(38).

Parametric survival models

Parametric survival models were applied with exponential, Weibull, Gompertz, log logistic, lognormal, and generalized gamma distributions. This was done to select an appropriate model. First, separated models were fitted for each distribution. For assessing the effect of each variable, adjusted hazard ratio was estimated for each model.

Exponential regression model: The exponential is a one-parameter distribution with a constant hazard (λ). This distribution assumes that the hazard is constant for each pattern of covariates(39).

$$S(t) = \exp(-\lambda t) \text{ and } h(t) = \lambda$$

Weibull regression model: is the most widely used parametric survival model. Its hazard function is $h(t) = \lambda p t^{p-1}$, where p and $\lambda > 0$ as with the exponential model, λ will be

re-parameterized with regression coefficients. The additional parameter p is called a shape parameter and determines the shape of the hazard function. If p> 1then the hazard increases as time increases. If p= 1 then the hazard is constant, and the Weibull model reduces to the exponential model (h (t) =λ). If p<1 then the hazard decreases over time(39,40).

The Weibull model has the property that if the AFT assumption holds then the PH assumption also holds and vice versa. This property is unique to the Weibull model and holds if p does not vary over different levels of covariates. The PH assumption allows for the estimation of a hazard ratio enabling a comparison of rates among different populations. The AFT assumption allows for the estimation of an acceleration factor, which can describe the direct effect of an exposure on survival time(39).

A graphical method for checking the validity of the Weibull assumption was used by plotting Kaplan-Meier log-log survival curves against log survival time.

The Gompertz regression model is a parametric proportional hazards model but not an AFT model. The model can be expressed in a form like that of a Cox PH model except that the baseline hazard is specified as the hazard of a Gompertz distribution containing a shape parameter ϒ. This model assumes that ln [h (t)] is a linear function of time(39,40).

If ϒ >0 then the hazard exponentially increases over time. If ϒ <0 then the hazard exponentially decreases over time. If ϒ =0 then the hazard is constant and reduces to the exponential model

$$H(t) = \exp(\Upsilon t) * \exp(\beta_o + \beta_1 x)$$

Parametrically specified, $h_o(t) = \exp(\Upsilon t)$

Log-logistic model: The log-logistic distribution accommodates an AFT model but not a PH model. The shape parameter is p (>0).

Log-logistic hazard: $h(t) = \frac{\lambda p t^{1-p}}{1+\lambda t^{p}}$

(Where p > 0 and λ> 0)

If p ≤ 1 the hazard decreases over time. If p > 1, however, the hazard increases to a maximum point and then decreases over time. In this case (p > 1), the hazard function is said to be unimodal

The log-logistic AFT model is a proportional odds (PO) model. A proportional odds survival model is a model in which the survival odds ratio is assumed to remain constant over time. This is analogous to a proportional hazard model where the hazard ratio is assumed to be constant over time. The log-logistic assumption will be graphically evaluated by plotting ln (1- $\hat{S}$ (t))/($\hat{S}$(t)) against ln(t) where $\hat{S}$(t) is the Kaplan–Meier survival estimates(39,40).

Lognormal model: The lognormal model also has a relatively complicated hazard and survival function that can only be expressed in terms of integrals. The shape of the lognormal distribution is very similar to the log-logistic distribution and yields similar model results. A difference is that although the lognormal model accommodates an accelerated failure time model, it is not a proportional hazard model(39).

If the survival times are assumed to have a log-normal distribution, the baseline survival function, and odds function.

$$S_o(t) = 1 - \phi\left(\frac{\log(t)-\mu}{\delta}\right) \text{ and } h(t) = \frac{\phi(\log(t)/\delta}{[1-\phi(\frac{\log(t)}{\delta})]\delta t}$$

Where μ and δ are parameters, ϕ(x) is the cumulative density function of the standard distribution

Generalized gamma model: The hazard and survival function for this model is complicated and can only be expressed in terms of integrals. The generalized gamma distribution has three parameters allowing for great flexibility in its shape. The gamma distribution includes as special cases the Weibull if κ= 1, in which case p= 1/σ; the exponential distribution if κ = σ= 1; and the lognormal distribution if κ = 0 (41).

$$S(t) = 1\text{-}I(Y, \mu) \text{ if } \kappa>0$$

$$1\text{-}\phi(z) \text{ if } \kappa=0$$

$$I(Y, \mu) \text{ if } \kappa<0$$

IV. Model Comparison and Selecting the Best Model

For the aim of comparison among semi-parametric and parametric models used Akaike information criterion (AIC), Bayesian information criterion and good LL to measure of the goodness of fit for statistical models. The AIC is a measure of the goodness of fit of regression models that are based on the concept of entropy. It can be viewed as the amount of information lost when a model is used to describe a set of observations. The AIC includes a penalty for the number of model parameters and thus represents the tradeoff between bias and variance. Lower AIC values indicate a better model fit (39). The formula for AIC is:

$$AIC = -2L \text{ likelihood} + 2(K+C)$$

Where log *L* is the log-likelihood of the proposed model, and k is the number of model covariates and C is the number of model specific distribution parameters.

Unlike the Cox-proportional hazard model, parametric survival models assume a specific functional form for the hazard function of the underlying data. We evaluate the fit of these models by plotting the appropriate transformed cumulative hazard against time.

Multivariable Regression Models

To model the VAP data, this study looks at the Cox-proportional hazard model and parametric survival models exponential, Weibull, Gompertz, log-logistic, lognormal, and generalized gamma distributions were considered to select the appropriate model. To build the model first separate model was fitted and an Akaike information criterion was used to select the best-fitted model. The lowest AIC, BIC and good LL leads to identifing the best one, accordingly the lognormal regression model was used to assess the independent predictors (Table 4).

Table 1 Comparison of Cox-regression model and parametric survival models using AIC for VAP patient's data

Baseline distribution	Model parameter	ll (model)	Df	AIC	BIC
Cox-regression	15	-480	33	1026	1135
Exponential	16	-132	35	3334	450
Weibull	17	-52	36	177	296
Gompertz	17	-80	36	233	352
Lognormal	17	-48	36	169	288
Log logistic	17	-49	36	171	291

V. Model diagnostics

PH Assumption

Goodness of Fit Using Residuals

The residuals are plotted versus some quantity, such as a covariate value, and the observed pattern is used to diagnose possible problems with the fitted model. Some residuals have the additional property of not only indicating problems but also suggesting remedies. That is the pattern of the plotted residuals may suggest an alternative model that fits the data better. Many of these residuals have been generalized to survival analysis. In addition, the fact that survival data evolves over time, and requires special assumptions such as proportional hazards, makes it necessary to develop additional diagnostic residual methods.

Log Cumulative Hazard Plots

If we are comparing survival times between two groups, there is a simple plot that can help us assess the proportional hazards assumption(42).

By using the log minus log survival plot we can proceed as follows;

$S_1(t) = [S_0(t)]^{\exp\beta}$, the survival function for the two groups and equivalently

$\text{Log}[-\log(S_1(t))] = \beta + \log[-\log(S_0(t))]$

Where β is the log of hazard ratio, this will give a simple graphical method for examining the proportional hazard assumption. Specifically, the log minus log transformed Kaplan Meier estimate of the survival function for the two groups (early and late groups) will be plotted against time and if the assumption holds true the two transformed functions will be parallel each other and separated β apart. If there is any patterns of convergence, divergence or crossing of the curves followed by divergence will be an evidence for non-proportionality.

Schoenfeld Residuals

Schoenfeld residual plots provide a useful way to assess this PH assumption. This approach is using the goodness of fit test (the global test). This is a test of correlation between the Schoenfeld residuals and survival time. A correlation of zero indicates that the model met the proportional hazards assumption.

If there is any time dependency a stratified analysis will be used for a categorical time varying covariate or an extended cox model with a time dependent covariate will be used to model the data.

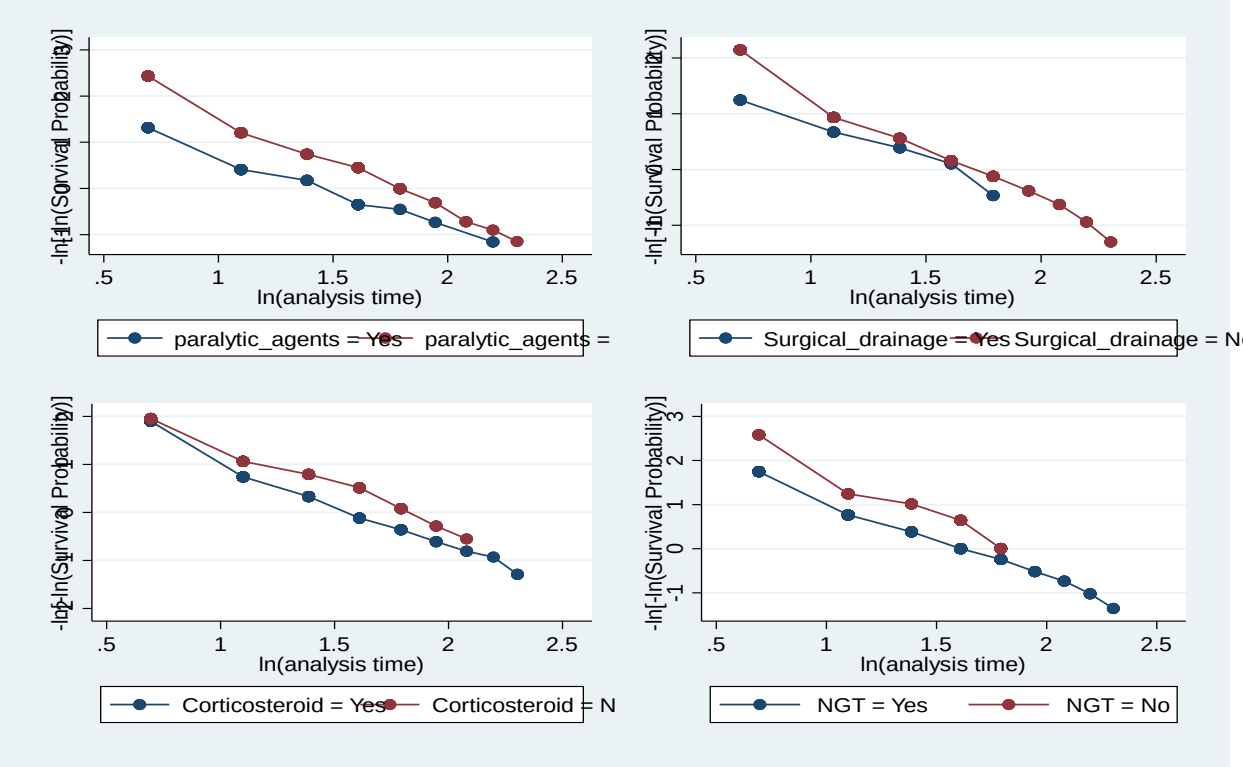

Figure 2: Schoenfeld residuals plot against time to test for independence between time and residuals based on exposure status among VAP patients admitted in adult ICU Ayder Hospital Mekelle, Tigray, Ethiopia

Assumptions of parametric survival analysis

Distribution Assumption

The distribution of the data was checked by using histogram and k-density and by visually observing the curves the distribution of the data was lognormal.

