PREDICTORS OF EXTUBATION FAILURE IN NEURO-CRITICALLY ILL PATIENTS IN KNH ICUs

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STUDENT'S DECLARATION

I, **Dr. Frank Kamau Gitonga**, do hereby declare that this dissertation is my original work and has not been previously submitted to any university or institution for examination or otherwise. All resources contained herein have been duly acknowledged.

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LIST OF ABBREVIATIONS AND ACRONYMS

ACS-	Airway Care Score
AFP-	Acute Flaccid Paralysis
CBF-	Cerebral Blood Flow
CCPs-	Critical Care Physicians or Critical Care Practitioners
CCU-	Critical Care Unit
CNS-	Central Nervous System
CPF-	Cough Peak Flow
CPIS-	Clinical Pulmonary Infection Score
CPP-	Cerebral Perfusion pressure
EDH-	Epidural Hematoma
EF-	Extubation Failure
ES-	Extubation Success
FOUR score-	Full Outline of Unresponsiveness Score
GBS-	Guillain–Barré syndrome
GCS-	Glasgow Coma Scale
GCS-M	Best Motor Response of the Glasgow Coma Scale
HAP-	Hospital-Acquired Pneumonia
ICH-	Intracranial Haemorrhage
ICU-	Intensive Care Unit
KNH	Kenyatta National Hospital
LOC-	Level of Consciousness
MV-	Mechanical Ventilation
NCC-	Neuro-Critical Care
PEEP-	Positive end-expiratory pressure
RCT-	Randomized Controlled Trial
SAH-	Subarachnoid Haemorrhage
SBT-	Spontaneous Breathing Trial
SDD-	Selective Digestive Decontamination
SOD-	Selective Oropharyngeal Decontamination
SDH-	Subdural Hematoma
TBI-	Traumatic Brain Injury
TWPs-	Traditional Weaning Parameters
VAP-	Ventilator-Associated Pneumonia
VISAGE-	Visual Pursuit, Swallowing, Age and GCS for Extubation Score
WCT-	White Card Test

OPERATIONAL DEFINITIONS

Extubation Failure: Is defined as reintubation and re-institution of mechanical ventilation within 24-72 hours of trans-laryngeal extubation.[1] Many current studies use the cut-off of 72 hours in the definition of extubation failure.[2,3]

Neuro-critical Care (Neuro-intensive care): This is a medical field that treats life-threatening diseases of the nervous system and identifies, prevents/treats secondary brain injury. Neuro-critical care is an evolving subspecialty of intensive care medicine that focuses on the care of critically ill patients with primary or secondary neurosurgical and neurological problems.[4] More recently, the concept of neuro-critical care has further developed to coordinate the management of critically ill neurosurgical and neurological patients within a single specialist unit. For the purpose of this study, neuro-critical care refers to the intensive care of all brain-injured patients rather than reference to a unit.

ABSTRACT

Background

Extubation decisions in brain-injured patients are often challenging to the critical care practitioner. Neuro-critically ill patients often undergo prolonged mechanical ventilation and intubation, are at high risk of extubation failure and have high morbidity and mortality. Extubation failure is an outcome to be avoided since it is associated with worse outcomes in ICU patients. Tools, scores and interventions to reduce extubation failure will be beneficial to the care of this subset of critically ill patients.

Objective

To determine the incidence and predictors of extubation failure in neuro-critically ill patients in Kenyatta National Hospital (KNH).

Methodology

A prospective observational cohort study of neuro-critically ill patients admitted in KNH critical care units. Patients included were ≥14 years, had neuro-critical illness and were mechanically ventilated for >24 hours. 105 patients were included into the study and 80 extubation events analyzed. The primary outcome was extubation failure within 72 hours of the index extubation.

Results

The incidence of extubation failure was 37.5%. Independent predictors of extubation failure included: a diagnosis of traumatic brain injury, pre-extubation FOUR score ≤10 and duration of mechanical ventilation > 10 days. Operative intervention was associated with reduced risk of extubation failure.

1.0 CHAPTER ONE: INTRODUCTION

The decision of whether a patient should be extubated is a critical one. It is often difficult to predict which patients will successfully tolerate extubation and which ones will fail. Extubation performed too early, risks failure and may require re-intubation. Multiple studies have shown increased morbidity and mortality in patients who require reintubation after failed extubation.[5–8] Delayed extubation, on the other hand, is associated with increased ICU length of stay, increased duration of mechanical ventilation and increased incidence of ventilator-associated pneumonia.[9]

Determining extubation readiness and identifying patients at high risk of failing extubation is an important aspect of intensive care medicine. Research is ongoing to establish reliable clinical predictors of extubation success.[10] Establishing simple bedside tools to assist critical care physicians in making extubation decisions will have tremendous benefit to the individual patient and allow better utilization of ICU resources.[2,11]

In the past, traditional weaning parameters (TWPs) have been used to aid intensivists in determining which patients are likely to wean successfully and liberate from mechanical ventilation.[12] However, traditional weaning parameters have proved to be ineffective in predicting extubation failure in brain-injured patients.[13] Many patients undergoing neuro-critical care due to pathologies causing brain injury will be intubated for airway protection due to coma. These patients often will have normal lungs and will pass ventilator weaning criteria. However, a proportion of these patients are likely to fail extubation despite successfully passing TWPs.[14]

The current practice at KNH critical care units is that patients are extubated once they meet the following criteria: resolution of acute neurological injury, no foreseeable surgical intervention in the next 72 hours, stable hemodynamically (on minimal or no vasopressor support), hemoglobin level of 8-9 g/dl and above, adequate cough reflex, Glasgow Coma Score (GCS) of 8 or higher and a patient's ability to successfully tolerate a spontaneous breathing trial using a T-piece or minimal support on pressure support ventilation (PSV). According to the Kenyatta National Hospital ICU/ HDU protocols booklet (2012), in the care of patients with traumatic brain injury, early extubation should be considered by day 7-10. If the GCS is less than 8 by this time an early tracheostomy should be considered.[15] Current

evidence supports the use of weaning/ extubation protocols and checklists.[16] This has been shown to standardize clinical practice, reduce the duration of mechanical ventilation and ICU length of stay.

Extubation failure is an outcome to be avoided due to its association with increased morbidity and mortality in critically ill patients. A previous study in the KNH ICU investigated the incidence of extubation failure in all ICU patients. The study did not carry out a sub-group analysis of the neuro-critically ill patients nor did it investigate the predictors of extubation failure in these patients.[47] There is need to conduct this study, firstly, to determine the incidence of extubation failure in neuro-critically ill patients. Secondly, to assess the association between various patient factors (such as age, diagnosis, pre-extubation level of consciousness, co-existent VAP) and extubation failure. Knowledge of potential predictors of extubation failure will enable critical care practitioners prevent extubation failure or offer elective tracheostomy to patients at risk of extubation failure.

2.0 CHAPTER TWO: LITERATURE REVIEW

2.1 Weaning, liberation and extubation

Endotracheal intubation and mechanical ventilation are useful and life-saving interventions commonly employed in the Intensive Care Unit. An equally important intervention in intensive care medicine is the process of liberating the patient from mechanical ventilation. Weaning is the process of gradual withdrawal of the patient from mechanical ventilation. Extubation is the final event in the liberation process in which the endotracheal tube is removed.

2.2 Determining weaning and extubation readiness

Weaning readiness is usually determined by several physiologic parameters such as:

- **a)** Measures of ventilatory performance and muscle strength such as tidal volume, the rapid shallow breathing index (RSBI) and frequency of respiration.
- **b)** Measurement of the drive to breathe e.g. $P_{0.1}$ (pressure on inspiration measured at 100 msec).
- **c)** Measurement and estimation of the work of breathing e.g. the CROP (dynamic compliance, respiratory rate, oxygenation, maximum inspiratory pressure) index.
- **d)** Measurement of the adequacy of oxygenation e.g. the PaO_2/FiO_2 ratio.

In addition to these parameters, The American College of Chest Physicians (ACCP)/ American Association for Respiratory Care (AARC)/ American College of Critical Care Medicine (ACCM) Evidence-Based Weaning Guidelines Task Force[17] recommend the following guidelines for discontinuation of mechanical ventilation and extubation:

a) Reversal of the underlying cause of respiratory failure.
b) Adequate oxygenation.
c) Ability to initiate inspiratory effort.
d) Normal acid-base status (pH $\geq$7.25).
e) Hemodynamic stability (absence of hypotension and no or minimal vasopressor support).

This consensus statement[17] emphasizes that weaning and extubation decisions should be individualized, basing these decisions on the patients' age, baseline lung function, hemodynamic status, neurologic status and patients' comorbidities.

One of the more commonly used and widely researched indices is the rapid shallow breathing index (RSBI). It is calculated as the frequency of respiration/ tidal volume in a spontaneously breathing patient. The normal value is 60 to 105. A figure greater than 105 indicates that the patient is unlikely to tolerate weaning and extubation. The cuff leak test is a common test conducted to determine if a patient is likely to tolerate extubation or not. During the cuff leak test, the difference between the expired and inspired tidal volume is measured after endotracheal tube balloon deflation. A low cuff leak volume of less than 110 millilitres around the endotracheal tube before extubation indicates tracheal edema and predicts a high risk of post-extubation upper airway obstruction. Studies have shown that patients who undergo steroid therapy after a negative cuff leak test have a lower incidence of post-extubation upper airway obstruction and stridor.[18]

Patients in ICU with neurological conditions or brain injury will often tolerate weaning from the ventilator, however, the decision to extubate is often challenging. This is often because neuro-critically ill patients have low neurological status, have difficulty managing oral and airway secretions, depressed airway reflexes (depressed cough and gag reflexes), cranial nerve palsies and ICU acquired neuro-myopathy.

2.3 Extubation failure

There is currently no consensus as to what exactly constitutes extubation failure (EF). An accepted definition is need for reintubation and re-institution of mechanical ventilation within 72 hours of extubation.[19] Some authors extend the definition to 1 week after extubation.[2]

The incidence of extubation failure is 10-20% in the general ICU population.[6,8] In the Neuro-ICU population the incidence is higher, estimated to be 20-40%.[14,20,21] A very low extubation failure rate in an ICU could signify an overly cautious weaning/ liberation approach. This would imply that patients may be spending longer on the mechanical ventilator with all its attendant complications. On the other hand, a very high extubation failure rate could signify an overly aggressive liberation approach. The ideal or acceptable extubation failure rate is

controversial. Some studies estimate an incidence of extubation failure of 8-15% as acceptable.[22]

2.4 Causes of extubation failure in the critically ill

Extubation failure as evidenced by post-extubation distress can have several underlying causes. The main causes include post-extubation upper airway obstruction, respiratory failure, cardiac failure, and encephalopathy.[5,19] Respiratory failure can cause extubation failure if it was the primary reason for intubation and is still unresolved at the time of extubation. Alternatively, the respiratory distress could be of new-onset: secondary to aspiration or cardiac failure.

A common cause of extubation failure is post-extubation upper airway obstruction which presents as stridor after extubation.[19] Causes of post-extubation upper airway obstruction include sub-glottic stenosis, laryngeal/ tracheal edema, laryngospasm and tracheomalacia. Risk factors associated with development of laryngeal edema include: prolonged duration of intubation, traumatic or difficult intubation, excessive endotracheal tube size, endotracheal tube mobility secondary to loose securement, frequent or aggressive tracheal suctioning and excessive cuff pressure. Following prolonged endotracheal intubation, airway mucosal injury is likely to occur. Granulation tissue and post-extubation contracting scar tissue due to mucosal injury can lead to airway obstruction.[23]

Cardiac dysfunction can cause extubation failure, conversely, it can itself be a complication induced by weaning and extubation. The cardiovascular consequences of the transition from mechanical ventilation to spontaneous breathing can cause weaning and extubation failure (in patients with left heart dysfunction) due to weaning induced myocardial ischemia or weaning induced pulmonary oedema (WIPO).[24] Current research has investigated the heart-brain axis which shows a close link between neurologic dysfunction and the development of cardiac pathology.[25] The autonomic and neuro-hormonal control of the cardiovascular system is a function of the central nervous system (CNS). Therefore, neurological pathology has a profound impact on cardiovascular function. The insular cortex and the nucleus of the tractus solitarius (NTS) are some of the centers in the brain that are involved with cardiovascular regulation.