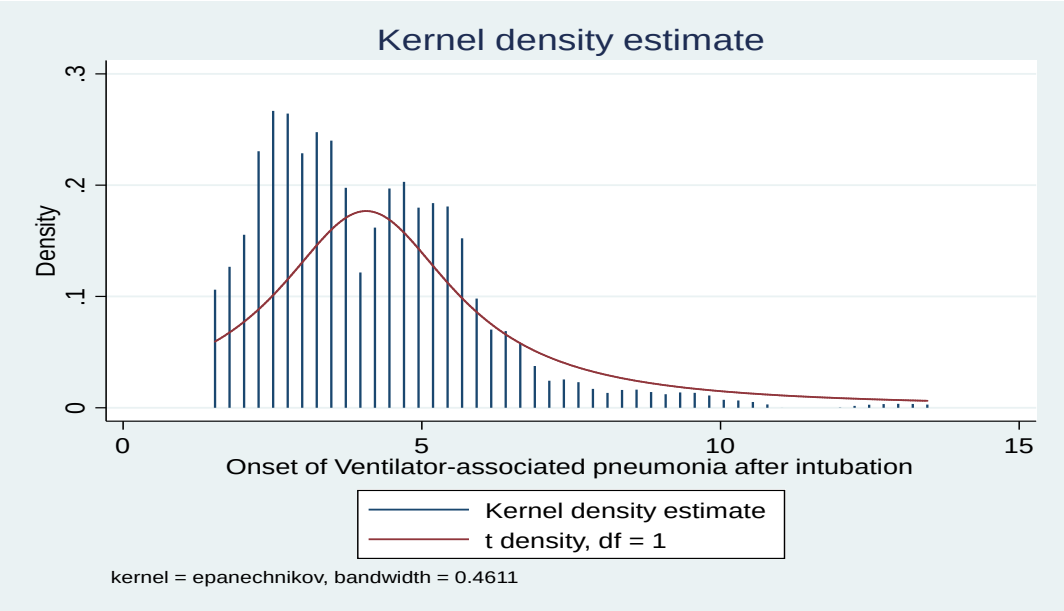

Figure 3: Kernel density estimate based on over all exposure status among VAP patients admitted in adult ICU Ayder Hospital Mekelle, Tigray, Ethiopia

Model fitness

The global test of the lognormal distribution assumption based on Schoenfeld residuals was performed and it was found that all the covariates and full model satisfy the lognormal distribution assumption (chi square =5.25 and p value=0.98).

Goodness of fit the final model using Cox Snell residuals plot was done and the hazard function follows the 45 degree line overall and we would conclude that the final model fits the data very well.

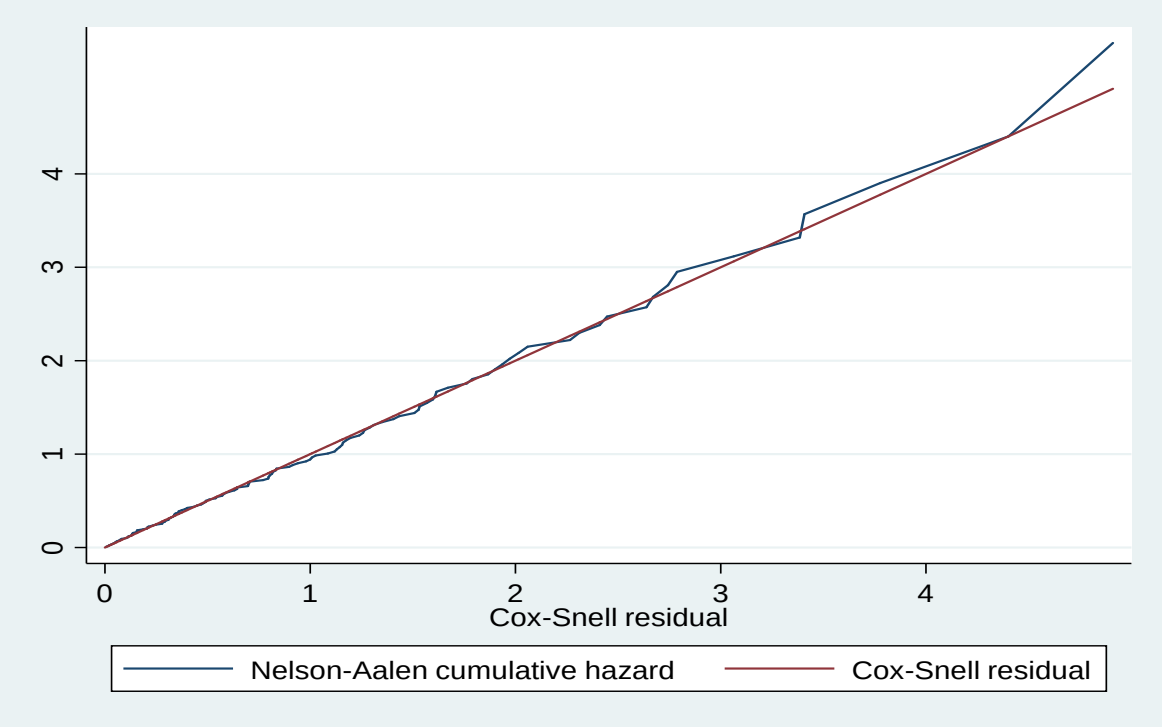

Figure 4: shows checking goodness of the final model using the Nelson-Aalen cumulative hazard graph against Cox-Snell residual plot for patients on VAP and admitted to the ICU in Ayder comprehensive specialized hospitals.

Multicollinearity

It was checked and found there is no Multicollinearity. The VIF value of all variables in the final model was < 5. This indicates there was no significant Multicollinearity.

Model Predictive Accuracy

Model Predictive Accuracy was evaluated by concordance index(C-index) it measures the discriminatory power of the model. The value of C-index ranges from 0.5 < C. I <1 and the value of C-index was 0.76 indicates that the model had good power of prediction.

4.12 Ethical Consideration

Ethical permission was obtained from the research and ethical committee of the College of Health Sciences, Mekelle University, and sought from the institutional review board (IRB) of ACSH. The data from patients and medical records were handled with confidentiality, neither the case records nor the data extracted was used for any other purpose and all the collected patient information was stored anonymously.

4.13 Dissemination of Findings

After completion of this research project the result will be presented and disseminated for all responsible individuals and institutions like Ayer comprehensive specialized hospital and Tigray regional health bureau. Finally, the thesis final work will be published in journal articles that will be accessed by others.

5 Results

5.1 Socio-Demographic Characteristics

The study involved 203 patients admitted to an adult ICU center, Who had undergone mechanical ventilation with a majority aged 18-35, (41.87%), 36-50 (30.54%), and >50 (27.59%). Similarly, majority were male 122 (60.1%), while 81 (39.9%) was female (Table1).

Table 2: Summary of socio-demographic characteristics and Log-rank test for the VAP patients at ACSH Mekelle, Tigray.

Socio-demographic Characteristics					
Covariates	**category**	**VAP status**		**Incidence rate/1000 with 95% CI**	**P-value for Log-rank test**
		Events (N=124)	**Censored (N=79)**		
Age	18-35	54 (63.53%)	31 (36.47%)	0.32(0.16, 0.64)	0.012*
	36-50	38(61.29%)	24(38.71%)	0.32(0.17, 0.62)	
	>50	32(57.14%)	24(42.86%)	0.017(0.01, 0.03)	
Sex	Male	68 (55.74%)	54 (44.26%)	.02(0.01, 0.032)	0.126*
	Female	56(69.08%)	25 (30.86%)	0.25(0.15, 0.40)	

5.2 Clinical Factors

Many patients were 88(66.67%) from medical ward, primary indication for intubation was RDS 73(35.96%), Acute pulmonary edema 29(14.29%), trauma 28(13.79%), coma or impaired consciousness 48 (23.65%), Neuro-muscular disease 21(10.34%) and aspiration 4(1.96%) diagnostic modalities for those who had VAP patient follow up was auscultation 66(32.51%) and CxR 47 (23.15%). Concerning the presence of comorbidity

in the ICU admitted patients were hypertension 28 (13.79 %), DM 7 (3.45%), and non-co-morbid 150(73.89%) patients. (Table2).

Table 3: Summary of Clinical Factors and Log-rank test for the VAP Patients at ACSH Mekelle, Tigray

Clinical factors					
Covariates	**category**	**VAP status**		**Incidence rate/ 1000 with 95% CI**	**P-value for Log-rank test**
		Events (N=124)	**Censored (N=79)**		
Admission	Medical ICU	88(66.67%)	44(33.33%)	0.036(0.023, 0.056)	0.44
	Surgical ICU	36(50.70%)	35(49.30%)	0.04(0.02, 0.07)	
P't transfer from	Medical	28(56%)	22(44%)	0.14(0.094, 0.19)	0.070*
	Surgical	7(46.67%)	8(53.33%)	0.106 (0.05, 0.22)	
	Emergency OPD	48(64%)	27(36%)	0.01(0.06, 0.01)	
	Operative room	2(100%)	0(0%)	0.5(0.07, 3.54)	
	Oby/ gyn	8(61.54%)	5(38.46%)	0.15(0.07, 0.30)	
	Other hospitals	31(64.58%)	17(35.42%)	0.06(0.02, 0.11)	
Cause of ICU Admission	Trauma	27(55.10%)	22(44.90%)	0.33(0.14, 0.80)	0.049*
	Respiratory disease,	25(75.76%)	8(24.24%)	0.19(0.12, 0.28)	
	Neurologic disorder,	30(73.17%)	11(26.83%)	0.06(0.03, 0.12)	
	CV disorder	13(43.33%)	17(56.67%)	0.01(0.003, 0.03)	
	Intra-abdominal disorder	7(38.89%)	11(61.11%)	0.4(0.10, 1.60)	
	Metabolic or renal	17(68%)	8(32%)	0.03(0.01, 0.06)	
	Other	5(71.43%)	2(28.57%)	0.5(0.07, 3.50)	
Primary Indication for intubation	ARDS	47(64.38%)	26(35.62%)	0.05(0.03, 0.09)	0.050*
	Ac. pulmonary edema	13(44.83%)	16(55.17%)	0.006(0.001,0.026)	

	Aspiration	4(100%)	0(0%)	0.5(0.07, 3.50)	
	Trauma	14(50%)	14(50%)	0.3(0.12, 1.16)	
	Coma	30(62.5%)	18(37.5%)	0.04(0.02, 0.07)	
	Neuro-Muscular dise.	16(76.19%)	5(23.81%)	0.33(0.08, 1.33)	
Duration of MV	<=5 days	82 (58.57%)	58(41.43%)	0.05(0.03, 0.07)	0.11*
	>5days	42(66.67%)	21(33.33%)	0.02(0.01, 0.44)	
Dx modalities	Sputum culture	2(0.99%)	0(0%)	0.33(0.046, 2.36)	0.000*
	CxR	48(23.65%)	0(0%)	0.32(0.19, 0.55)	
	Auscultation	66(32.51%)	0(0%)	0.25(0.15,0.42)	
	Fever, Ausc. and CxR	8(3.94%)	0(0%)	0.5(0.07, 3.54)	
	None	0(0%)	79(38.92%)	-	
Presence of Comorbidity	HTN	15(12.10%)	13(16.46%)	0.13 (0.08, 0.23)	0.128*
	DM	6(4.84%)	2(2.53%)	0.21(0.09, 0.46)	
	HIV	9(7.26%)	3(3.80%)	0.22(0.11, 0.42)	
	CKD	2(1.61%)	1(1.27%)	0.5(0.07, 3.55)	
	Malignancy	1(0.81%)	1(1.27%)	0.11(0.02, 0.79)	
	None	91(73.39%)	59(74.68%)	0.15(0.12, 0.18)	

5.3 Other Possible Clinical Exposed Factors

Considering the other possible clinical conditions, 21(10.34%) were tracheostomies, 7(3.45%) were bronchoscopies, 8 (3.94%) were re-intubated, 145(71.43%) on NGT, 108(53.2%) patients took corticosteroid, 57(28.08%) surgical patients, 68(33.5%) had taken paralytic agent, 10(4.93%) of them were traumatic/emergency intubation, and 128(63.05%) was inotropic medications (Table3).

Table 4: Summary of Clinical Factors and Log-rank test for the VAP Patients at ACSH Mekelle, Tigray

Covariates	category	VAP status		Incidence rate/1000 with 95% CI	P-value for Log-rank test
		Events (N=124)	Censored (N=79)		
Tracheostomy	Yes	16(76.19%)	5(23.81%)	0.18 (0.11, 0.30)	0.685
	No	108(59.34%)	74(40.66%)	0.15 (0.12, 0.18)	
Bronchoscopy	Yes	4(57.14%)	3(42.86%)	0.10 (0.04, 0.27)	0.69
	No	120(61.22%)	76(38.78%)	0.16 (0.13, 0.18)	
Aspiration	Yes	34(91%)	3(8.11%)	0.23 (0.16, 0.32)	0.141*
	No	90(54.22%)	76(45.78%)	0.13 (0.11, 0.17)	
Re-intubation	Yes	6(75%)	2(25%)	0.23 (0.10, 0.51)	0.003*
	No	118(124%)	77(39.49%)	0.15 (0.12, 0.18)	
NGT	Yes	103(71.03%)	42(28.97%)	0.17(0.14, 0.21)	0.21*
	No	21(36.21%)	37(63.79%)	0.10 (0.6, 0.15)	
Corticosteroid	Yes	78(72.22%)	30(27.78%)	0.18 (0.14, 0.22)	0.054*
	No	46(48.42%)	49(51.58%)	0.12 (0.09, 0.16)	
P't transfer out from ICU after intubation	Yes	4(80%)	1(20%)	0.18 (0.07, 0.48)	0.954
	No	120(60.61%)	78(39.39%)	0.15 (0.13, 0.18)	
Surgical pt	Yes	32(56.14%)	25(43.86%)	0.16(0.11, 0.22)	0.14*
	No	92(63.01%)	54(36.99%)	0.15 (0.12, 0.18)	
Surgical Drainage	Yes	21(56.76%)	16(43.24%)	0.17 (0.11, 0.26)	0.075*
	No	103(62.05%)	63(37.95%)	0.15 (0.12, 0.18)	
Paralytic Agent	Yes	55(80.88%)	13(19.12%)	0.21 (0.16, 0.27)	0.10*
	No	69(51.11%)	66(48.89%)	0.12 (0.10, 0.16)	
Traumatic injury	Yes	7(70%)	3(30%)	0.16 (0.08, 0.34)	0.56
	No	117(60.62%)	76(39.38%)	0.15 (0.13, 0.18)	
P't on dialysis	Yes	4(80%)	1(20%)	0.15 (0.06, 0.41)	0.62
	No	120(60.61%)	78(39.39%)	0.15 (0.13, 0.18)	
Inotropic medications	Yes	85(66.41%)	43(33.59%)	0.17 (0.13, 0.20)	0.18*
	No	39(52%)	36(48%)	0.13 (0.10, 0.18)	

Notes: * According to the long rank test statistically significant at P-value >0.25

This study included 203 mechanical ventilated patients who undergo a VAP in Ayder Hospital Mekelle. Most of the patients 124 (61.08%), developed VAP while 79 (38.92%) were censored.

The overall exposure status, median survival time 6 days (CI: 95% 5, 8) and Overall incidence rate of occurrence of VAP was 15.3% (CI: 95% 0.13, 0.18) with total percentile of 813 - day person.

5.3.1 Overall Kaplan - Meier Survival Estimate

The results of Kaplan-Meier estimation showed that the highest occurrence of VAP happened in the early days over the analysis time in day of intubation and it gradually decreases over time after some time of follow-up time (Figure 2).

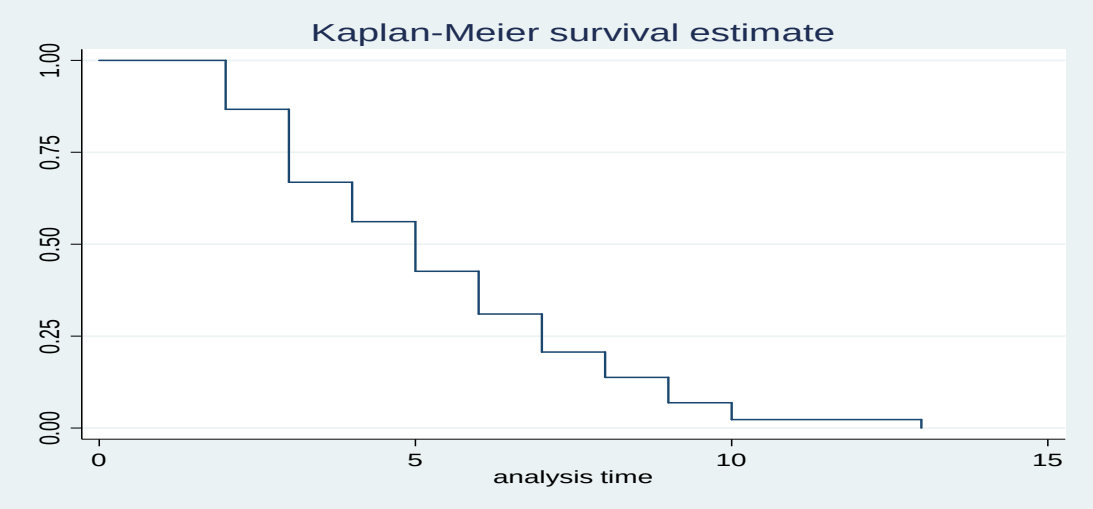

Figure 5: Kaplan-Meier survival estimates based on over all exposure status among VAP patients admitted in adult ICU Ayder Hospital Mekelle, Tigray, Ethiopia