Effects of neurologic dysfunction on cardiovascular function include electrocardiographic (ECG) changes such as cerebral T waves, prominent U waves, ventricular tachycardia, premature ventricular complexes (PVCs), and prolongation of the QT interval. Sympathetic over-activity during brain injury is thought to cause myocardial calcium influx which causes the release of degrading enzymes leading to myocytolysis and damage to the sub-endocardial conductive network.[25] Other manifestations of a dysfunctional heart-brain axis include neurogenic cardiac failure, stress-induced cardiomyopathy and paroxysmal sympathetic hyperactivity (PSH). Cardiovascular changes are especially prevalent after aneurysmal subarachnoid haemorrhage (SAH) especially in women with high-grade SAH.[25] These changes include PSH, prolonged QT and fatal ventricular arrhythmias such as torsades de pointes. A vicious cycle occurs in which brain injury worsens cardiac function and worsening cardiac function causes further neurologic insult. This is due to the occurrence of cardiogenic shock, arrhythmias and decrease in cerebral perfusion pressure. Weaning of these patients may be difficult and attempts at extubation may worsen cardiac function manifesting as extubation failure. Extubation of a patient who had previously tolerated low levels of ventilator support may unmask underlying borderline cardio-respiratory dysfunction. The acute decompensation may manifest as extubation failure.[26]

Swallowing dysfunction is prevalent in patients who have had prolonged intubation. It is postulated that the swallowing dysfunction is a result of muscle freezing due to disuse. Besides, mucosal injury causes loss of receptors along the aero-digestive tract which are important in co-ordinating the swallowing process.[27] Leder et al investigated the incidence of aspiration in trauma patients who had prolonged intubation and MV. Using trans-nasal endoscopy they found the incidence of aspiration to be 45% of the patients they investigated. They concluded that patients admitted in ICU after trauma, who undergo prolonged intubation and mechanical ventilation have a high incidence of swallowing dysfunction and aspiration and this is a significant cause of post-extubation pneumonia.[28]

Other causes of extubation failure include ineffective cough with secretion build-up, encephalopathy, laryngeal injury, vocal cord dysmotility, diaphragmatic dysfunction, and ICU acquired polyneuropathy. Macroglossia can also be a cause of airway obstruction, making reintubation necessary but potentially difficult.[23] In the post-operative patient, macroglossia can be due to prolonged surgery in the prone or Trendelenburg position. In the ICU patient, severe macroglossia can occur in the setting of fluid overload or tongue trauma.

2.5 Consequences of extubation failure and re-intubation

Patients who fail extubation and need reintubation have higher morbidity than patients who extubate successfully.[29] They have a higher incidence of ventilator-associated pneumonia (VAP), longer ICU length of stay and more days spent on the mechanical ventilator.[9] Studies have shown that patients who fail extubation have six-fold higher mortality than patients who extubate successfully[8,9]. The reason for this high mortality is unknown. One hypothesis is that patients who fail extubation have greater severity of illness and are therefore likely to have higher mortality due to their underlying illness.[30]

The morbidity and mortality of patients with extubation failure increase in proportion to the duration of time it takes between the failure of extubation and reintubation. Among patients whose decision to re-intubate is delayed after extubation, the mortality is very high.[12] Therefore, the decision to re-intubate after extubation failure should be expedited.

2.6 Risk factors for extubation failure in neuro-critically ill patients

Risk factors associated with extubation failure include low neurological status, poor cough reflex, inability to clear oral/ airway secretions, fluid overload, ventilator-associated pneumonia, cardiac dysfunction, prolonged intubation, etc. Patients with brain injury secondary to various etiologies are at high risk of extubation failure. Research into tools or factors which can predict extubation success or failure in brain-injured patients will, therefore, have great utility.

In a study by Asehnoune and colleagues, 99 out of 437 brain-injured patients included in their study failed extubation (22.7%). In this study, they created a simple bedside score: the presence of visual pursuit, ability to swallow, age less than 40 and GCS greater than 10 (VISAGE score) to predict the probability of extubation success in patients with brain injury. In multivariate analysis, these four factors were associated with extubation success (ES). In the VISAGE score, each component had a score of one. A score of 3 or 4 was associated with 90% extubation success.[11]

Extubation failure (EF) has been associated with a reduced level of consciousness (LOC). The probable reason for this is that patients with reduced LOC have increased volume of

airway secretions, as well as swallowing and cough deficiency. Traditionally most CCPs have been reluctant to extubate patients with a GCS of 8 or less. However, there is controversy around the association between patients' LOC and their extubation outcomes. This especially applies to brain-injured patients with a chronically low LOC. Coplin et al showed that patients with a GCS of 8 or less had an 80% ES rate provided that the only indication for intubation was airway preservation.[9] In this study, it was also demonstrated that delaying extubation due to a low neurological status only increased complications such as pneumonia and prolonged ICU LOS. Nameen and colleagues, however, showed an increased risk of EF in patients with a GCS of less than 8. [31]

Currently utilized methods of assessment of neurological status in brain-injured patients have been faulted as being inadequate in testing airway protective reflexes, and therefore unhelpful in predicting extubation tolerance.[32] Alternative neurologic assessment tools such as the FOUR (Full Outline of Unresponsiveness) score have been developed.[20] Ko et al, however, did not find any correlation between higher FOUR scores and ES.[13]

Since its development in 1974 by Teasdale and colleagues, the Glasgow Coma Scale has gained widespread acceptance as a simple and accurate tool of neurologic assessment. However, its use in intubated brain-injured patients has several limitations, including inter-rater variability and confounders which can make one or more components of the scale untestable.[33] Some of the confounders include: drugs (for example anaesthetics, neuromuscular blockade and sedatives), intubation or tracheostomy, cranial nerve injuries, intoxication (alcohol or drugs), hearing impairment, limb or spinal-cord injuries, dysphasia, pre-existing disorders (psychiatric disorders or dementia), eye trauma, orbital swelling and language barrier.

In a study by Anderson et al, the ability of the patient to follow 4 commands (close eyes, wiggle toes, show two fingers, cough on command) was found to be highly predictive of ES.[3] A study by Salaam et al had a similar finding in which the ability of patients to follow certain commands was predictive of extubation outcome.[34] Therefore a focused neurologic assessment may be more beneficial in predicting extubation outcomes than traditional scores of neurologic assessment such as the GCS.

The inability to handle oral-respiratory secretions has been found in several studies to be highly predictive of extubation outcomes.[34,35] Heavy secretion load in a patient with impaired airway reflexes may cause EF. In a study by Khamiees et al, the likelihood of extubation failure was eight times more in patients with moderate or abundant secretions compared to patients with minimal or no secretions.[36]

Currently, however, there are very few tools or technologies for objectively or quantitatively assessing secretion volume or texture. Those that exist are expensive and difficult to use at the bedside. Therefore, researchers have come up with qualitative and semi-quantitative scores for overall assessment of airway hygiene by quantifying parameters such as cough strength, presence or absence of gag reflex, secretion texture, frequency of suctioning etc. One such score, called the airway care score (ACS) was developed and used by Coplin et al[9], as well as Manno et al.[37] This score relies on nurses or respiratory physiotherapist scoring of the patients' cough strength, suctioning frequency and sputum/ respiratory secretions characteristics. A higher airway care score has been associated with an increased risk of extubation failure. Visual inspection of ventilator waveforms, especially the flow-volume curves can give a fairly accurate assessment of volume of secretions and indicate the need for suctioning.[38]

Several methods have been employed in the assessment of cough strength including subjective assessment, use of peak flow meters and the white card test (WCT). In their study, Khamiees et al used the WCT to objectively assess cough strength. During the test, the researchers placed a white card 1 to 2 cm from the end of the endotracheal tube and asked patients to cough, up to three to four times, just prior to endotracheal extubation. If any wetness appeared on the card, it was classified as a positive WCT result.[36] A negative WCT predicted extubation failure. Salaam and colleagues used pneumotachograph-calibrated peak flow meters placed in series with the endotracheal tube to measure the cough peak flows (CPF). The CPF significantly correlated with the outcome of extubation and patients who had CPF of less than 60 l/min were five times more likely to fail extubation than those who had higher CPFs.[34]

Anaemia is prevalent in critically ill patients with acute brain injury. In the general ICU population, up to 60% of critically ill patients have anaemia. Anaemia is associated with poor outcomes in critically ill patients, for example in patients with TBI, anaemia is thought to

exacerbate secondary brain injury.[39] It is postulated that anaemia could contribute to extubation failure in brain-injured patients via two mechanisms: by worsening neurologic function through secondary brain injury or by causing cardiac dysfunction. Oxygen delivery to the brain is a product of the arterial O_2 content and the cerebral blood flow (CBF). Anaemia causes a reduction in the arterial O_2 content and therefore the O_2 delivery to the brain. Several physiologic compensatory responses to anaemia take place to maintain O_2 delivery to the brain, for example, an increase in the heart rate, increase in CBF through cerebral vasodilatation (secondary to increased endothelial nitric oxide production) and increased cerebral oxygen tissue extraction. Below the critical hemoglobin threshold of 5-6 g/dl these compensatory mechanisms fail since there is maximal cerebral vasodilation and maximal oxygen tissue extraction, causing anaemia induced cerebral dysfunction.[39]

In patients who are critically ill, fluid therapy is a useful intervention especially during resuscitation. Fluid therapy is necessary to restore cardiac output, systemic blood pressure and vital organ perfusion. In patients undergoing neuro-critical care, fluid therapy is essential for maintaining cerebral perfusion pressure (CPP). However, the risk of fluid overload exists and should be vigilantly monitored. Consequences of fluid overload include cerebral, pulmonary, renal, gut and tissue edema. Frutos-Vivar et al, in a study analyzing factors associated with reintubation in patients who had successfully passed a SBT, identified a positive fluid balance 24 hours prior to extubation as a predictor of EF.[40]

Hospital-acquired pneumonia (HAP) is prevalent in the critically ill population. In patients with traumatic brain injury (TBI), the rate of HAP varies from 30-50%. HAP increases the risk of intracranial hypertension, prolongs duration of MV and ICU stay and increase the likelihood of tracheostomy.[41] Coplin et al showed that patients with prolonged duration of intubation and whose extubation is delayed have a high risk of developing VAP.[9] In a prospective observational study, Zygun et al[42] studied 134 patients with severe TBI undergoing MV. In this group of patients, 60 of the 134 patients (45%) were diagnosed with VAP. They concluded that patients with severe TBI are at a high risk of VAP. They also demonstrated that brain-injured patients who develop VAP experience more non-neurological organ dysfunction than those who do not develop VAP. The association between VAP in neurologically injured patients and extubation outcomes is one of the factors that this study aims to explore. Different scores and tools have been used to screen patients for VAP. The

Clinical Pulmonary Infection Score (CPIS) is a validated tool for screening for VAP in mechanically ventilated ICU patients.[43]

Diaphragmatic dysfunction is increasingly appreciated as a major contributor to weaning and extubation failure. This is especially the case in patients who undergo prolonged critical illness with difficult weaning. These patients may get ICU acquired weakness: a complex syndrome of polyneuropathy and myopathy involving multiple muscle groups including respiratory muscles. Point of care ultrasound is gaining prominence as a reliable tool to assess lung aeration, diaphragmatic excursions, diaphragmatic thickness and heart function in the context of weaning, liberation and extubation.[44,45]

There is no local data on the incidence and factors predictive of extubation failure in neuro-critical care patients. In a 2010 study, Mathangani W.[46] analyzed 66 extubation events in 151 ICU patients: 38 (planned) and 28 (unplanned). The investigator concluded that the incidence of unplanned extubations in KNH ICU was 18.5% and the success rate of unplanned extubation was 35.7%. Self extubations were more successful than accidental extubations, but the overall success rate of unplanned extubations was lower than that for planned extubations. The incidence of extubation failure after planned extubation in KNH ICU was 21%.

2.7 Justification

Extubation failure is associated with increased morbidity and mortality in ICU patients. Extubation failure and reintubation are associated with higher odds of aspiration, ventilator-associated pneumonia (VAP), prolonged mechanical ventilation and increased incidence of tracheostomy.[29] In addition delays between extubation failure and reintubation predispose the patient to hypoxemia and hypercapnia which may cause secondary brain injury.

Hesitancy to extubate patients also has pitfalls including higher incidence of VAP, ventilator dependence, increased ventilator days and prolonged ICU admission. Coplin et al found increased morbidity in brain-injured patients who had delayed extubation and no improvement in their neurologic status during the delay.[9] Therefore identification of patients at risk of extubation failure and mobilizing resources to optimize patients prior to extubation is a useful intervention in intensive care medicine.

The incidence or factors predictive of extubation failure in neuro-critically ill patients in KNH Critical Care Units had not been previously investigated. This study adds to the body of knowledge on this topic, creates awareness about the extent of the problem and create a basis for further research into solutions to extubation failure.

2.8 Study Questions

a) What is the incidence of extubation failure among patients undergoing neuro-critical care in KNH Critical Care Units?

b) What factors predict extubation failure in neuro-critically ill patients?

2.9 Objectives/ Aims of the Study

2.9.1 Broad Objective

To determine predictors of extubation failure in neuro-critically ill patients in Kenyatta National Hospital.

2.9.2 Specific Objectives

a) To determine the incidence of extubation failure in neuro-critically ill patients.

b) To determine the association between extubation failure and the neurologic diagnosis, peri-extubation level of consciousness as assessed by the FOUR score and the GCS, co-existent ventilator-associated pneumonia and duration of mechanical ventilation in neuro-critically ill patients.

3.0 CHAPTER THREE:

STUDY METHODOLOGY

3.1 Study Design

A single-center prospective observational cohort study.

3.2 Study Area Description

Kenyatta National Hospital is a tertiary level referral and teaching hospital in Nairobi, Kenya. There are 6 Critical Care Units with a capacity of up to 55 critically ill patients: Surgical ICU (has a capacity of 21), Medical ICU (8), Neonatal ICU (8), Pediatric ICU (5), Private Wing/9A HDU (5) and the Cardio-thoracic CCU (4). In addition, emergency critical care service can occasionally be provided to an additional 4 patients in the Accident and Emergency department Resuscitation rooms. Neuro-critical care patients fitting the inclusion criteria were enrolled into the study from the adult population of critically ill patients in the Surgical ICU, Medical ICU, 9A HDU and Resuscitation rooms.

3.3 Inclusion Criteria

- Patients 14 years and above admitted into the ICU due to a central nervous system pathology, with a Glasgow Coma Score of 14 or less before endotracheal intubation and requiring invasive mechanical ventilation for more than 24 hours.
- Patients admitted in ICU due to increased intracranial pressure, traumatic brain injury, stroke (ischemic and hemorrhagic stroke), status epilepticus, meningoencephalitis, brain tumors and other brain space-occupying lesions and post-operative neurosurgical patients.

3.4 Exclusion Criteria

a) Patients with spinal cord injury above the 4^{th} Thoracic Vertebrae.

b) Acute flaccid paralysis/ Guillain–Barré syndrome (GBS) / Acute non-traumatic weakness.

c) Patients post-cardiac arrest.

d) Eclampsia.

e) Brain dead patients.

f) Primary tracheostomy without trial of extubation.

3.5 Sample Size Determination

Sample size calculation for a finite population.

$$n = \frac{Nz^2pq}{E^2(N-1) + z^2pq}$$

n = Desired sample size

N = population size (Appendix 7).

Z = value from standard normal distribution corresponding to desired confidence level (Z=1.96 for 95% CI)

p = expected true proportion (Incidence of extubation failure was 22.6%, from a study conducted by Asehnoune et al.)[11]

$q = 1 - p$

E = desired precision (0.05)

$$n = \frac{132\ x\ 1.96^2\ x\ 0.23\ x\ 0.77}{0.05^2(132-1) + (1.96^2\ x\ 0.23\ x\ 0.77)} = 89$$

105 patients were consecutively enrolled into the study.

3.6 Sampling procedure/ Selection of study participants.

Consecutive sampling was used to enroll patients into the study.

3.7 Variables.

3.7.1 Dependent Variables.

a) Extubation outcome: Either Extubation success or failure within an observation period of 72 hours post-extubation.

3.7.2 Independent Variables.

a) Demographic data.

b) Neurologic status and assessment.

c) Duration of mechanical ventilation.

d) CPIS Score.

3.8 Data Collection Procedures.

Data was obtained from patients' clinical records, clinical examination and interaction with primary nurses, laboratory and radiologic investigations requested by the ICU team and collected using a research assistant administered questionnaire. The focus of this study was to investigate the factors affecting extubation outcome of the **first** extubation event.

3.9 Research Assistants

Enrollment of patients into the study was done by the principal investigator. Thereafter, the data collection was designated to trained research assistants on behalf of the principal investigator. Five research assistants participated in the study. The research assistants included 2 Level 6 MBChB students of the University of Nairobi and 3 ICU nurses who had undergone training on the study protocol, data collection and ethical considerations of the study. Overall supervision of the research assistants and responsibility was borne by the principal investigator.

3.10 Data collected

Data collected included:

I. Demographic data (for example, the gender and age).
II. Diagnosis.
III. Duration of intubation.
IV. Interventions.
V. Co-morbidities.
VI. Serial neurological assessment using the Full outline of unresponsiveness (FOUR) score and the GCS.
VII. Ventilator-associated pneumonia screening using the Clinical Pulmonary Infection Score (CPIS).
VIII. Extubation outcome.

3.11Data Analysis

Data was collected using researcher administered questionnaires and stored in Microsoft Excel. IBMM SPSS 25 was used to generate tables and run hypothesis tests. R Software version 3.6.3 was used to run the regression model.

Ordinal discrete data such as the GCS, FOUR Score and CPIS Score were compared with the outcome variable using the Mann-Whitney U test.

Non-parametric data (categorical variables) such as the age, gender, diagnosis, intervention and duration of mechanical ventilation were compared with the outcome variable using the chi-square test.

Categorical variables were expressed as absolute and relative frequencies (percentages) and this was presented in tables, bar graphs and pie charts. Continuous variables were expressed as medians (Inter-quartile ranges).

After univariate analysis, the independent variables with a $p \leq 0.05$ were included in the multivariate logistic model. Stepwise binary logistic regression was then used to assess for independent predictors of extubation failure. Different logistic regression models were used and the model with the best fit (lowest Akaike Information Criterion, AIC) was selected.

3.12Ethical Considerations

This study was conducted in due regard to the ethical principles espoused by the Declaration of Helsinki (2013) and the ICH-Good Clinical Practice Guidelines.[47]

I. Permission to conduct the study was sought from KNH administration and from the KNH/ University of Nairobi Ethics and Research Committee before commencement.
II. Participants were enrolled after the nature of the study had been explained to them or their next of kin and informed consent or assent obtained.
III. Confidentiality was maintained at all stages of the study.
IV. No additional therapy or intervention was given or denied to any patient participating in the study and the patients did not incur any additional cost for participating in this study. No extra investigation or therapy was requested outside of the practice of the ICU team.
V. There was no financial incentive to patients or their next of kin for participation in this study.

4.0 CHAPTER FOUR:

RESULTS AND DISCUSSION.

The study was conducted from January to June 2020. During this period there was a total of 691 admissions to the critical care units. 105 neuro-critically ill patients were included into the study, having fit the inclusion criteria and 80 extubation events were analysed. Only the first extubation event per patient was analysed.

Figure 1: Flowchart.

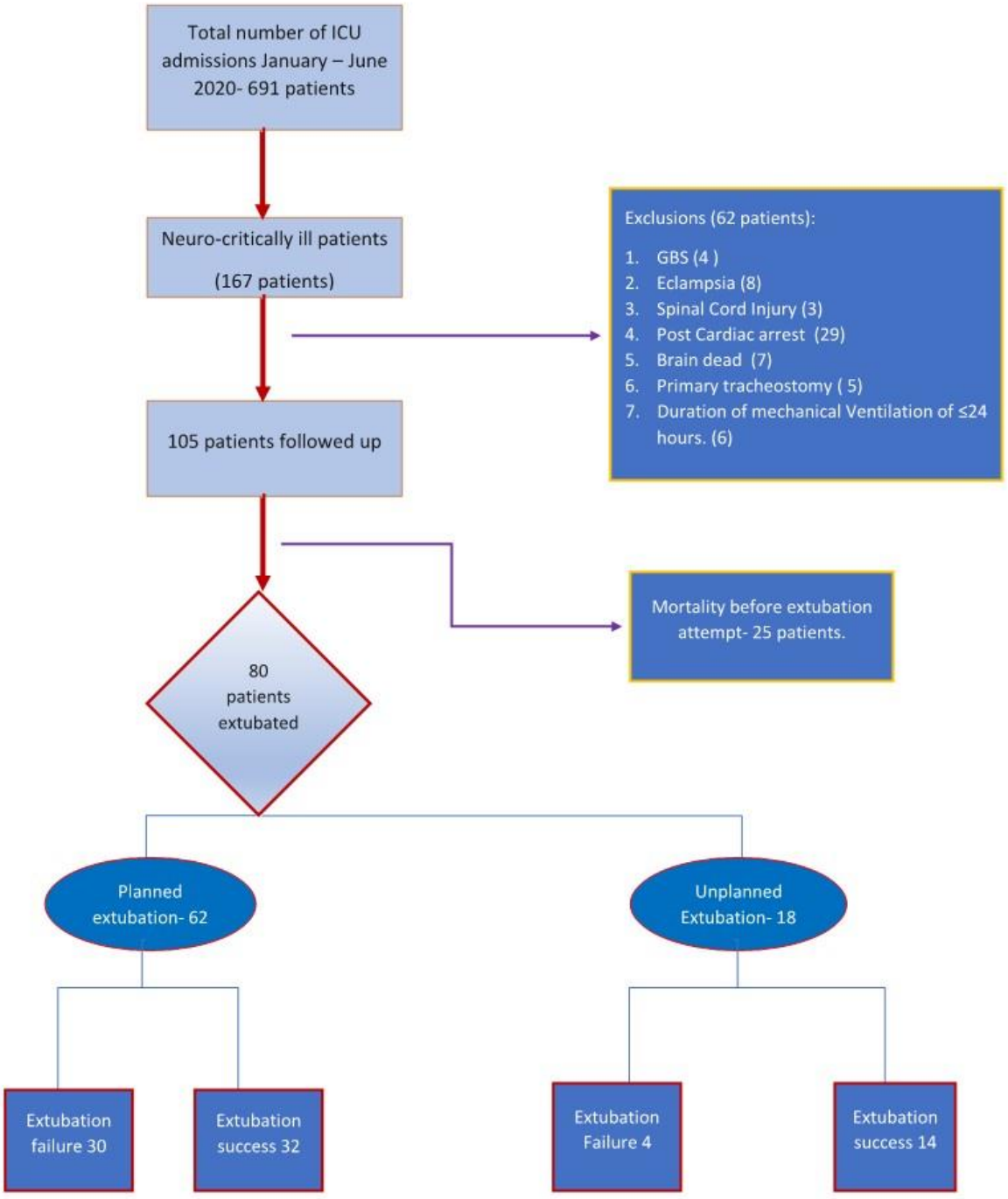


Table 1: Patients' gender and extubation outcome.

Characteristic: **Gender, n (%)**	**Total (n=80)**	**Extubation failure n=34 (42.5%)**	**Extubation success n=46 (57.5%)**	**p-value**
Male	61 (76.3%)	30 (88.2%)	31 (67.4%)	0.03
Female	19 (23.7%)	4 (11.8%)	15 (32.6%)	

Table 2: Patients' age and extubation outcome.

Characteristic: **Age, n (%)**	**Total (n=80)**	**Extubation failure n=34 (42.5%)**	**Extubation success n=46 (57.5%)**	**p-value**
14-30	24 (30.0%)	11 (32.4%)	13 (28.3%)	0.865
31-40	26 (32.5%)	10 (29.4%)	16 (34.7%)	
≥40	30 (37.5%)	13 (38.2%)	17 (37.0%)	

Table 3: Patients diagnosis on ICU admission and the extubation outcome.

Characteristic: **Diagnosis, n (%)**	**Total (n=80)**	**Extubation failure n=34 (42.5%)**	**Extubation success n=46 (57.5%)**	**p-value**
Traumatic Brain Injury	51 (63.8%)	27 (79.4%)	24 (52.2%)	0.012
Non-traumatic brain injury	29 (36.2%)	7 (20.6%)	22 (47.8%)	

Table 4: Intervention performed and extubation outcome.

Characteristic: **Intervention, n (%)**	**Total (n=80)**	**Extubation failure n=34 (42.5%)**	**Extubation success n=46 (57.5%)**	**p-value**
Non-operative	24 (30.0%)	16 (47.1%)	8 (17.4%)	0.004
Operative	56 (70.0%)	18 (52.9%)	38 (82.6%)	

Table 5: Hemoglobin level on ICU admission and the extubation outcome.

Characteristic: **Hb, n (%)**	**Total (n=80)**	**Extubation failure n=34 (42.5%)**	**Extubation success n=46 (57.5%)**	**p-value**
≤9g/dl	21 (26.3%)	10 (29.4%)	11 (23.9%)	0.858
9.1-11 g/dl	27 (33.7%)	11 (32.4%)	16 (34.8%)	
≥11	32 (40.0%)	13 (38.2%)	19 (41.3%)	

Table 6: Time to index extubation and the extubation outcome.

Characteristic: **Duration of mechanical ventilation/ Time to index extubation, n (%)**	**Total (n=80)**	**Extubation failure n=34 (42.5%)**	**Extubation success n=46 (57.5%)**	**p-value**
≤6 days	30 (37.5%)	7	23	0.011
7-10 days	21 (26.3%)	7	14	
≥10 days	29 (36.2%)	20	9	

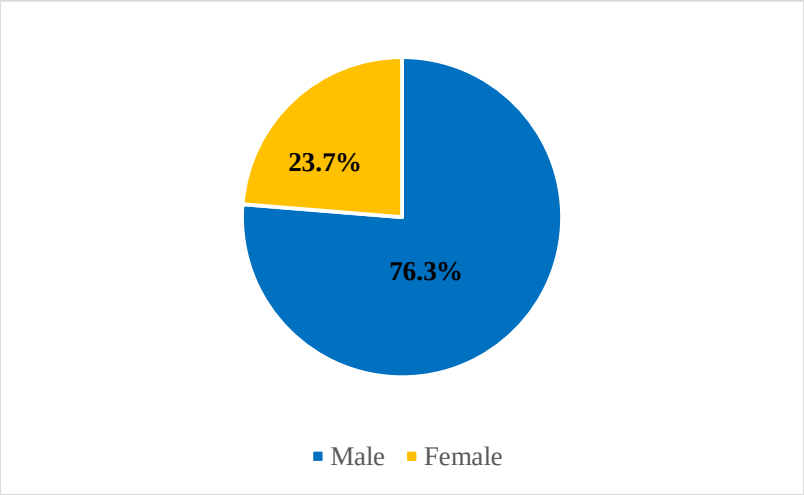


Figure 2: Pie chart showing the gender distribution of neuro-critically ill patients.