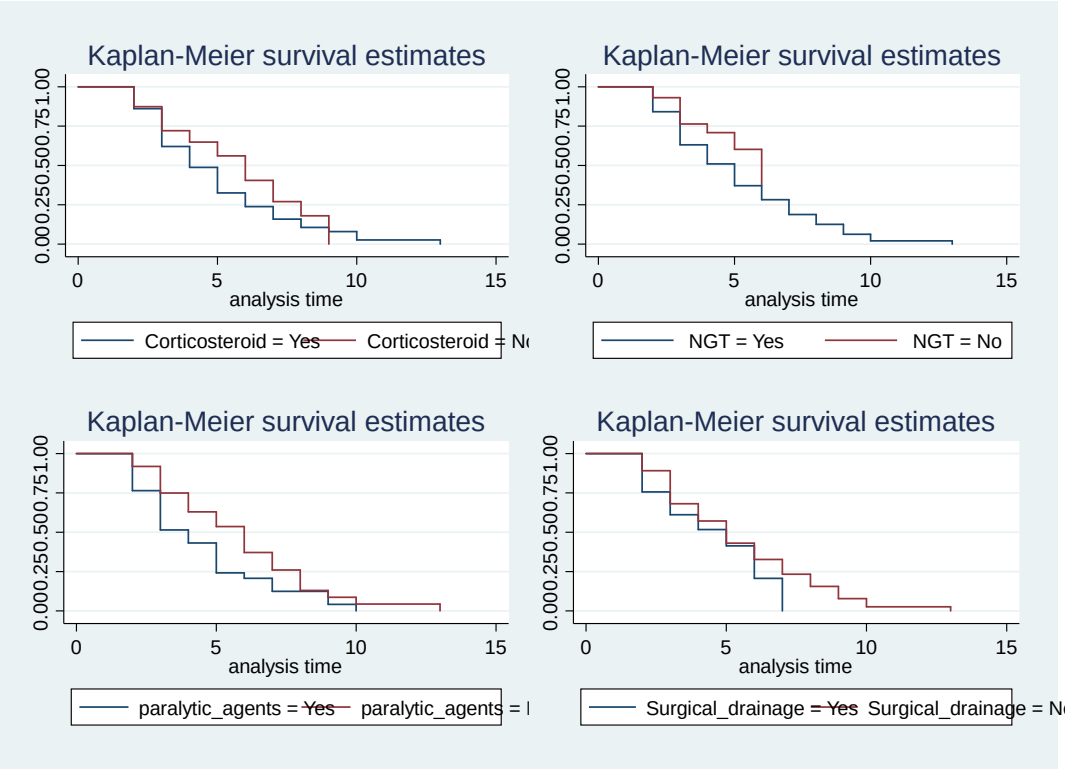

Figure 6: Kaplan-Meier survival estimates with corticosteroid, paralytic agent, NGT and surgical drainage among VAP patients admitted in adult ICU Ayder Hospital Mekelle, Tigray, Ethiopia

There was a graphically significant difference in the probability of occurrence of VAP across a given category of patients on corticosteroid, paralytic agents, NGT and surgical drainage.

In the final multivariable regression model, variables were selected using stepwise regression. The variables selected for the multivariable analysis were age, Sex, Patient transfer, cause of ICU admission, primary indication for intubation, dialysis, duration of MV, diagnosis modalities, comorbidity, corticosteroid, aspiration of gastric contents, re-intubation, NGT, surgical patient, surgical drainage, paralytic agents and inotropic medications.

The multivariable regression model on VAP data shows that, this study looks at the lognormal model. The significant variables selected for the multivariable analysis were sex, cause of ICU admission, primary indication for intubation and duration of MV (Table 5).

The multivariable lognormal regression model shows that Sex of patient was significantly associated with the hazard of the occurring VAP. The hazard of developing VAP for the female patients decreases by 15% (AHR=0.85, 95%CI: 0.73, 0.98) than compared male patients.

The hazard of occurring VAP among primary indication for intubation patients who with trauma was lower by 28% with (AHR=0.72, 95%CI: 0.53, 0.98) while compared to ARDS.

The hazard of occurring VAP among cause of admission to ICU patients with Respiratory disease was lower by 28% with (AHR=0.72, 95%CI: 0.53, 0.98) while compared to Trauma.

The hazard of occurring VAP for the duration of MV, late pneumonia (>=5 days) 1.32 times higher with (AHR=1.32, 95%CI: 1.16, 1.63) than those who had early pneumonia (<5 days).

Table 5: Parametric lognormal regression model for predictors of time to development ventilator associated pneumonia

Covariates		AHR	P-value	95% CI	
Age	<18-35	1			
	36-50	0.91	0.284	0.76	1.08
	>50	0.94	0.508	0.78	1.13
Sex	Male	1			
	Female	0.85	0.047*	0.73	0.98
Patient Transfer	Medical ward	1			
	Surgical ward	1.35	0.113	0.93	1.95
	Emergency OPD	0.84	0.086	0.69	1.03
	Operative Room	1.00	0.991	0.49	2.03
	OBY/ GYN ward	0.82	0.265	0.59	1.16
	Other Hospital	0.82	0.076	0.66	1.02
Cause of ICU admission	Trauma	1			
	Respiratory disease	0.72	0.041*	0.53	0.98
	Neurologic disorder	0.87	0.406	0.63	1.21
	Cardiovascular disorder	1.15	0.539	0.73	1.80
	GI-disorder	0.76	0.168	0.52	1.12
	Metabolic or renal	0.90	0.551	0.63	1.28
	Other	0.88	0.609	0.54	1.43
Primary Indication for intubation	ARDS	1			
	CHF	0.71	0.079	0.49	1.04
	Aspiration,	1.31	0.216	0.85	2.02

	Trauma	0.72	0.038*	0.53	0.98
	Coma	0.87	0.170	0.71	1.06
	Neuro-muscular diseases (GBS…)	1.09	0.570	0.81	1.47
Dialysis	Yes	1.48	0.095	0.93	2.35
	No	1			
Duration of MV	< 5 days	1			
	>= 5 days	1.32	0.001**	1.13	1.55
DX modalities	Sputum culture	1			
	CxR	1.15	0.630	0.65	2.03
	Auscultation	1.17	0.581	0.67	2.06
	Fever, Auscultation and CxR	0.74	0.378	0.38	1.44
Corticosteroid	Yes	1			
	No	0.98	0.796	0.84	1.15
Aspiration of gastric content	Yes	0.89	0.214	0.75	1.07
	No	1			
Re-intubation	Yes	1.17	0.372	0.83	1.66
	No	1			
NGT	Yes	1.16	0.153	0.95	1.41
	No	1			
Surgical patient	Yes	0.93	0.547	0.73	1.18
	No	1			
Surgical drainage	Yes	0.93	0.547	0.73	1.18
	No	1			
Paralytic agents	Yes	0.87	0.064	0.74	1.01

Inotropic Medications	No	1			
	Yes	1.03	0.734	0.88	1.20
_Cons	No	1			
		0.19	0.985	0.00	1E+72
/lnsigma		0.36	0.001	0.32	0.40
AIC		168			

Notes: 1: *=shows significance difference at p<0.05, **= shows significance difference at p<0.001, reference category, CI: confidence interval, AHR: Adjusted hazard ratio, MV: Mechanical ventilator. VAP: ventilator associated pneumonia, ICU: Intensive care unit, Pt: patient, ARDS: acute respiratory syndrome, GBS: Guillain-Barre syndrome, CHF: cardiac heart frailer, NGT: nasogastric tube, CxR: chest x-ray, GI: gastrointestinal, Oby/Gyn: obstetrics and gynecology, OPD: outpatient department.

6 Discussion

This retrospective cohort study aimed to assess predictors and time to pneumonia development in mechanically ventilated adult patients in the ICU at Ayder Comprehensive Specialized Hospital.

The cumulative incidence of ventilator associated pneumonia (VAP) was higher as person-days of observation increased. This finding is in-line with the study conducted in Gondar comprehensive specialized hospital (28); while it is higher than studies conducted in China, Taiwan(17), and Zewuditu hospital (17, 21, 22). This might be due to a poorer health care system in Ethiopia and worse in Tigray region as compared to Zewditu Hospital, Addis Ababa.

The difference may be due to study time, which currently is investigation access, and different infection prevention infrastructures that have a high quality of detection and prevention of pneumonia. The level of development of the health system affects the occurrence of pneumonia due to the presence or absence of equipment and pneumonia control measurements. The other reason may be due to differences in study participants; in those studies, the participants were in different wards, such as ICU, emergency wards, and surgical wards, which may be a higher risk of developing pneumonia (33,43).

This study revealed that as duration of MV increases the probability of VAP increases. This result is supported by other studies done in Portuguese and southern Taiwan (17). This is because longer intubation is a high risk of exposing respiratory tract to microorganisms causing pneumonia and deriving from handling of healthcare personnel during intubation.

In this study, respiratory disease as cause of ICU admission was decreasing the hazard of developing pneumonia. While we compared with the patients who have trauma as a cause of intensive care unit admission. This finding was contradicting with study conducted in teaching and referral hospital ICUs of Southern Ethiopia (29). Respiratory disease and pneumonia have a close relationship but this finding may be because of from a combination of factors, including differences in patient management, characteristics, and treatment protocols.

Patients with primary indication for intubation due to trauma were decreasing the hazard of developing pneumonia as compared with ARDS. This finding was similar with studies conducted in Europe and Addis Ababa (13).

This may be due to more focus and care for trauma patients. And more traumatic patients died with short period of time after admitted to ICU because of the trauma degree seriousness. Moreover, patients with Respiratory tract infection may have chance of descending infection due to the mechanical ventilation.

Patients' sex being female was decreasing the hazard of developing ventilator associated pneumonia as compared to their counterparts. This finding is in-line with the study conducted in France and Berlin(25, 26). This may be the reason that females generally have smaller and more compliant airways compared to males (anatomically). This may make them less prone to airway complications and development of VAP. Additionally, this may be because of sociocultural differences females are less likely to using substances.

7 Strength and Limitations of the study

7.1 Strength

The parametric survival analysis was more efficient, accurate and good statically power of analysis increase the strength of analysis.

7.2 Limitations

To conduct the study secondary data was used for these reason important variables like the process of nursing care given to the patients, hygiene, sterilization technique and sanitation couldn't be assessed.

8 Conclusion and Recommendations

8.1 Conclusion

The cumulative incidence of pneumonia among mechanical ventilated patients in the Ayder Comprehensive Specialized Hospital was high. Female patients, respiratory disease, duration of mechanical ventilation and trauma patients were significant predictors for the occurring of pneumonia among adult patients with MV in ICU. The lognormal regression survival regression model which had the lowest AIC, BIC and good log likely hood value as compared to the other survival parametric models and selected as a best fitted model.

8.2 Recommendations

For ACSH ICU administration:

Decision-makers would be butter prioritizing resources allocation for those who are under mechanical ventilation to minimize the incidence of pneumonia.

For ACSH, ICU Clinicians and Nurses:

Increased monitoring of high-risk populations: VAP is more likely to develop in males, trauma patients, respiratory diseases and those who need longer ventilation; as a result, these patients need to be closely monitored. Due to their substantial correlation with VAP risk, trauma and respiratory disease admissions should be assigned to particular care packages.

Shorten the Mechanical Ventilation Length: Reduce the risk for VAP by minimizing the amount of time patients are on mechanical ventilation when clinically feasible. This can be done by routinely evaluating the patients' potential to be weaned off ventilation, which will shorten exposure time.

For researchers:

A prospective and multicenter study is may be necessary to validate the disease burden and risk factors identified in this study.

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Annex

Annex – I

Information sheet

Greetings:

My name is **Masresha Gebru** with currently I am a post graduate student of Biostatistics in department of Biostatistics, school of public health, college of health science Mekelle University.

The objective of the study is to determine Predictors and time to pneumonia development in mechanically ventilated adults in the ICU at Ayder Comprehensive Specialized Hospital, Mekelle, Tigray (2024). Around 203 patient folders were reviewed in the study. In each patient folder it reviews the status of client related to ventilation associated events. Even though study is conducted for the partial fulfillment of master program in biostatistics, it is believed to contribute much to the understanding predictors and time to pneumonia development in mechanically ventilated adults' patients with contributing to the existing situations.

Name was not written on the Checklist and all the information taken was kept strictly confidential.

Thank you!

Contact

Name: Masresha Gebru

Tel: 251-913-93-1992 E-mail: g.kibrof@gmail.com

Annex – II

Checklist for Information extraction format

Medical registration number of patients_____

I. Socio demographic characteristics				Remark
	Sex of client	A. Male	B. Female	
	Age of client	_____(years)		
II. Clinical characteristics				
	Presence of Mechanical ventilation-associated pneumonia	A. Yes	B. No	
	Date of intubation under mechanical ventilator	_____		
	Date of extubation from mechanical ventilator	_____		
	Duration of mechanical ventilation	_____(days)		
	Onset of Ventilator-associated pneumonia after intubation	_____(days)		
	Admission ICU	A. Medical ICU B. Surgical ICU		
	Patient transfer from	A. Medical ward B. Surgical ward C. Emergency OPD D. Operative room E. Oby/Gyn ward F. Other hospitals		
	Primary indication for mechanical ventilation	I. ARDS II. Acute pulmonary edema/CHF III. Aspiration, IV. Trauma V. Coma or impaired consciousness VI. Neuro-muscular diseases (GBS, myasthenia gravis)		
	Causes of ICU admission	A. Trauma B. Respiratory disease, C. Neurologic disorder, D. Cardiovascular disorder, E. Intra-abdominal disorder (GI),		

		F. Poisoning (usually attempted suicide), or intoxication G. Metabolic or Renal H. Others _____	
	Place of intubation	A. ICU B. Emergency C. Operating room D. Other hospital	
	Presence of Co-morbidity	A. Hypertension B. Diabetes C. Immune-compromised (AIDS) D. Chronic kidney disease E. Presence of malignancy (cancer) F. Chronic liver disease G. Others _____	
	Length of stay in the ICU	_____(days)	

III. Other Possible exposed clinical factors for ventilator-associated pneumonia

		Yes	**No**	
	Tracheostomy			
	Bronchoscopy			
	Aspiration of gastric content			
	Re-intubation			
	Presence central venous and arterial catheters, duration of central venous and arterial catheters,			
	NGT and enteral feeding			
	Prior use of antibiotics before intubation and on intubation			
	Corticosteroid			
	Transfer out of the hospital (ICU) after intubation			
	Does the p't surgery			
	Surgical drainage (mainly thoracic or thoraco-abdominal)			
	Paralytic agents, continuous intravenous sedation			
	Traumatic intubation (Emergency intubation)			

	Does the p't Dialysis?			
	Ionotropic medication			

Annex II

. vif

Variable	VIF	1/VIF
surgical_pt	1.65	0.607662
Surgical_d~e	1.44	0.695445
DX_modalit~t	1.40	0.713999
cause_ICU_~n	1.38	0.724903
Aspiration~t	1.31	0.761807
NGT	1.27	0.786456
paralytic_~s	1.26	0.793113
Sex	1.23	0.815969
Corticoste~d	1.18	0.845042
indication~n	1.18	0.847110
Dialysis	1.12	0.893564
Duration_M~g	1.10	0.906263
Age_cat	1.10	0.907598
Patient_tr~r	1.10	0.910511
Ionotropic~n	1.10	0.911899
Re_intubat~n	1.10	0.912323
Mean VIF	1.24	

Cox regression -- Breslow method for ties

No. of subjects =	203	Number of obs =	203
No. of failures =	124		
Time at risk =	826		
		LR chi2(33) =	158.46
Log likelihood =	-479.95186	Prob > chi2 =	0.0000

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Presence_MVAP	1.70e-21	.	.	.	.	.
Age_cat						
36-50 years	1.276349	.344398	0.90	0.366	.7521234	2.165956
>50 years	.905477	.2810492	-0.32	0.749	.4928044	1.66372
Sex						
Female	1.467465	.3434668	1.64	0.101	.9275558	2.321642
Patient_transfer						
surgical ward	.382472	.2316112	-1.59	0.112	.1167193	1.253304
Emergency OPD	1.454929	.469776	1.16	0.246	.7726824	2.739573
Operative Room	.9293381	.9450179	-0.07	0.943	.1266516	6.819253
Oby/ gyn ward	1.4951	.8106189	0.74	0.458	.5166099	4.32691
Other hospital	1.306424	.4249769	0.82	0.411	.6905422	2.4716
cause_ICU_admission						
Respiratory disease	2.748856	1.314337	2.11	0.034	1.076859	7.0169
Neurologic disorder	1.396341	.6974952	0.67	0.504	.5245686	3.716898
Cardiovascular disorder	.8623154	.5178744	-0.25	0.805	.2657458	2.798117
Intra-abdominal disorder (GI)	1.798943	1.00039	1.06	0.291	.6048739	5.350197
Metabolic or renal	1.418084	.7922929	0.63	0.532	.4743837	4.239102
Other	1.795487	1.294911	0.81	0.417	.4368102	7.38026
indication_intubation						
Acute pulmonary edema/CHF	2.025437	1.079457	1.32	0.185	.7126409	5.756607
Aspiration	.4751011	.3222778	-1.10	0.273	.1257147	1.795502
Trauma	2.16695	1.098131	1.53	0.127	.8025855	5.850684
Coma or impaired consciousness	1.525171	.4759693	1.35	0.176	.8273304	2.81163
Neuro-muscular diseases (GBS, myasthenia grav..	.9883807	.4328688	-0.03	0.979	.4189229	2.331924
Dialysis						
Yes	.584293	.4377453	-0.72	0.473	.1345615	2.537118
2.Duration_MV_catg1	.4896736	.1234433	-2.83	0.005	.2987616	.8025805
DX_modalities_cat						
CxR	.6083092	.5773622	-0.52	0.600	.0946731	3.908608
Auscultation	.5850736	.5476315	-0.57	0.567	.0934291	3.663861
Fever, Auscultation and CxR	2.002823	2.099782	0.66	0.508	.2565864	15.63334
99	2.365348	3.372548	0.60	0.546	.1446238	38.68571
Corticosteroid						
No	1.293062	.3288694	1.01	0.312	.7854711	2.128672
Aspiration_gastric_cont						
Yes	1.376008	.3668177	1.20	0.231	.8160308	2.320252
Re_intubation						
Yes	.648456	.3430318	-0.82	0.413	.2299306	1.828792
NGT						
Yes	.7086313	.2157552	-1.13	0.258	.390173	1.287015
surgical_pt						
Yes	1.611891	.7312589	1.05	0.293	.6624839	3.921897
Surgical_drainage						
Yes	1.181498	.4475047	0.44	0.660	.5623823	2.482187
paralytic_agents						
Yes	1.583157	.364762	1.99	0.046	1.007873	2.486808
Ionotropic_medication						
Yes	.96398	.2331179	-0.15	0.879	.6000993	1.548506

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Akaike's information criterion and Bayesian information criterion

Model	Obs	ll(null)	ll(model)	df	AIC	BIC
.	203	-559.1831	-479.9519	33	1025.904	1135.24

Note: N=Obs used in calculating BIC; see **[R] BIC note**.

Loglogistic AFT regression

No. of subjects =	203	Number of obs =	203
No. of failures =	124		
Time at risk =	826		
		LR chi2(34) =	185.34
Log likelihood =	-49.624501	Prob > chi2 =	0.0000