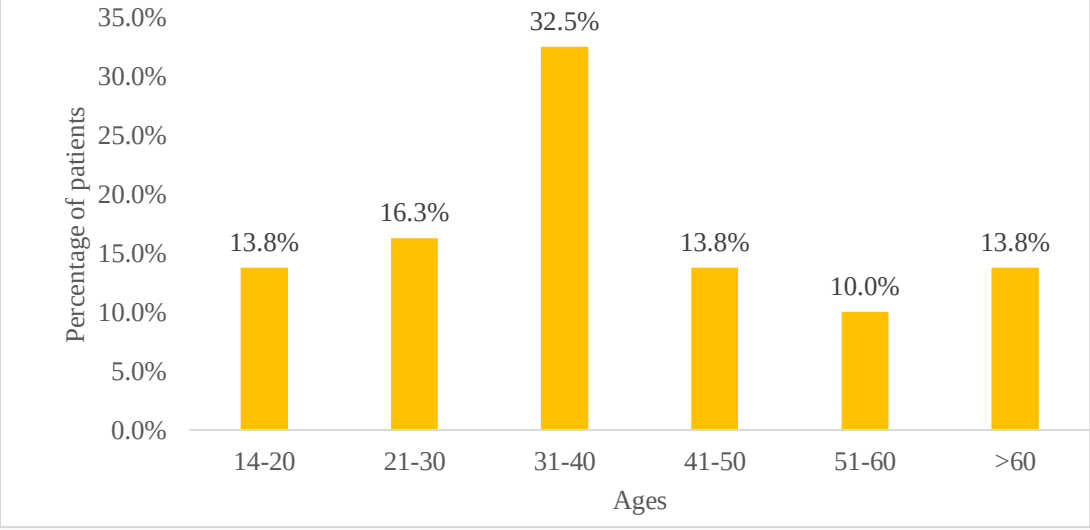


Figure 3: Age distribution of patients

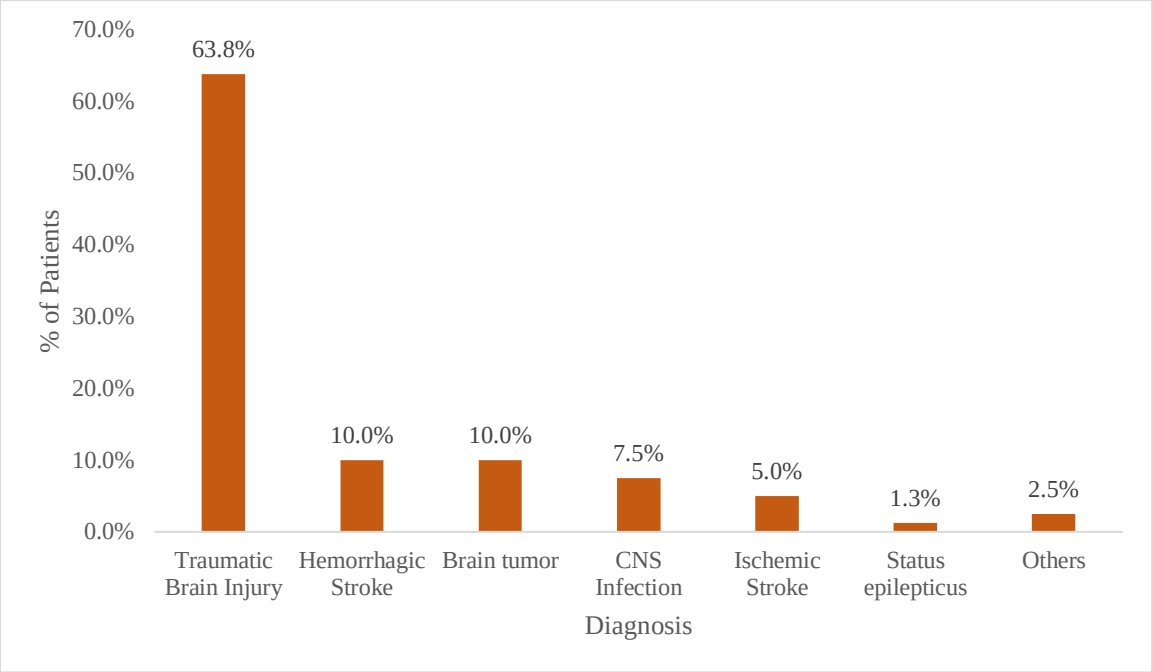


Figure 4: Distribution of neuro-critically ill patients according to their diagnosis.

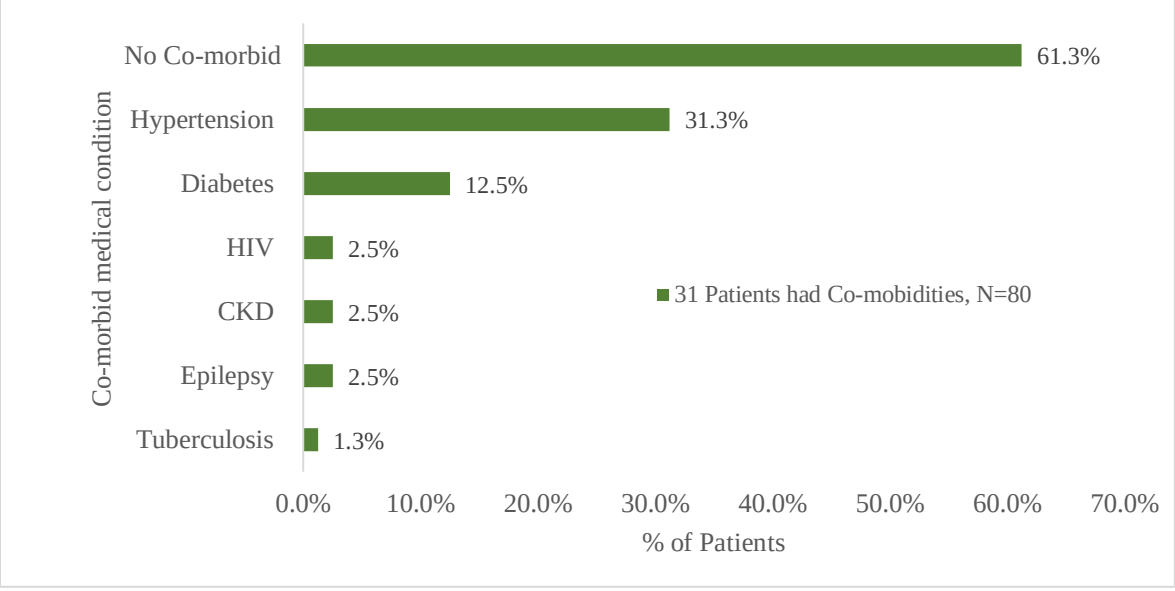


Figure 5: Proportion of patients with baseline co-morbidities.

Of the eighty patients who had an extubation event, 63.8% of the patients had traumatic brain injury. This sample of neuro-critically ill patients were predominantly male (76.3%) with majority being between the age of 31-40 years. 61.3% of patients in the cohort had no baseline co-morbid on admission to the ICU. Hypertension and diabetes were the commonest co-morbids on admission into critical care.

Traumatic brain injury remains a significant cause of ICU admission. Neuro-critical illness and specifically, traumatic brain injury is a major cause of morbidity and mortality in developing countries.[48] 27.08 million cases of traumatic brain injury were recorded worldwide in the year 2016, causing significant disability and cost to the health system.[49]

In our study, traumatic brain injury accounted for 7.4% of all ICU admissions. This represents a decline from a previous study which showed that TBI accounted for up to 14% of all admissions, according to a study by Opondo et al in KNH ICU.[50] This could be explained by the fact that since this 2007 study more ICUs have opened up in KNH, with diversification of the patient population. The commonest CT/ MRI finding on ICU admission was epidural hematoma (17% of patients with TBI), subdural hematoma (12.5%) and diffuse axonal injury (12.5%). This study has also shown predominance of males with the diagnosis of TBI, and most are between the ages of 31-40. This demographic pattern in traumatic brain injury was similarly reported by Wekesa et al[51] and Tobi et al. [52]

25 out of 105 (23.8%) patients died before an extubation attempt. There was a statistically significant difference in mortality outcome in relation to the GCS and FOUR Scores on ICU admission (OR 0.71; p =0.00 and OR 0.77; p=0.00 respectively). However, since the primary outcome (either extubation failure or success) was not attained by these patients, further sub-analysis of these patients was not conducted.

Table 7: Comparison of various clinical scores in patients with extubation failure versus extubation success

Characteristic: **Continuous Variable (Range)**	**Median, IQR**	**Extubation failure Median, IQR**	**Extubation success Median, IQR**	**p-value**
CPIS Score (0-12)	3 (1-6)	5 (2-6)	2 (1-5)	0.013
GCS on Admission (3-15)	8 (6-9)	7 (4-8)	9 (7-11)	0.000
GCS at Extubation (3-15)	8 (6-9)	7 (5-9)	8 (7-10)	0.016
GCS-M on Admission (1-6)	4 (2-5)	3 (2-4)	4 (3-5)	0.002
GCS-M at Extubation (1-6)	4 (3-5)	4 (2-4)	4 (3-5)	0.009
FOUR score on Admission (0-16)	10 (9-12)	9 (7-10)	11 (10-13)	0.000
FOUR score at Extubation (0-16)	11 (9-13)	10 (6-12)	12 (10-15)	0.001

On ICU admission, the median GCS was 8 (IQR 6-9) while the median FOUR Score was 10 (IQR 9-12). For patients who had extubation failure, the median GCS was 7 (IQR 5-9), while for patients with extubation success the median GCS was 8 (IQR 7-10); p=0.016. Patients with extubation failure had a FOUR score median of 10 (IQR 6-12) while patients with extubation success had FOUR Score median of 12 (IQR 10-15); p value= 0.001.

Table 8: Number of neuro-critically ill patients with probable Ventilator associated Pneumonia.

Diagnosis	Number of patents with CPIS≥6
Traumatic Brain Injury	19
Stroke	1
CNS Infection	4

Screening for Ventilator associated pneumonia was done using the Clinical Pulmonary Infection Score. A probable diagnosis of VAP was made when CPIS was ≥6. 24/80 patients had a CPIS score ≥6 (Incidence of 30%). The incidence of probable VAP in traumatic head injury patients was 37.3%.

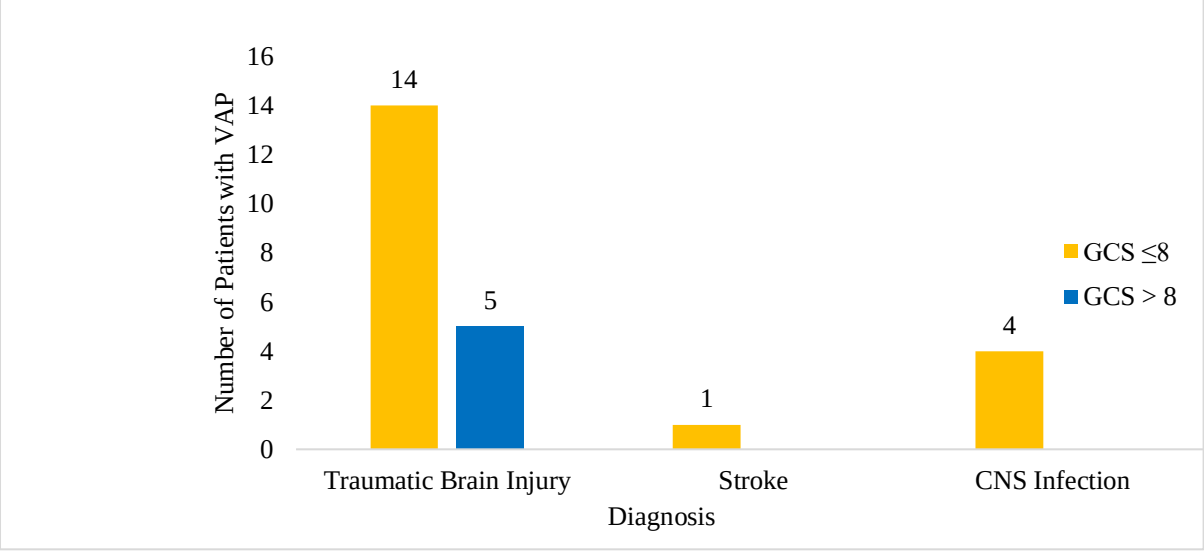


Figure 6: Number of patients with probable VAP (CPIS score ≥6), in relation to their diagnosis and Level of consciousness (as assessed by the GCS).

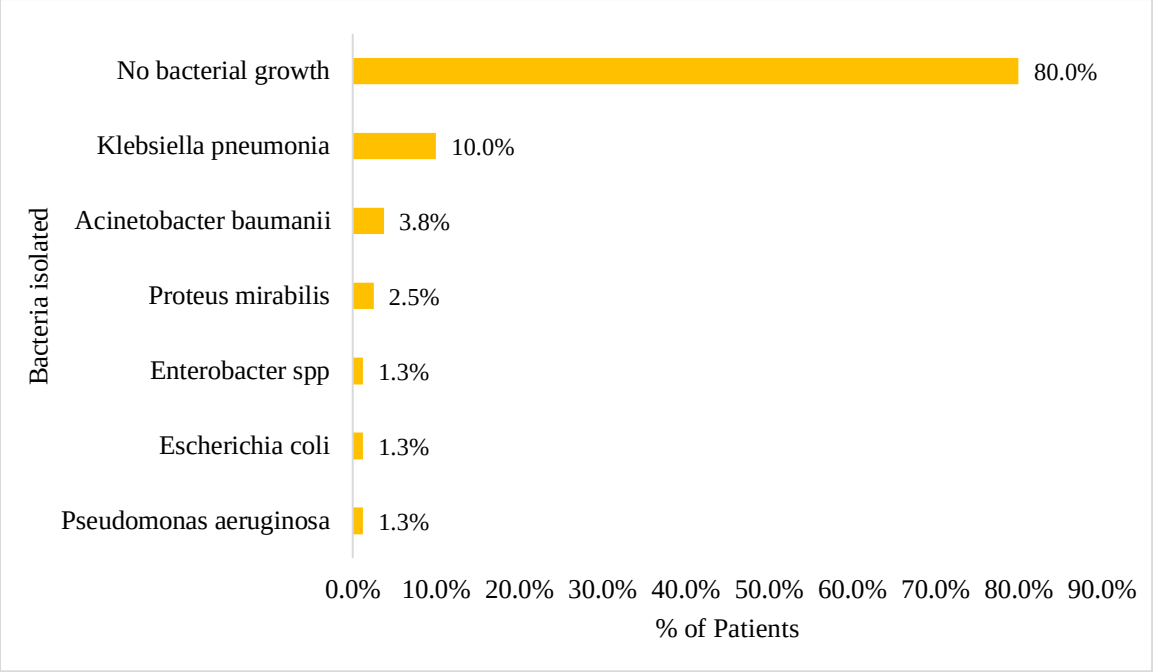
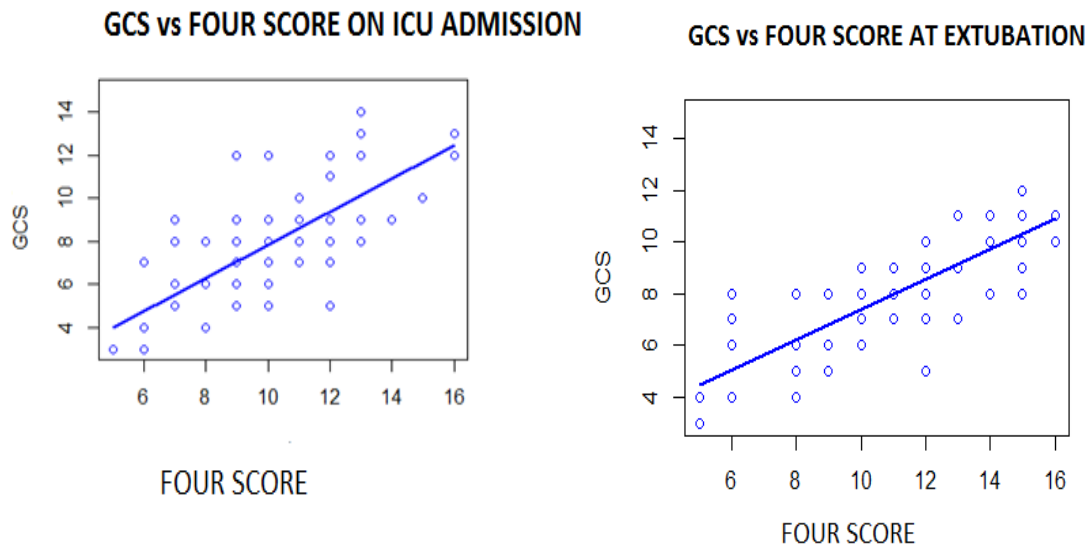


Figure 7: Bacterial isolates from tracheal aspirates for all patients in the cohort.

Ventilator associated pneumonia was not found to be an independent predictor of extubation failure. Ventilator associated pneumonia is prevalent in neuro-critically ill patients, with very high incidence in traumatic brain injury. In this study, 37.3% of the patients with TBI had VAP. The commonest organisms isolated were gram negative organisms including *Klebsiella pneumonia* (10% of patients), *Acinetobacter baumanii* (3.8% of patients) and *Proteus mirabilis* (2.5% of patients). In a meta-analysis done in 2020, Li et al showed an incidence of 36% in TBI.[53] In a randomized case control study in KNH ICU, Wangari-Siika et al showed an overall incidence of VAP of 20.6%.[54] The high incidence of VAP in patients with traumatic brain injury could be due to prolonged intubation, CNS injury induced immunodeficiency syndrome (CIDS) and high risk of aspiration. CIDS has become a recognized phenomenon with better understanding of the neural-immune systems crosstalk. The CNS is known to provide a homeostatic anti-inflammatory response to systemic inflammation. The CNS does this through neuro-hormonal mechanisms such as the hypothalamic-pituitary-adrenal axis. In TBI, the injured brain is unable to maintain a homeostatic balance, tipping the immune system to a dysregulated pro-inflammatory state and predisposing a patient to sepsis. [55]

Compliance with VAP prevention bundles could reduce the incidence of VAP in ICU, especially in these at-risk patients. The 2014 study by Wangari-Siika et al showed a high concordance between bacteria cultured from the gastric and tracheal aspirate of patients with VAP. 63.6% of paired samples grew the same organism from both the tracheal and gastric aspirates.[54] Selective oropharyngeal decontamination (SOD) or selective digestive decontamination (SDD) may be considered as a strategy to prevent VAP in neuro-critically ill patients.[56,57] Tracheostomy has not been shown to reduce incidence of VAP.[58]



Scatter Plot A

Scatter Plot B

Key:

Scatter plot A shows the correlation between the GCS and FOUR Score on ICU Admission. Spearman correlation coefficient of 0.66.

Scatter plot B shows the correlation between the GCS and FOUR score at extubation Spearman correlation coefficient of 0.76.

Figure 7: Correlation of the GCS and FOUR Scores on ICU admission and at extubation.

In this study both the GCS and the FOUR score were utilized for serial neurologic assessment of patients. There was a strong linear positive correlation between the FOUR score and the GCS (Spearman's correlation co-efficient of 0.66-076). Patients scored at lower GCS (for example GCS 3), could score FOUR scores ranging from 4-6, allowing better characterization of patients at lower levels of consciousness.[59] The FOUR score has demonstrated validity and good inter-rater reliability when used to assess neuro-critically ill patients, especially traumatic brain injury patients. It is easy to learn, and its use could overcome some limitations of the GCS. The FOUR Score could be used as an alternative to the GCS in neurological assessment of intubated brain injured patients due to its extensive validation in multiple populations of intubated, mechanically ventilated patients in neurocritical care units.[60,61,62]

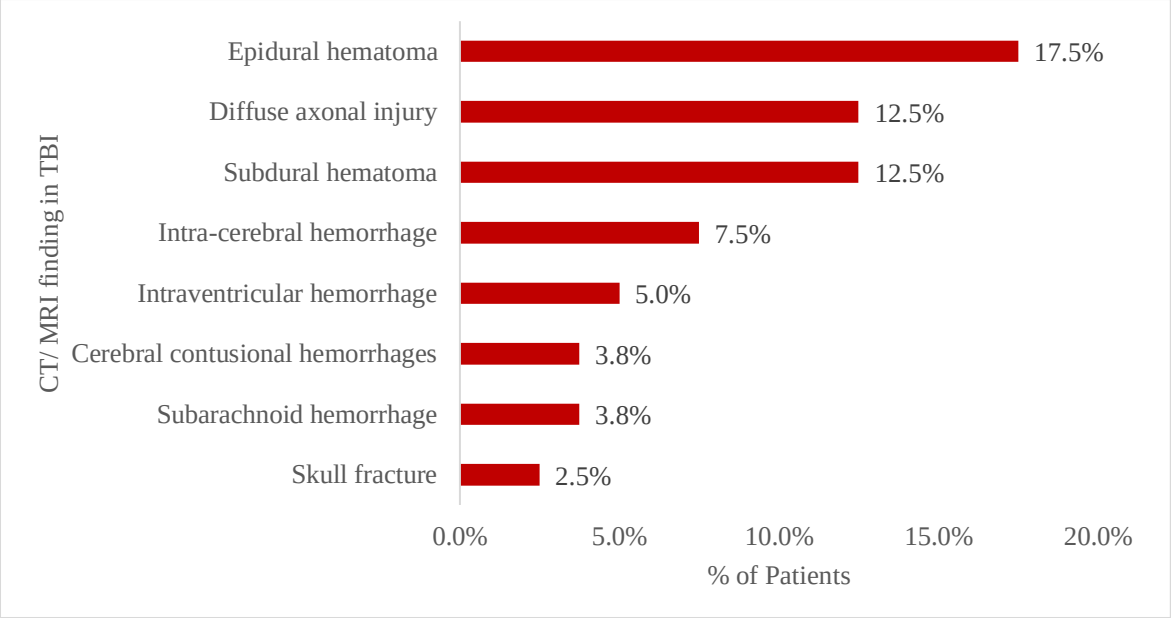


Figure 8: Bar graph showing the CT/ MRI findings in Traumatic Brain Injury patients.

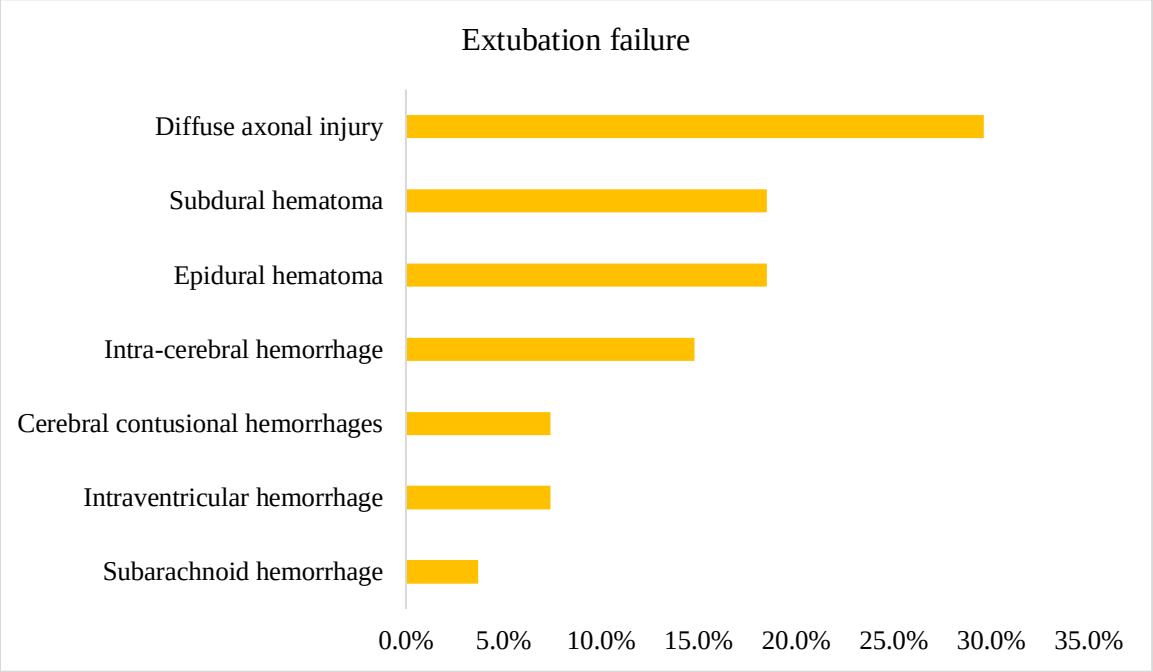


Figure 9: Proportions of Traumatic brain injury patients with extubation failure in relation to their CT/MRI finding at ICU admission.

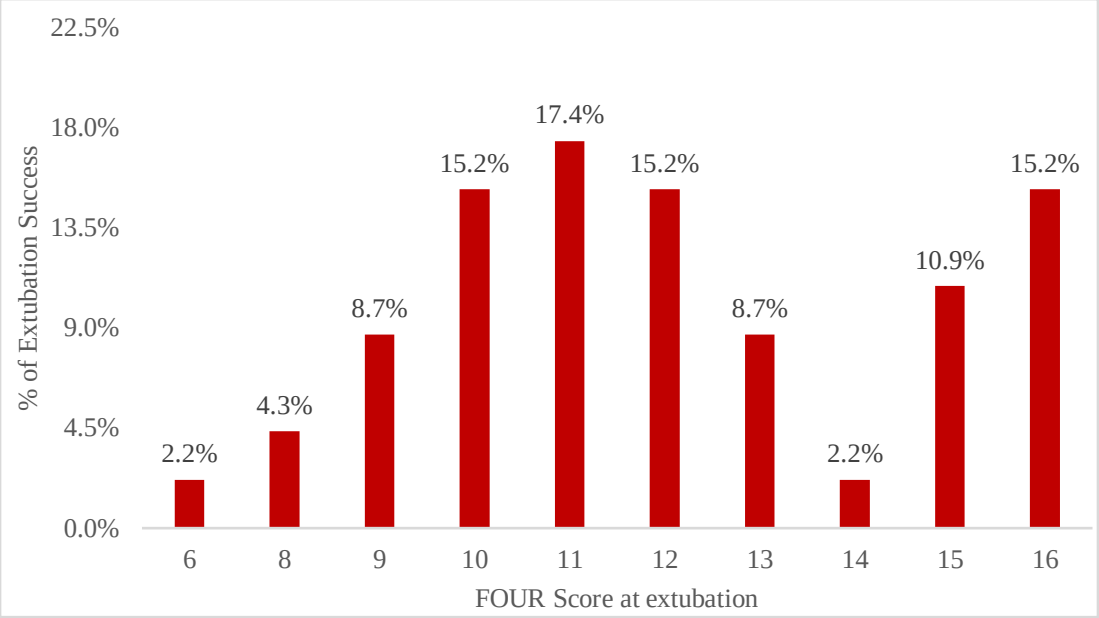


Figure 10: Percentage of patients with successful extubations and their respective FOUR scores.