_t	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Presence_MVAP	4.59776	250.9546	0.02	0.985	-487.2643	496.4598
Age_cat						
36-50 years	-.1004167	.088931	-1.13	0.259	-.2747182	.0738849
>50 years	-.1058922	.0982152	-1.08	0.281	-.2983904	.0866061
Sex						
Female	-.1599848	.0808266	-1.98	0.048	-.3184021	-.0015676
Patient_transfer						
surgical ward	.2593259	.196456	1.32	0.187	-.1257207	.6443725
Emergency OPD	-.2222121	.1011342	-2.20	0.028	-.4204314	-.0239928
Operative Room	.0118048	.3360756	0.04	0.972	-.6468913	.6705009
Oby/ gyn ward	-.2206021	.1702049	-1.30	0.195	-.5541974	.1129933
Other hospital	-.2442098	.1162942	-2.10	0.036	-.4721422	-.0162774
cause_ICU_admission						
Respiratory disease	-.3822671	.1617489	-2.36	0.018	-.699289	-.0652451
Neurologic disorder	-.1695772	.184717	-0.92	0.359	-.5316159	.1924615
Cardiovascular disorder	.0796112	.2550697	0.31	0.755	-.4203162	.5795386
Intra-abdominal disorder (GI)	-.2740415	.1968989	-1.39	0.164	-.6599562	.1118732
Metabolic or renal	-.172305	.1857932	-0.93	0.354	-.5364529	.1918429
Other	-.146336	.2460542	-0.59	0.552	-.6285933	.3359213
indication_intubation						
Acute pulmonary edema/CHF	-.3500958	.2115213	-1.66	0.098	-.76467	.0644783
Aspiration	.30997	.2480299	1.25	0.211	-.1761596	.7960996
Trauma	-.3904485	.1593894	-2.45	0.014	-.7028461	-.0780509
Coma or impaired consciousness	-.1758823	.1059753	-1.66	0.097	-.38359	.0318255
Neuro-muscular diseases (GBS, myasthenia grav..	.0432692	.1662706	0.26	0.795	-.2826153	.3691536
Dialysis						
Yes	.503992	.2633542	1.91	0.056	-.0121727	1.020157
2.Duration_MV_catg1	.2783063	.083354	3.34	0.001	.1149355	.441677
DX_modalities_cat						
CxR	.2072855	.2834639	0.73	0.465	-.3482936	.7628647
Auscultation	.223469	.283886	0.79	0.431	-.3329374	.7798753
Fever, Auscultation and CxR	-.2623524	.3331695	-0.79	0.431	-.9153527	.3906479
99	-.1729163	.4131051	-0.42	0.676	-.9825873	.6367548
Corticosteroid						
No	-.0262063	.0815234	-0.32	0.748	-.1859893	.1335768
Aspiration_gastric_cont						
Yes	-.1149009	.0942022	-1.22	0.223	-.2995338	.0697319
Re_intubation						
Yes	.144616	.1834995	0.79	0.431	-.2150363	.5042684
NGT						
Yes	.1079282	.0986193	1.09	0.274	-.0853621	.3012186
surgical_pt						
Yes	-.1393695	.1448116	-0.96	0.336	-.423195	.144456
Surgical_drainage						
Yes	-.0705735	.1279272	-0.55	0.581	-.3213062	.1801592
paralytic_agents						
Yes	-.1347541	.0821679	-1.64	0.101	-.2958003	.0262921
Ionotropic_medication						
Yes	.0455149	.0845461	0.54	0.590	-.1201924	.2112223
_cons	-3.041427	250.9549	-0.01	0.990	-494.9039	488.8211
/lngamma	-1.589869	.0749887	-21.20	0.000	-1.736844	-1.442894
gamma	.2039524	.0152941			.1760752	.2362432

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Akaike's information criterion and Bayesian information criterion

Model	Obs	ll(null)	ll(model)	df	AIC	BIC
.	203	-142.2931	-49.6245	36	171.249	290.5244

Note: N=Obs used in calculating BIC; see **[R] BIC note**.

Lognormal AFT regression

No. of subjects =	203	Number of obs =	203
No. of failures =	124		
Time at risk =	826		
		LR chi2(34) =	178.64
Log likelihood =	-48.26562	Prob > chi2 =	0.0000

_t	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Presence_MVAP	3.174012	85.55921	0.04	0.970	-164.519	170.867
Age_cat						
36-50 years	-.0967904	.0902842	-1.07	0.284	-.2737442	.0801635
>50 years	-.0636579	.0962044	-0.66	0.508	-.252215	.1248992
Sex						
Female	-.1567079	.0788944	-1.99	0.047	-.3113381	-.0020778
Patient_transfer						
surgical ward	.2993929	.1889412	1.58	0.113	-.0709251	.6697109
Emergency OPD	-.1755485	.1023248	-1.72	0.086	-.3761015	.0250044
Operative Room	-.0042557	.3632081	-0.01	0.991	-.7161306	.7076192
Oby/ gyn ward	-.1936321	.1736952	-1.11	0.265	-.5340685	.1468043
Other hospital	-.2000282	.1126951	-1.77	0.076	-.4209065	.0208501
cause_ICU_admission						
Respiratory disease	-.3238189	.1582879	-2.05	0.041	-.6340575	-.0135802
Neurologic disorder	-.1389452	.1673404	-0.83	0.406	-.4669263	.1890359
Cardiovascular disorder	.1406839	.2292291	0.61	0.539	-.3085969	.5899648
Intra-abdominal disorder (GI)	-.2721547	.1975073	-1.38	0.168	-.659262	.1149525
Metabolic or renal	-.1074741	.1802471	-0.60	0.551	-.460752	.2458037
Other	-.1269439	.2480375	-0.51	0.609	-.6130884	.3592006
indication_intubation						
Acute pulmonary edema/CHF	-.3379809	.1926321	-1.75	0.079	-.715533	.0395711
Aspiration	.2713257	.2191453	1.24	0.216	-.1581911	.7008426
Trauma	-.3247984	.1565499	-2.07	0.038	-.6316305	-.0179662
Coma or impaired consciousness	-.1399643	.1020939	-1.37	0.170	-.3400646	.0601361
Neuro-muscular diseases (GBS, myasthenia grav..	.0871306	.1535793	0.57	0.570	-.2138792	.3881404
Dialysis						
Yes	.394022	.2359375	1.67	0.095	-.068407	.8564511
2.Duration_MV_catg1	.2769157	.0808645	3.42	0.001	.1184241	.4354073
DX_modalities_cat						
CxR	.1401678	.2909638	0.48	0.630	-.4301107	.7104462
Auscultation	.159193	.2884863	0.55	0.581	-.4062297	.7246157
Fever, Auscultation and CxR	-.2960116	.336105	-0.88	0.378	-.9547653	.3627421
99	-.2624634	.4708088	-0.56	0.577	-1.185232	.6603049
Corticosteroid						
No	-.0208073	.0804737	-0.26	0.796	-.1785329	.1369182
Aspiration_gastric_cont						
Yes	-.1120988	.0902662	-1.24	0.214	-.2890173	.0648198
Re_intubation						
Yes	.1593583	.1784453	0.89	0.372	-.1903881	.5091046
NGT						
Yes	.1448077	.1012257	1.43	0.153	-.053591	.3432064
surgical_pt						
Yes	-.162892	.1333912	-1.22	0.222	-.4243339	.09855
Surgical_drainage						
Yes	-.0731792	.1213768	-0.60	0.547	-.3110735	.164715
paralytic_agents						
Yes	-.143999	.0777863	-1.85	0.064	-.2964574	.0084593
Ionotropic_medication						
Yes	.0274276	.0806296	0.34	0.734	-.1306035	.1854588
_cons	-1.657314	85.55979	-0.02	0.985	-169.3514	166.0368
/lnsigma	-1.029664	.0635023	-16.21	0.000	-1.154127	-.9052022
sigma	.3571268	.0226784			.3153328	.4044601

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Akaike's information criterion and Bayesian information criterion

Model	Obs	ll(null)	ll(model)	df	AIC	BIC
.	203	-137.5852	-48.26562	36	168.5312	287.8067

Note: N=Obs used in calculating BIC; see **[R] BIC note**.

Gompertz PH regression

No. of subjects = 203 Number of obs = 203
No. of failures = 124
Time at risk = 826
LR chi2(34) = 166.99
Log likelihood = -80.270131 Prob > chi2 = 0.0000

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Presence_MVAP	2.23e-09	2.11e-06	-0.02	0.983	0	.
Age_cat						
36-50 years	1.268531	.3547259	0.85	0.395	.7332895	2.194457
>50 years	.6031323	.2057229	-1.48	0.138	.3090833	1.176927
Sex						
Female	1.722757	.4152518	2.26	0.024	1.074116	2.763102
Patient_transfer						
surgical ward	.2665002	.1713483	-2.06	0.040	.0755807	.9396886
Emergency OPD	1.129223	.3794061	0.36	0.718	.5845014	2.181593
Operative Room	.4829325	.4883175	-0.72	0.472	.066557	3.504124
Oby/ gyn ward	1.142572	.641649	0.24	0.812	.3800697	3.434819
Other hospital	1.006062	.3401628	0.02	0.986	.5185881	1.951764
cause_ICU_admission						
Respiratory disease	3.134256	1.539784	2.33	0.020	1.196629	8.20936
Neurologic disorder	1.847601	.9526402	1.19	0.234	.6725443	5.075696
Cardiovascular disorder	.6571744	.4043144	-0.68	0.495	.1967862	2.194657
Intra-abdominal disorder (GI)	1.787884	.9924458	1.05	0.295	.60234	5.306855
Metabolic or renal	1.460838	.85976	0.64	0.520	.4609322	4.629853
Other	2.369843	1.744336	1.17	0.241	.56	10.02885
indication_intubation						
Acute pulmonary edema/CHF	2.478462	1.337234	1.68	0.093	.8608418	7.135773
Aspiration	.3313734	.2270125	-1.61	0.107	.0865344	1.268956
Trauma	1.910803	1.00324	1.23	0.217	.682817	5.347212
Coma or impaired consciousness	1.303011	.4192676	0.82	0.411	.6935189	2.448148
Neuro-muscular diseases (GBS, myasthenia grav..	.4791217	.2180832	-1.62	0.106	.196337	1.169202
Dialysis						
Yes	.6219827	.4837413	-0.61	0.542	.1354454	2.856225
2.Duration_MV_catg1	.4454628	.115892	-3.11	0.002	.2675236	.7417555
DX_modalities_cat						
CxR	.525075	.4985333	-0.68	0.497	.081667	3.37595
Auscultation	.4226284	.3948074	-0.92	0.357	.0677315	2.637101
Fever, Auscultation and CxR	1.544003	1.604464	0.42	0.676	.2014255	11.83536
99	2.711016	3.875656	0.70	0.485	.164535	44.66896
Corticosteroid						
No	1.341306	.3475006	1.13	0.257	.8072383	2.228712
Aspiration_gastric_cont						
Yes	1.482798	.4014216	1.46	0.146	.8722595	2.520685
Re_intubation						
Yes	.6476709	.3395502	-0.83	0.407	.2317931	1.809707
NGT						
Yes	.5675141	.1839588	-1.75	0.081	.3006499	1.071254
surgical_pt						
Yes	2.16272	1.08799	1.53	0.125	.8068453	5.797095
Surgical_drainage						
Yes	1.103793	.4326576	0.25	0.801	.5119635	2.379776
paralytic_agents						
Yes	1.709262	.398374	2.30	0.021	1.082483	2.69896
Ionotropic_medication						
Yes	1.233067	.3103886	0.83	0.405	.7528727	2.019537
_cons	2.35e+07	2.22e+10	0.02	0.986	0	.
/gamma	.4742176	.0487492	9.73	0.000	.3786709	.5697643

Note: Estimates are transformed only in the first equation.
Note: _cons estimates baseline hazard.

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Akaike's information criterion and Bayesian information criterion

Model	Obs	ll(null)	ll(model)	df	AIC	BIC
.	203	-163.7642	-80.27013	36	232.5403	351.8157

Note: N=Obs used in calculating BIC; see **[R] BIC note**.

Weibull PH regression

No. of subjects =	203	Number of obs =	203
No. of failures =	124		
Time at risk =	826		
		LR chi2(34) =	187.29
Log likelihood =	-52.334067	Prob > chi2 =	0.0000

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Presence_MVAP	3.16e-10	4.86e-07	-0.01	0.989	0	.
Age_cat						
36-50 years	1.395106	.4011049	1.16	0.247	.7941077	2.450952
>50 years	.73531	.2488362	-0.91	0.364	.3788048	1.427334
Sex						
Female	1.813561	.4431281	2.44	0.015	1.123436	2.927628
Patient_transfer						
surgical ward	.1947359	.1298981	-2.45	0.014	.052681	.7198429
Emergency OPD	1.441794	.5027866	1.05	0.294	.7278963	2.855858
Operative Room	.5825171	.5945826	-0.53	0.597	.078791	4.306663
Oby/ gyn ward	1.562838	.9111962	0.77	0.444	.4984593	4.900022
Other hospital	1.260122	.429213	0.68	0.497	.6463728	2.456644
cause_ICU_admission						
Respiratory disease	4.628278	2.352858	3.01	0.003	1.708826	12.53549
Neurologic disorder	1.827186	.9559498	1.15	0.249	.6553146	5.094665
Cardiovascular disorder	.7037739	.4362671	-0.57	0.571	.2088219	2.371866
Intra-abdominal disorder (GI)	2.166885	1.234431	1.36	0.175	.7094526	6.61833
Metabolic or renal	1.626604	.9774644	0.81	0.418	.5009277	5.281882
Other	2.767463	2.045974	1.38	0.169	.6498182	11.78614
indication_intubation						
Acute pulmonary edema/CHF	2.695217	1.48494	1.80	0.072	.9154211	7.935357
Aspiration	.2790574	.2004601	-1.78	0.076	.0682708	1.140649
Trauma	3.010177	1.655741	2.00	0.045	1.024213	8.84695
Coma or impaired consciousness	1.820364	.6051716	1.80	0.072	.948812	3.492499
Neuro-muscular diseases (GBS, myasthenia grav..	.8070657	.3523278	-0.49	0.623	.3430152	1.89891
Dialysis						
Yes	.5818767	.461897	-0.68	0.495	.1227842	2.757526
2.Duration_MV_catg1	.3250931	.0882978	-4.14	0.000	.1909039	.5536058
DX_modalities_cat						
CxR	.4223436	.4311439	-0.84	0.398	.0571121	3.123229
Auscultation	.3619524	.3612938	-1.02	0.309	.051168	2.560379
Fever, Auscultation and CxR	2.22404	2.470585	0.72	0.472	.2521051	19.62021
99	4.062161	6.042144	0.94	0.346	.2201213	74.96391
Corticosteroid						
No	1.53507	.4182277	1.57	0.116	.8999522	2.618405
Aspiration_gastric_cont						
Yes	1.662344	.4605973	1.83	0.067	.9657676	2.861339
Re_intubation						
Yes	.5439529	.2952213	-1.12	0.262	.1877526	1.575929
NGT						
Yes	.5145641	.1702766	-2.01	0.045	.2690078	.9842699
surgical_pt						
Yes	2.204023	1.127449	1.54	0.122	.8087074	6.006768
Surgical_drainage						
Yes	1.179988	.4781785	0.41	0.683	.5332571	2.611071
paralytic_agents						
Yes	2.024605	.481562	2.97	0.003	1.270217	3.227028
Ionotropic_medication						
Yes	1.07927	.2707202	0.30	0.761	.6601118	1.764584
_cons	2.03e+07	3.13e+10	0.01	0.991	0	.
/ln_p	1.146741	.072011	15.92	0.000	1.005602	1.28788
p	3.147918	.2266847			2.733553	3.625094
1/p	.3176703	.0228758			.2758549	.3658243

Note: Estimates are transformed only in the first equation.
Note: _cons estimates baseline hazard.

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Akaike's information criterion and Bayesian information criterion

Model	Obs	ll(null)	ll(model)	df	AIC	BIC
.	203	-145.9775	-52.33407	36	176.6681	295.9435

Note: N=Obs used in calculating BIC; see **[R] BIC note**.

Exponential PH regression

No. of subjects =	203	Number of obs =	203
No. of failures =	124		
Time at risk =	826		
		LR chi2(34) =	133.42
Log likelihood =	-131.9692	Prob > chi2 =	0.0000

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Presence_MVAP	1.89e-08	.0000116	-0.03	0.977	0	.
Age_cat						
36-50 years	1.103004	.2826201	0.38	0.702	.6675372	1.822545
>50 years	.9957686	.2776322	-0.02	0.988	.576545	1.719822
Sex						
Female	1.185787	.2616802	0.77	0.440	.7694193	1.82747
Patient_transfer						
surgical ward	.6992488	.381101	-0.66	0.512	.2402781	2.034929
Emergency OPD	1.164919	.3435999	0.52	0.605	.6534748	2.076647
Operative Room	.9607457	.9608688	-0.04	0.968	.1353	6.822115
Oby/ gyn ward	1.179875	.5943459	0.33	0.743	.4395972	3.166774
Other hospital	1.16743	.3660696	0.49	0.622	.6314231	2.158445
cause_ICU_admission						
Respiratory disease	1.466677	.6546414	0.86	0.391	.6115141	3.51773
Neurologic disorder	1.159602	.5507712	0.31	0.755	.4571062	2.941715
Cardiovascular disorder	.8705671	.5261043	-0.23	0.819	.2663183	2.845794
Intra-abdominal disorder (GI)	1.294453	.7014281	0.48	0.634	.4475525	3.743939
Metabolic or renal	1.140667	.5936613	0.25	0.800	.4112917	3.163498
Other	1.192572	.8342179	0.25	0.801	.3027328	4.697966
indication_intubation						
Acute pulmonary edema/CHF	1.412451	.7386477	0.66	0.509	.5067965	3.936526
Aspiration	.7262736	.4522148	-0.51	0.607	.2143379	2.460943
Trauma	1.399319	.6383585	0.74	0.461	.5722754	3.421593
Coma or impaired consciousness	1.16417	.3366171	0.53	0.599	.6605316	2.051821
Neuro-muscular diseases (GBS, myasthenia grav..	.9185376	.3892727	-0.20	0.841	.4002774	2.107817
Dialysis						
Yes	.7026344	.4850882	-0.51	0.609	.181582	2.718855
2.Duration_MV_catg1	.7423641	.1696113	-1.30	0.192	.4743939	1.161702
DX_modalities_cat						
CxR	.8211491	.7012265	-0.23	0.818	.154004	4.378366
Auscultation	.7972812	.6735311	-0.27	0.789	.1522402	4.175358
Fever, Auscultation and CxR	1.286209	1.239658	0.26	0.794	.1944991	8.505616
99	1.373593	1.852283	0.24	0.814	.0977276	19.30629
Corticosteroid						
No	1.064745	.2474252	0.27	0.787	.6752173	1.678988
Aspiration_gastric_cont						
Yes	1.131738	.2869645	0.49	0.626	.6885166	1.860276
Re_intubation						
Yes	.8319223	.4200217	-0.36	0.716	.3092625	2.237887
NGT						
Yes	.8451048	.2414529	-0.59	0.556	.4827428	1.479467
surgical_pt						
Yes	1.208357	.4795042	0.48	0.633	.5551609	2.630098
Surgical_drainage						
Yes	1.074692	.3776472	0.20	0.838	.5397238	2.139916
paralytic_agents						
Yes	1.199954	.2609662	0.84	0.402	.7835113	1.83774
Ionotropic_medication						
Yes	.9872733	.2267329	-0.06	0.956	.6294397	1.548534
_cons	1.14e+07	7.00e+09	0.03	0.979	0	.

Note: _cons estimates baseline hazard.

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Akaike's information criterion and Bayesian information criterion

Model	Obs	ll(null)	ll(model)	df	AIC	BIC
.	203	-198.6788	-131.9692	35	333.9384	449.9006

Note: N=Obs used in calculating BIC; see **[R] BIC note**.