In this study, 15.2% of patients extubated successfully had FOUR Scores of 6-9. However, in several instances there was a lag between the neurological assessment and the actual extubation event (in 3 patients the extubation was done up to 48 hours after the documented research neurological assessment). This is because, being an observational study extubation decisions were at the discretion of the ICU team. Studies by Coplin et al[9] and Manno et al[37] have, however, demonstrated extubation success in patients with low FOUR and GCS Scores.

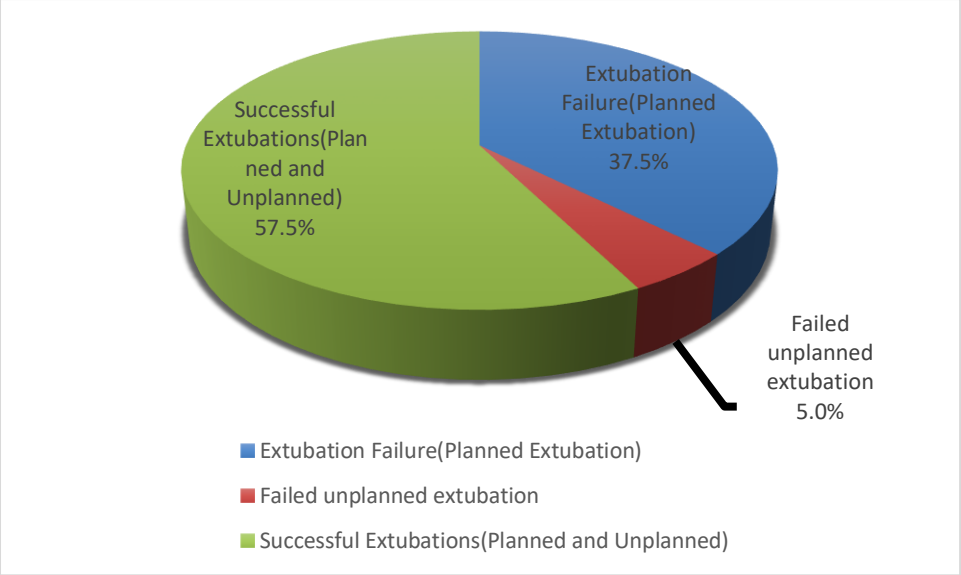


Figure 11: Incidence of Extubation Failure.

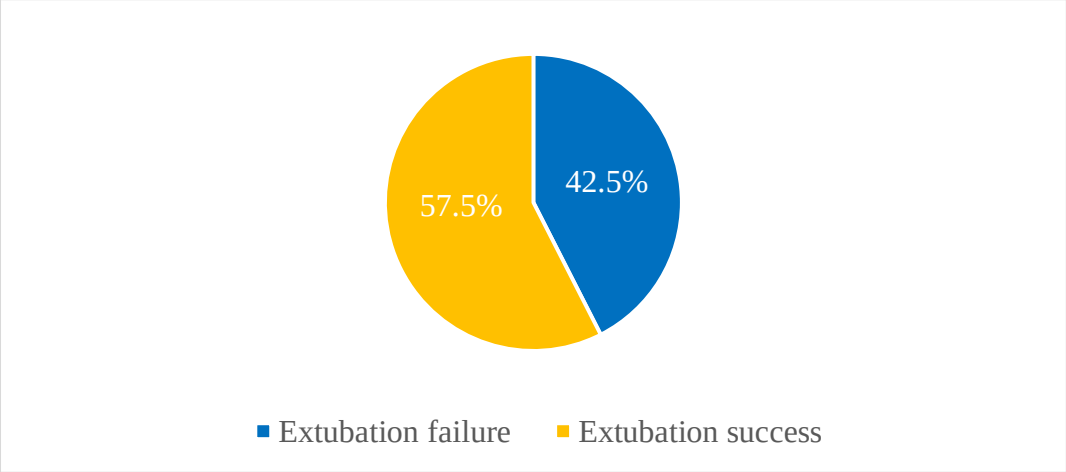


Figure 12: Relative proportion of extubation outcome for all extubations (both planned and unplanned extubations).

Figure 13: Percentages of extubation success and failure in planned extubations.

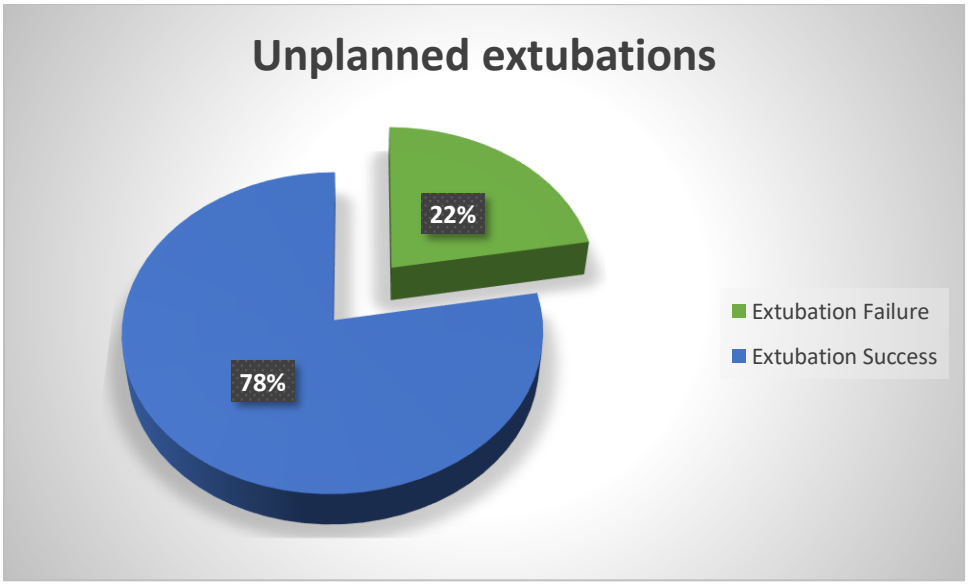


Figure 14: Percentages of extubation success and failure in unplanned extubations.

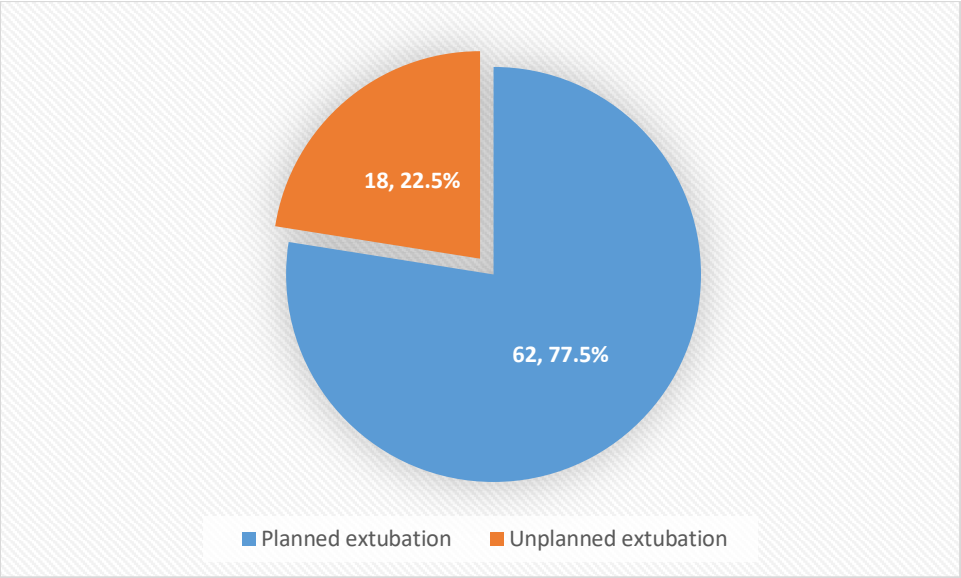


Figure 15: Number and percentage of planned and unplanned extubations.

Table 9: Extubation outcomes of planned versus unplanned extubations.

Nature of extubation	Extubation outcome		TOTAL	P value
	Extubation Failure	Extubation success		
Planned extubation	30	32	62	0.088
Unplanned extubation	4	14	18	
TOTAL	**34**	**46**	**80**	

The incidence of extubation failure was 37.5%. The methodology used for computation of the incidence of extubation failure used was similar to that by Asehnoune et al. [11] The number of failed planned extubations was calculated as a proportion of total planned and unplanned extubations. Different studies have used varying methodologies, with a variant denominator yielding a wide range of findings (extubation failure rate of 6-40%) and making comparisons across studies difficult.[63] The high incidence of extubation failure in brain injured patients has been demonstrated by other investigators including Namen et al[31] (extubation failure rate of 38% in neurosurgical ICU patient) and Steidl et al[64] (extubation failure rate of 37% in stroke patients).

The incidence of unplanned extubation was 18/80 (22.5%). This is comparable to the incidence of unplanned extubation of 18.5% in the general ICU population by Mathangani et al in KNH ICU.[46] The same study found a success rate of 35.7% in patients who had unplanned extubation, quite different from our finding of a high success rate (78%) in

unplanned extubations. However, on statistical analysis, the difference in extubation outcome (extubation failure or success) in patients who had planned or unplanned extubation was not statistically significant (p=0.088). Unplanned extubation could be associated with extubation delay in neuro-critically ill patients. Patients with brain injury could remain intubated due to low neurological status despite meeting standard weaning criteria.[9] During the extubation delay patients could have auto-extubation or accidental extubation.

Regression Analysis

Table 10: Univariate analysis.

Characteristics	Univariate Analysis		
	Odds Ratio	95% CI	P value
Gender - Female	0.28	0.08-0.93	0.04
Intervention - operative	0.24	0.09-0.65	0.01
Age - 31-40	0.74	0.24-2.28	0.6
Age- >- 40	0.9	0.31-2.66	0.85
GCS on admission	0.72	0.59-0.88	0.00
GCS at Extubation	0.74	0.59-0.92	0.01
GCS ≤ 8 at Extubation	1.47	0.58-3.72	0.41
GCS-M on Admission	0.61	0.44-0.84	0.00
GCS-M at Extubation	0.6	0.42-0.87	0.01
GCS-M <4 at Extubation	2.29	0.91-5.74	0.08
FOUR Score on Admission	0.7	0.56-0.88	0.00
FOUR Score at Extubation	0.75	0.63-0.89	0.00
FOUR Score ≤ 10 at Extubation	3.75	1.29-8.26	0.01
Diagnosis - Traumatic Brain Injury	3.54	1.28-9.73	0.01
CPIS Score	1.23	1.03-1.47	0.02
CPIS Score ≥6	2.52	0.95-6.70	0.06
HB - 9.1-11 g/dl	0.76	0.24-2.39	0.63
HB - >11 g/dl	0.75	0.25-2.28	0.62
Time to index extubation 3-10days	1.69	0.48-5.92	0.41
Time to index extubation >10	4.25	1.57-11.52	0.00

Stepwise binary logistic regression was used to test for independent predictors of extubation failure. The regression model had the following parameters.

1. Age
2. Gender
3. Hb
4. Diagnosis
5. Intervention
6. CPIS Score ≥ 6
7. GCS ≤8 at Extubation
8. GCS-M <4 at Extubation
9. FOUR Score ≤ 10 at Extubation
10. Time to index extubation >10 days

The results from the regression model are as follows:

Table 11. Multivariate logistic regression.

Characteristics	Odd Ratio	95% CI	P-value
Diagnosis - Traumatic Brain Injury	6.7	1.76-25.52	0.01
Intervention - Operative	0.14	0.03-0.61	0.01
GCS ≤8 at Extubation	0.21	0.04-1.16	0.07
FOUR Score ≤10 at Extubation	5.15	1.14-23.24	0.03
Time to index extubation >10 days	3.39	1.01-11.42	0.05

Through multivariate analysis, four covariates were found to be independent predictors of extubation failure that is, traumatic brain injury with OR of 6.7 (95% CI, 1.76-25.52, p = 0.01), operative intervention with OR of 0.14 (95% CI, 0.03-0.61, p=0.01), FOUR score ≤ 10 at extubation with OR of 5.15 (95% CI, 1.14-23.24, p=0.03) and time to index extubation > 10 days with OR of 3.39 (95% CI, 1.01-11.42, p=0.05).