Annex II

Used STATA commands

// to generate catagory coding missed variables //

codebook onset_MVAP ……. //To describe onset of MVAP data contents //

tab onset_MVAP // To tabulate onset_MVAP table of frequencies //

list if onset_MVAP =. 99

mvencode 99 // To change missing values to numeric values and vice versa //

mvencode

mvencode onset_MVAP =99

mvencode onset_MVAP =99

mvencode onset_MVAP = 99

mvencode onset_MVAP , mv(99)

codebook onset_MVAP

tab onset_MVAP

mvencode DX_modalities , mv(99)

gen Age_cat=. // to create Age_ cat new variable //

replace Age_cat =1 if Age >=18 & Age <35

replace Age_cat =2 if Age >=35 & Age <=50

replace Age_cat =3 if Age >50

replace Age_cat =2 if Age >=35 & Age <50

replace Age_cat =3 if Age >50

drop Age_cat

```
gen Age_cat=.
replace Age_cat =1 if Age >=18 & Age <35
replace Age_cat =2 if Age >=35 & Age <50
replace Age_cat =3 if Age >=50
drop Age_cat
gen Age_cat=.
replace Age_cat =1 if Age >=18 & Age <35
replace Age_cat =2 if Age >=35 & Age <=50
replace Age_cat =3 if Age >50
label define Age_cat  1">=18-35 years" 2"36-50 years" 3">50 years"
gen Duration_MV_catg=.
replace Duration_MV_catg = 2 if Duration_MV > 5
replace Duration_MV_catg = 1 if Duration_MV <= 5
label define duration_labels 1 "early vap" 2 "late vap"
label define Duration_MV_catg 1 "early vap" 2 "late vap"
drop Duration_MV_catg
tab Age_cat
replace Age_cat =1 if Age >=18 & Age <35
replace Age_cat =1 if Age >=35 & Age <50
replace Age_cat =1 if Age >=35 & Age <=50
replace Age_cat =1 if Age >=18 & Age <35
replace Age_cat =1 if Age >=18 & Age <35
replace Age_cat =2 if Age >=35 & Age <50
```

```
replace Age_cat =2 if Age >=35 & Age <=50

replace Age_cat =2 if Age >50

tab Age_cat

replace Age_cat =3 if Age >50

tab Age_cat

tab Age_cat

label value Age_cat Age_cat

tab Age_cat

**// Recoding and labling varibles//**

recode co_morbidity (1  =1 " HTN") (2 12  =2 " DM")(3  =3 " Immune-compromized HIV/AIDS)")(4  =4 " CKD")(5  =5 " Malignancy ca")(6  =6 " CLD") (7  =7 " None"), gen (co_morbidity_cat)

tab co_morbidity_cat

recode DX_modalities (2  =1 " Sputem culture") (3  =2 " CxR")(4  =3 "Auscultation ")(13 31 14 41 34 314  =4 " Fever, Auscultation and CxR"), gen ( DX_modalities_cat )

tab DX_modalities_cat

gen Duration_MV_catg=.

replace Duration_MV_catg = 2 if Duration_MV > 5

replace Duration_MV_catg = 1 if Duration_MV <= 5

label values Duration_MV_catg duration_labels

tab Duration_MV_catg

tab Presence_MVAP

label define stt 0 "censored" 1 "event"
```

```
rename onset_MVAP time

**//to declare survival analysis //**

 gen stt=.

tab Presence_MVAP

recode Presence_MVAP (2  =0 " censored") (1  =1 " Event"), gen ( stt_outcome )

tab stt_outcome

drop stt

tab stt_outcome

tab stt_outcome

stset time, failure(stt_outcome)

tab _st

tab _d

**//logrank testing//**

stir Sex

sts test Sex, logrank

stset time , failure( st_numeric ) id( mrn )

stptime, by( Sex ) dd(1) per(100)

stptime, by( Sex )

stptime, by( Admission_ICU )

stptime, by( Admission_ICU ) dd(1) per(100)

sts test Admission_ICU, logrank

stptime, by( Patient_transfer )

stptime, by( Patient_transfer ) dd(1) per(100)
```

```
stptime, by( Patient_transfer )

sts test Patient_transfer, logrank

stptime, by( Age )

stptime, by( age_categ ) dd(1) per(100)

stptime, by( age_categ )

sts test age_categ , logrank

stptime, by( cause_ICU_admission )

stptime, by( cause_ICU_admission ) dd(1) per(100)

sts test cause_ICU_admission , logrank

stptime, by( indication_intubation )

sts test indication_intubation , logrank

stptime, by( Duration_MV )

stptime, by( Duration_MV_catg )

sts test Duration_MV_catg , logrank

stptime, by( Presence_MVAP )

stptime, by( DX_modalities )

sts test DX_modalities , logrank

**// graphing //**

sts graph

sts graph, by (sex)

sts graph, by( Sex )

sts graph, by( NGT )

sts graph, by( Corticosteroid )
```

```
sts graph, by( paralytic_agents )

sts graph, by( Surgical_drainage )

**// model comparison and building //**

reg Presence_MVAP Age_cat Sex Patient_transfer cause_ICU_admission indication_intubation
Dialysis Duration_MV_catg Corticosteroid Aspiration_gastric_cont Re_intubation NGT
surgical_pt Surgical_drainage paralytic_agents Ionotropic_medication DX_modalities_cat

vif

streg Presence_MVAP ib1.Age_cat ib1.Sex ib1.Patient_transfer ib1.cause_ICU_admission
ib1.indication_intubation ib2.Dialysis ib1.Duration_MV_catg1 ib1.DX_modalities_cat
ib1.Corticosteroid ib2.Aspiration_gastric_cont ib2.Re_intubation ib2.NGT ib2.surgical_pt
ib2.Surgical_drainage ib2.paralytic_agents ib2.Ionotropic_medication, distribution(exponential)

estat ic

streg Presence_MVAP ib1.Age_cat ib1.Sex ib1.Patient_transfer ib1.cause_ICU_admission
ib1.indication_intubation ib2.Dialysis ib1.Duration_MV_catg1 ib1.DX_modalities_cat
ib1.Corticosteroid ib2.Aspiration_gastric_cont ib2.Re_intubation ib2.NGT ib2.surgical_pt
ib2.Surgical_drainage ib2.paralytic_agents ib2.Ionotropic_medication, distribution(weibull)

estat ic

streg Presence_MVAP ib1.Age_cat ib1.Sex ib1.Patient_transfer ib1.cause_ICU_admission
ib1.indication_intubation ib2.Dialysis ib1.Duration_MV_catg1 ib1.DX_modalities_cat
ib1.Corticosteroid ib2.Aspiration_gastric_cont ib2.Re_intubation ib2.NGT ib2.surgical_pt
ib2.Surgical_drainage ib2.paralytic_agents ib2.Ionotropic_medication, distribution(gompertz)

estat ic

streg Presence_MVAP ib1.Age_cat ib1.Sex ib1.Patient_transfer ib1.cause_ICU_admission
ib1.indication_intubation ib2.Dialysis ib1.Duration_MV_catg1 ib1.DX_modalities_cat
ib1.Corticosteroid ib2.Aspiration_gastric_cont ib2.Re_intubation ib2.NGT ib2.surgical_pt
ib2.Surgical_drainage ib2.paralytic_agents ib2.Ionotropic_medication, distribution(logn)

estat ic
```

streg Presence_MVAP ib1.Age_cat ib1.Sex ib1.Patient_transfer ib1.cause_ICU_admission ib1.indication_intubation ib2.Dialysis ib1.Duration_MV_catg1 ib1.DX_modalities_cat ib1.Corticosteroid ib2.Aspiration_gastric_cont ib2.Re_intubation ib2.NGT ib2.surgical_pt ib2.Surgical_drainage ib2.paralytic_agents ib2.Ionotropic_medication, distribution(loglog)

estat ic

stcox Presence_MVAP ib1.Age_cat ib1.Sex ib1.Patient_transfer ib1.cause_ICU_admission ib1.indication_intubation ib2.Dialysis ib1.Duration_MV_catg1 ib1.DX_modalities_cat ib1.Corticosteroid ib2.Aspiration_gastric_cont ib2.Re_intubation ib2.NGT ib2.surgical_pt ib2.Surgical_drainage ib2.paralytic_agents ib2.Ionotropic_medication

estat ic

//C-INDEX//

stcox Presence_MVAP ib1.Age_cat ib1.Sex ib1.Patient_transfer ib1.cause_ICU_admission ib1.indication_intubation ib2.Dialysis ib1.Duration_MV_catg1 ib1.DX_modalities_cat ib1.Corticosteroid ib2.Aspiration_gastric_cont ib2.Re_intubation ib2.NGT ib2.surgical_pt ib2.Surgical_drainage ib2.paralytic_agents ib2.Ionotropic_medication, efron

estat concordance

//over all model graph//

kdensity time, student(1) recast(spike) legend(on)

//cox-snail and Schoenfeld graph//

sts test Tracheostomy Presence_MVAP, logrank

sts test Corticosteroid , logrank

stir Sex

stphplot, by (Sex)

stcox Presence_MVAP ib1.Age_cat ib1.Sex ib1.Patient_transfer ib1.cause_ICU_admission ib1.indication_intubation ib2.Dialysis ib1.Duration_MV_catg1 ib1.DX_modalities_cat

ib1.Corticosteroid ib2.Aspiration_gastric_cont ib2.Re_intubation ib2.NGT ib2.surgical_pt ib2.Surgical_drainage ib2.paralytic_agents ib2.Ionotropic_medication

estat phtest

predict cs, csnell

sts generate M = na

stset cs, failure(Presence_MVAP)

line M cs cs, sort xlab(0 1 to 4) ylab(0 1 to 4)

drop cs

drop M

tab stt_outcome

sts generate M = na

drop M

sts generate M = na

stcox Presence_MVAP ib1.Age_cat ib1.Sex ib1.Patient_transfer ib1.cause_ICU_admission ib1.indication_intubation ib2.Dialysis ib1.Duration_MV_catg1 ib1.DX_modalities_cat ib1.Corticosteroid ib2.Aspiration_gastric_cont ib2.Re_intubation ib2.NGT ib2.surgical_pt ib2.Surgical_drainage ib2.paralytic_agents ib2.Ionotropic_medication

predict cs, csnell

sts generate M = na

stset cs, failure(stt_outcome)

line M cs cs, sort xlab(0 1 to 3) ylab(0 1 to 3)

stcox Presence_MVAP ib1.Age_cat ib1.Sex ib1.Patient_transfer ib1.cause_ICU_admission ib1.indication_intubation ib2.Dialysis ib1.Duration_MV_catg1 ib1.DX_modalities_cat ib1.Corticosteroid ib2.Aspiration_gastric_cont ib2.Re_intubation ib2.NGT ib2.surgical_pt ib2.Surgical_drainage ib2.paralytic_agents ib2.Ionotropic_medication

```
predict coxsnell, csnell

gen coxsnell_resid = exp(coxsnell) - 1

predict cs, csnell

stset cs, failure( stt_outcome )

sts generate M = na

line M cs cs, sort xlab(0 1 to 4) ylab(0 1 to 4)

drop M

sts generate H = na

line H cs cs, sort xlab(0 1 to 4) ylab(0 1 to 4)
```