A FOUR score ≤10 was found to be an independent predictor of extubation failure (FOUR ≤ 10 at extubation with OR of 5.15 (95% CI, 1.14-23.24, p=0.03). The FOUR score, a relatively novel neurological assessment tool was developed in 2005 by Wijdicks et al to address the shortcomings of the Glasgow Coma Scale.[65] One of the main shortcomings of the GCS in intubated patients is the inability to assess the verbal component. Therefore, in this study an arbitrary score of 1 was assigned for all intubated patients. A similar method was used by Manno et al[37], Kutchak et al[66] and Reis et al[67] in their studies involving neuro-critically ill patients. The FOUR score has been validated in intubated ICU patients.[68,69,70]

Few studies have shown a correlation between the FOUR score and extubation outcome. In a study by Said et al, the FOUR score was found to be a more accurate predictor of extubation failure in comparison to the GCS, 14 days after intubation. In this prospective observational study, 101 intubated patients had neurological assessment using the FOUR score and the GCS before extubation. The extubation outcome was then observed at 14 days post intubation. The AUC, was found to be higher with the FOUR Score, as compared to the GCS (0.867 CI: 95% [0.790-0.944] and 0.832 CI: 95% [0.741-0.923]; p=0.014, respectively).[32] In a retrospective observational study of 62 patients in a neurological intensive care unit, Ko et al found that conventional weaning parameters did not predict extubation failure. In these patients there was no significant difference in the FOUR scale scores between patients who had extubation failure and those who were successfully extubated.[13]

In our study, both GCS and GCS-M (best Motor Score of the GCS) were not found to be independent predictors of extubation failure. The correlation between the GCS and patients' extubation outcome is controversial. Despite there being no evidence of extubation success with higher scores, higher GCS is generally preferred prior to extubation.

Low GCS has been found to be an independent predictor of extubation failure. In a meta-analysis by Wang et al, low GCS (7-9T) was an independent predictor of extubation failure in

neuro-critical care patients.[71] In this meta-analysis, a patient's inability to follow commands was also identified as a significant predictor of extubation failure. In a randomized control trial comparing a respiratory therapist driven weaning protocol versus standard practice in a neurosurgical ICU, Namen and co-workers demonstrated that GCS was strongly associated with extubation success ($p < 0.001$). Patients who had a GCS of ≥ 8 at the time of extubation were successfully extubated in 75% of the cases, whereas patients with GCS of ≤ 7 were successfully extubated in 36% of the cases. The odds of successful extubation increased by 39% for every increment in GCS score. [31]

In a review article, King et al critiqued studies showing low GCS as a predictor of extubation failure and several studies showing that it is safe to extubate neuro-critically ill patients with low GCS. The review article however recommended that impaired neurological status could be a predictor of extubation failure and current good practice recommends so until randomized controlled trial (RCT) data supports the safety of extubating brain injured patients with low GCS.[72]

In our study, the diagnosis of traumatic brain injury was an independent predictor of extubation failure. Vallverdu et al showed a higher incidence of extubation failure in neuro-critically ill patients.[14] Our study also demonstrated that patients with a CT scan/ MRI finding of diffuse axonal injury had the highest proportion of extubation failure among patients with TBI (29.6% of patients with TBI and extubation failure had diffuse axonal injury: Figure 9). A possible explanation is that patients with TBI tended to suffer more severe, high impact brain trauma, with longer periods of intubation, predisposing them to extubation failure.

Operative intervention was an independent predictor of extubation failure (**OR 0.14**, 0.03-0.61 95% CI, p=0.01). This means that patients who had an operative intervention had reduced likelihood of extubation failure. In a study investigating post-operative reintubation in patients undergoing elective intracranial surgery, Hayashi et al found significant correlation between post-operative reintubation and re-operation.[73]

Duration of mechanical ventilation > 10 days is an independent predictor of extubation failure according to this study. OR of 3.39 (95% CI, 1.01-11.42, p=0.05). Studies have shown neuro-critically ill patients to have more prolonged mechanical ventilation in comparison to general ICU patients.[74, 75] A study by Reis et al in traumatic brain injury patients showed intubation for >10 days to be an independent predictor of extubation failure.[67] The association between prolonged mechanical ventilation and extubation failure could be explained by ventilator induced diaphragmatic dysfunction. Interaction of several factors could lead to critical illness weakness, making it difficult for patients to be successfully liberated. Proposed pathophysiological processes are: disuse atrophy due to prolonged unloading of the diaphragm and intercostal muscles as well as pathologic proteolysis due to upregulation of ubiquitin.[76] Oversedation is prevalent in neuro-critically ill patients and could lead to prolonged intubation and possibly extubation failure.[77]

36.2% (29/80) of patients had an attempt at extubation 10 days after intubation (Table 6). According to the institutional protocol for the management of traumatic brain injury patients

(KNH ICU protocol booklet 2012), early extubation should be considered by day 7-10, but if GCS is <8 by this time a tracheostomy should be performed.[15] There were notable delays in performance of tracheostomies despite a timely intention and request for the tracheostomy from the ENT service (at the time the study was conducted, all tracheostomies in KNH critical care units were performed by ENT surgeons and residents). Four unplanned extubations (which all failed) happened during the interval wait for the tracheostomy. The other 25 patients had a planned extubation because some clinical improvement during the delayed tracheostomy justified an attempt at extubation. Percutaneous dilatational tracheostomy performed by intensivists is as safe and effective as surgical tracheostomy.[58,78,79] Training of anaesthesiologists/ intensivists in safe performance of percutaneous dilatational tracheostomy in the critical care units would be a feasible way to reduce logistical delays.[80]

STRENGTHS AND LIMITATIONS OF THE STUDY

STRENGTHS

1. The cohort was selected to only include neuro-critically ill patients. The sample was relatively homogenous.
2. Use of novel validated tools such as the FOUR Score as well as traditional tools such as GCS.

LIMITATIONS

1. Extubation failure is poorly defined and therefore it is difficult to interpret the incidence across studies. For example, variation in the duration of post-extubation follow up, ranging from 24 hours up to 1 week in different studies.
2. This study was limited to neuro-critically ill patients and its findings may not be generalizable to other populations of ICU patients.
3. The sample size was relatively small and limited to a single centre.
4. During data collection, some continuous variables such as the age and duration of intubation were categorized making data analysis challenging.
5. For this study, patients were classified as having had either operative management or non-operative management. It was assumed that operative management was a single entity. In reality, patients undergo a wide range of neurosurgical interventions depending on their specific pathology.
6. Unplanned extubations constituted 22.5% of all extubations. Unplanned extubations are an important quality of care metric and data should have been collected to analyse possible causes.

CONCLUSIONS AND RECOMMENDATION.

CONCLUSIONS

1. The incidence of extubation failure in neuro-critically ill patients in KNH critical care units is 37.5%.
2. Independent predictors of extubation failure are a diagnosis of traumatic brain injury, FOUR Score ≤10 at extubation and duration of intubation >10 days. Operative intervention was associated with reduced risk of extubation failure.

RECOMMENDATION

1. The FOUR score is recommended as a useful tool in the care of neuro-critically ill patients; its use is recommended especially in prediction of extubation failure in these patients.

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APPENDICES

Appendix I (a): Consent Explanation Form (English)

My name is Dr. Frank Gitonga, a postgraduate student pursuing a Masters' degree in Anaesthesia at the University of Nairobi. I am conducting a study on determining the **'Predictors of extubation failure in neuro-critically ill patients in KNH ICUs'**.

Dear Sir or Madam: Your relative is invited to participate in a study to investigate why patients with brain injury fail extubation. Before deciding whether or not he/she should take part in this study, we request that you carefully read the following information which explains the study's objectives and the implications of his/ her possible participation.

Study Description

We will collect information from his/her medical charts concerning previous and current illnesses, the events during the intensive care unit course and the data regarding the management of extubation. During the intensive care unit course, the investigator will collect the data. We will analyze the laboratory and radiologic investigations done in the course of the patient's ICU stay.

Study Objective

The main objective is to investigate the incidence of extubation failure in brain-injured patients in the ICU and to investigate factors which contribute to extubation failure.

Voluntariness of participation

Your relative's participation is voluntary and opt-out from this proposed study will not affect the medical care he/ she will receive. A decision not to participate in this study will not alter his/ her treatment.

Benefits and Risks

The treating doctors will not modify their decisions, neither during the hospital stay nor after discharge, because you relative has participated or not. No extra biological samples, laboratory or radiological tests will be performed for the need of the study outside of the

patient's necessary care. There are no financial benefits accrued by participation in this research.

Right of withdrawal

Even though you have agreed that your relative participates, he/she may leave the study whenever you wish and, moreover, without having to offer any kind of explanation. You will not have to justify your decision.

Confidentiality

In order to carry out the study it will be necessary to consult and make use of some of the information that appears in the medical record. Your acceptance will authorize us to consult and process the information in the following manner:

- Information will be stored in a computerized database for all the participants.
- All information will be stored and anonymized. All clinical information that is obtained for the study will be identified by a number. No data concerning personal identification will be stored in the database.

Results of the Research Study

The results obtained in the present study will be published in a medical journal and the information and knowledge gained will be of benefit to many critically ill ICU patients.

For further information and clarification, you may contact:

Principal Investigator: **Dr. Frank Gitonga**

Telephone: 0710 904411

Or,

Research Supervisors: **Dr. Antony Gatheru/ Dr. Idris Chikophe**

Telephone 1: 0721 654806

Telephone 2: 0721436926

If you have any questions related to the patients' rights as a participant in the study you can get in touch with (Kenyatta National Hospital/ University of Nairobi Ethics and Research Committee):

Telephone: 2726300

Thank you for taking time to read this information sheet. I wish your loved one a speedy recovery.

Appendix I (b): Consent Explanation Form (Swahili)/ Kiambatisho I (b) : Fomu Ya Makubaliano Ya Kujiunga Na Utafiti.

Jina langu ni Dkt. Frank Gitonga, mwanafunzi wa shahada ya juu ya Anaesthesia katika Chuo Kikuu cha Nairobi.

Mada ya Utafiti: **"Predictors of extubation failure in neuro-critically ill patients in KNH ICUs."**

Bwana au Bibi: jamaa yako anaalikwa kushiriki katika utafiti wa kuchunguza kwa nini wagonjwa wenye magonjwa mahututi ya ubongo hushindwa kupumua bila usaidizi wa mashine. Kabla ya kuamua kama jamaa yako atashiriki katika utafiti huu, tunakuomba makini kusoma taarifa ifuatayo inayoelezea malengo ya utafiti na matokeo ya ushiriki wake katika utafiti huu.

Maelezo ya Utafiti.

Sisi watafiti tutakusanya taarifa ya mgonjwa kutoka chati zake za matibabu kuhusu magonjwa ya zamani na ya sasa na matukio wakati anapolazwa kwenye sadaruki. Tutachambua pia matokeo ya vipimo vya maabara na picha zitakazoitishwa atakapokuwa amelazwa kwenye ICU.

Lengo La Utafiti.

Utafiti huu una nia ya kuchunguza sababu za "Extubation Failure" (wagonjwa waliolazwa kwenye sadaruki kushindwa kupumua bila usaidizi wa mashine). Utafiti huu utahusisha wagonjwa mahututi waliolazwa kwenye sadaruki (ICU) kwa sababu ya magonjwa mahututi ya ubongo.

Utaratibu wa utafiti

Kama wewe hukubaliani kwa jamaa yako kushiriki katika utafiti huu, uamuzi huu hautaadhiri huduma ya matibabu yake. Madaktari wake hawatambagua kwa jinsi yoyote, wala kubadilisha maamuzi ya kimatibabu kwa sababu ya kutoshiriki utafiti huu. Hakuna sampuli za maabara wala picha za kiradiologia za ziada zitakazoagizwa zaidi ya zile zinazoagizwa na

madaktari wake wa ICU. Hakuna faida ya kifedha utakayozawadiwa kwa kushirikisha jamaa yako kwa utafiti huu.

Kujiondoa kutoka utafiti.

Ingawa umekubali kwamba jamaa yako ashiriki kwa utafiti huu, una uhuru wa kuagiza aachishwe utafiti wakati wowote bila aina yoyote ya maelezo. Hakuna madhara, wala ubaguzi wa kimatibabu wala adhabu yoyote itakayofuatia uamuzi huu. Hautatakiwa kuhalalisha uamuzi wako.

Faragha na matumizi ya maelezo ya kimatibabu.

Ili kutimiliza utafiti huu itakuwa muhimu kushauriana na kutumia baadhi ya taarifa zilizo kwenye rekodi ya matibabu. Idhini yako inatupa ruhusa ya kushauriana na kusindika taarifa kwa njia ifuatayo:

- Habari itahifadhiwa katika hifadhidata ya tarakilishi iliyositiriwa ila tu kwa mtafiti mkuu na wasimamizi wa utafiti.
- Taarifa zote ya mgonjwa, hasa jina la mgonjwa na taarifa ya kutambulisha zitasitiriwa. Badala yake, mgonjwa atatambulika kwa nambari fiche kwenye hifadhidata.

Matokeo ya utafiti.

Matokeo ya utafiti huu yatahifadhiwa katika maktaba ya Chuo Kikuu cha Nairobi na kuchapishwa katika jarida la matibabu. Matokeo ya utafiti huu pia yatafafanua na kuongezea ujuzi wa utabibu wa wagonjwa wa ICU wanaougua magonjwa mahututi ya ubongo.

Kwa maelezo ya ziada na ufafanuzi wasiliana na:

Mtafiti mkuu**: Dkt. Frank Gitonga**

Nambari ya simu: 0710 904411

Au,

Wasimamizi wa Utafiti: **Dkt. Antony Gatheru/ Dkt. Idris Chikophe**

Namabri ya simu 1: **0721 654806**

Nambari ya simu 2: **0721436926**

Maswali yoyote kuhusu haki ya jamaa yako kuhusishwa kwa utafiti zaweza pia kuwasilishwa kwa Kamati ya Maadili ya Utabibu na Utafiti ya Hospitali ya Rufaa ya Kenyatta/ Chuo Kikuu cha Nairobi.

Nambari ya simu: 2726300

Ahsante kwa kuusoma ujumbe huu.

Namuwia mpendwa wako afueni.

Appendix II (a): Assent Form (English)

I, (Your name) _____, have been explained the purpose and condition of my Next of Kin's/ relative's involvement in the study by Dr. Frank Gitonga. I agree to the above and do give consent for:

(Patient's name) _____

To be included in the study, by virtue of being a critically ill patient undergoing neuro-critical care.

Name: _____

Signature: _____

Thumb print: _____

Date: _____

Appendix II (b): Assent Form (Swahili)

Mimi, (jina lako) _____, nimeelezwa madhumuni na masharti ya mgonjwa wangu kushirikishwa katika utafiti wa Dkt. Frank Gitonga. Nakubaliana na maelezo hayo na nimemruhusu daktari kufanya utafiti huo kwa jamaa wangu:

(Jina la mgonjwa) _____.

Naidhinisha ruhusa kwa niaba ya mgonjwa kwa sababu kwa wakati huu, ugonjwa mahututi wa ubongo haumwezeshi kutoa idhini kamilifu.

Jina: _____

Sahihi: _____

Kidole Cha Gumba: _____

Tarehe: _____

Appendix II (c) Consent Form

I, (Your name) _____, have been explained the purpose and condition of my involvement in the study by Dr. Frank Gitonga. I agree to the above and do give consent for my inclusion in the study

Signature: _____

Thumb print: _____

Date:_____

Appendix II (d): Consent Form (Swahili)

Mimi, (jina lako) _____, nimeelezwa madhumuni na masharti ya kushirikishwa katika utafiti wa Dkt. Frank Gitonga. Nakubaliana na maelezo hayo na nimemruhusu daktari kunishirikisha katika utafiti huo.

Sahihi: _____

Kidole Cha Gumba: _____

Tarehe: _____

Appendix III: Data Collection Form

1. Questionnaire Serial Number:
2. Age:
    - 14-20years
    - 21-30years
    - 31-40years
    - 41-50years
    - 51-60 years
    - 61-70 years
    - >70 years

3. Gender:

    Male: ☐ Female: ☐

4. Diagnosis:

    I. Traumatic Brain Injury

        CT/ MRI finding:

        a) Epidural hematoma

        b) Subdural hematoma

        c) Subarachnoid hemorrhage

        d) Intraventricular hemorrhage

        e) Cerebral edema

        f) Others: _____

    II. Ischemic Stroke

    III. Hemorrhagic Stroke

    IV. CNS Infection

    V. Brain tumor

        CT/ MRI finding:

        a) Posterior cranial fossa tumor

        b) Others:_____

    VI. Status epilepticus

    VII. Others:_____

5. Date of intubation: Time of intubation:

6. Date of extubation: Time of extubation:
7. History of co-morbid medical condition:
    a. COPD
    b. Asthma
    c. Hypertension
    d. Diabetes
    e. Epilepsy
    f. CKD
    g. HIV
    h. Others: (Specify):_____

8. Intervention:

    Non-Operative:

    Operative:

        If Operative:

        I. External Ventricular Drain (EVD)
        II. Ventriculo-peritoneal (VP) shunt
        III. Craniotomy for tumor excision
        IV. Craniotomy for clot evacuation
        V. Others:_____

9. Glasgow Coma Scale Table

	EVENT				
GCS Component Score	Pre-intubation	Pre-extubation	Day 1 post-extubation	Day 2 post-extubation	Day 3 post-extubation
Eye-opening	/4	/4	/4	/4	4
Motor	/6	/6	/6	/6	/6
Verbal	/5	/5 or T	/5 or T	/5 or T	/5 or T

10. FOUR Score Table

	EVENT				
FOUR Score Component	Pre-intubation	Pre-extubation	Day 1 post-extubation	Day 2 post-extubation	Day 3 post-extubation
Eye response	/4	/4	/4	/4	/4
Motor response	/4	/4	/4	/4	/4
Brainstem reflexes	/4	/4	/4	/4	/4
Respiration	/4	/4	/4	/4	/4

11. CPIS

CPIS POINTS	0	1	2
Tracheal Secretions	Rare	Abundant	Purulent
Leucocyte Count	4, 000-11, 000	<4, 000 or >11,000	<4, 000 or >11,000 + Band forms
Temperature	36.5-38.4	38.5-38.9	>39 OR <36
P/F ratio	>240		≤240
CXR	No infiltrate	Diffuse infiltrate	Localized infiltrate
Culture of T/A	Negative	-	Positive
TOTAL			

12. Duration of mechanical ventilation/ Time to index extubation:

- Less than 3 days
- 3-6 days
- 7-10 days
- 11-14 days
- 15-18 days
- 19-21 days
- More than 21 days.

13. Outcomes post extubation:

Day(s) post extubation	
Day 1	Remains extubated, re-intubated, tracheostomy, other.
Day 2	Remains extubated, re-intubated, tracheostomy, other
Day 3	Remains extubated, re-intubated, tracheostomy, other
Day4-14	Remains extubated, re-intubated, tracheostomy, other
Day 15-28	Remains extubated, re-intubated, tracheostomy, other

Appendix IV: FOUR Score.

FOUR Score

Eye Response

4= eyelids open or opened, tracking, or blinking to command
3= eyelids open but not tracking
2= eyelids closed but open to loud voice
1= eyelids closed but open to pain
0= eyelids remain closed with pain

Motor Response

4= thumbs-up, fist, or peace sign
3= localizing to pain
2= flexion response to pain
1= extension response to pain
0= no response to pain or generalized myoclonus status

Brainstem Reflexes

4= pupillary and corneal reflexes present
3= one pupil wide and fixed
2= pupillary or corneal reflexes absent
1= pupillary and corneal reflexes absent
0= absent pupillary, corneal, and cough reflex

Respiration

4= not intubated, regular breathing pattern
3= not intubated, Cheyne-Stokes breathing pattern
2= not intubated, irregular breathing pattern
1= intubated, breathes above ventilator rate
0= intubated, breathes at ventilator rate or apnea

Appendix V: Glasgow Coma Scale (GCS)

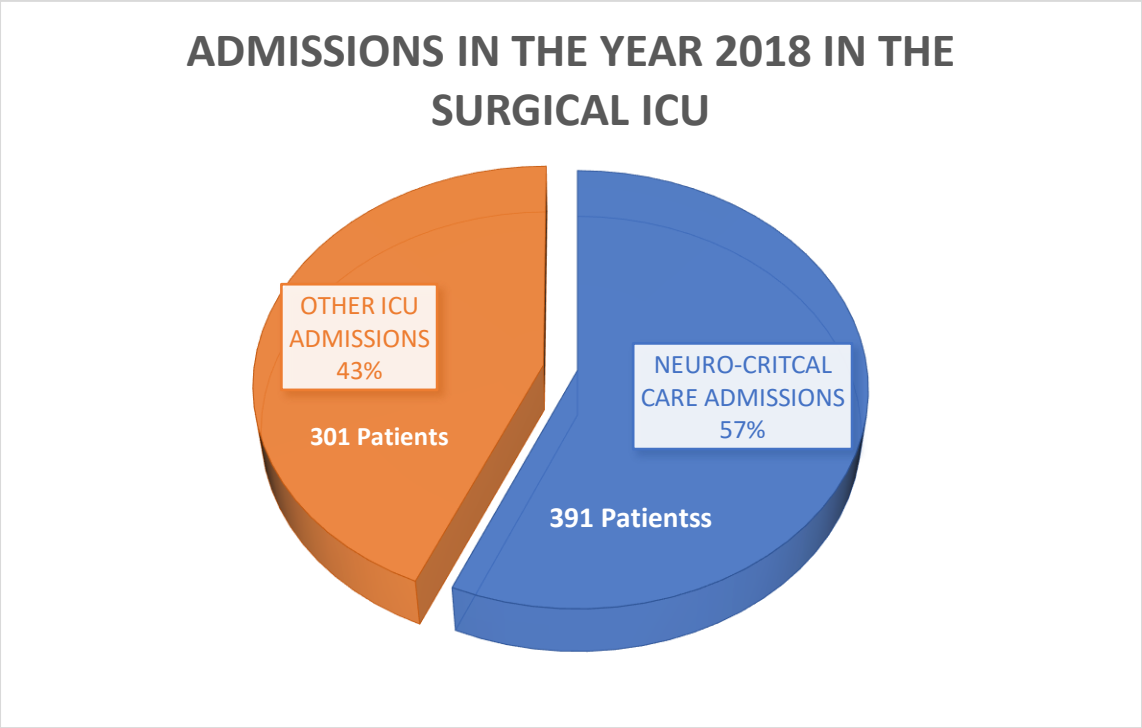
Feature	Response	Score
Best eye response	Open spontaneously	4
	Open to verbal command	3
	Open to pain	2
	No eye opening	1
Best verbal response	Orientated	5
	Confused	4
	Inappropriate words	3
	Incomprehensible sounds	2
	No verbal response	1
Best motor response	Obeys commands	6
	Localising pain	5
	Withdrawal from pain	4
	Flexion to pain	3
	Extension to pain	2
	No motor response	1

Appendix VI: CPIS Score

CPIS points	0	1	2
Tracheal secretions	Rare	Abundant	Purulent
Leukocyte count (mm^3)	>4,000 and <11,000	<4,000 and >11,000	<4,000 or >11,000 + band forms
Temperature (°C)	>36.5 and <38.4	>38.5 and <38.9	>39 or <36
PaO_2/FIO_2 ratio (mmHg)	>240 or ARDS	-	≤240 and no ARDS
Chest radiograph	No infiltrate	Diffuse infiltrate	Localized infiltrate
Culture of tracheal aspirate	Negative	-	Positive

CPIS: Clinical pulmonary infection scoring

Appendix VII: ICU admission statistics.



Year	Total Admissions (1 year) 2018	Total Admissions 2020 (Half year)	Neuro-critical care admissions (1 year) 2018	Neuro-critical care admissions (Half year) 2020
Surgical/ Main ICU	692	315	391	167
Medical ICU	395	141	97	*
Private Wing ICU	*	182	*	*

- Between 42.7%- 56.5% of patients admitted in the Surgical ICU were neuro-critically ill patients.
- On average 27-33 neuro-critically ill patients were admitted per month in the Surgical ICU.

Appendix VIII: Budget and Study timeline.

BUDGET

ITEM	COST
STATIONERY	8,000
STATISTICIAN	30,000
ERC FEE	2,000
CONTINGENCY FEE	10,000
RESEARCH ASSISTANTS	100,000
TOTAL	150,000

STUDY TIMELINE

ACTIVITY	TIMELINE
RESEARCH PROPOSAL PRESENTATION	OCTOBER 2019
APPROVAL FROM KNH/ UNIVERSITY OF NAIROBI ERC	JANUARY 2020
DATA COLLECTION	JANUARY 2020 TO JUNE 2020
DATA ANALYSIS	JULY 2020
THESIS RESULTS PRESENTATION	AUGUST 2020

Appendix IX: KNH ERC Approval letter.

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
Tel:(254-020) 2726300 Ext 44355

KNH-UON ERC
Email: uonknh_erc@uonbi.ac.ke
Website: http://www.erc.uonbi.ac.ke
Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/31

27th January 2020

Dr. Frank Kamau Gitonga
Reg. No.H58/87398/2016
Dept. of Anaesthesia
School of Medicine
College of Health Sciences
University of Nairobi

Dear Dr. Kamau

RESEARCH PROPOSAL: PREDICTORS OF EXTUBATION FAILURE IN NEURO-CRITICAL CARE PATIENTS IN K.N.H. ICUs (P868/10/2019)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above research proposal. The approval period is 27th January 2020 – 26th January 2021.

This approval is subject to compliance with the following requirements:

a. Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b. All changes (amendments, deviations, violations etc.) are submitted for review and approval by KNH-UoN ERC before implementation.
c. Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d. Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
f. Submission of an *executive summary* report within 90 days upon completion of the study. This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

For more details consult the KNH- UoN ERC website**http://www.erc.uonbi.ac.ke**

Yours sincerely,

PROF. M. L. CHINDIA
SECRETARY, KNH-UoN ERC

c.c. The Principal, College of Health Sciences, UoN
The Director, CS, KNH
The Chairperson, KNH- UoN ERC
The Assistant Director, Health Information, KNH
The Dean, School of Medicine, UoN
The Chair, Dept. of Anaesthesia, UoN
Supervisors: Dr. Antony Gatheru, Dept. of Anaesthesia, UoN
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