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EFFECTS OF FLUID BALANCE ON OUTCOMES AMONG CHILDREN IN THE INTENSIVE CARE UNIT AT KENYATTA NATIONAL HOSPITAL

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ABBREVIATIONS

ADH- Antidiuretic hormone

AKI- Acute kidney injury

ARDS-Acute respiratory distress syndrome

CNS-Central Nervous System

CFB-Cumulative Fluid Balance

EDV- End diastolic volume

EGDT-Early Goal-Directed Therapy

FB- Fluid Balance

FEAST- Fluid Expansion as Supportive Therapy

Fi02-Fraction of inspired Oxygen

GCS-Glasgow Coma Scale

INR-International Normalized Ratio

ICU-Intensive Care Unit

KNH- Kenyatta National Hospital

LOS-Length of stay

LR-Ringers Lactate

MV- Mechanical ventilation

NS-Normal saline

Pa02-Partial pressure of oxygen in arterial blood

PaC02-partial pressure of carbon dioxide

PD- Peritoneal dialysis

PEEP-Positive end-expiratory pressure

PELOD- Pediatric logistic organ dysfunction

PICU- Paediatric Intensive Care Unit

RCT -Randomized Control Trial

RRT-Renal Replacement Therapy

SBP-Systolic Blood Pressure

UON-University of Nairobi

VASST- Vasopressin in Septic Shock Trial

ICU- Intensive Care Unit

OPERATIONAL DEFINITIONS

Fluid overload: Is the condition of having too much fluid in the body and implies a degree of pulmonary or peripheral oedema.

Absolute fluid overload: Refers to the cumulative total volume input minus the total volume output over a given period. Manifestation of peripheral oedema suggests an overload.

Relative volume balance: This is defined as the absolute volume balance (in litres) divided by the patient's body weight (in kilograms) and is expressed as per cent volume (or fluid) balance.

Positive fluid balance refers to a net fluid accumulation.

Fluids overload per cent: The total fluid input in 24hrs - total fluid output in 24hrs (ml)/weight at admission (kilograms)*100. Usually implies a degree of pulmonary or peripheral oedema.

Significant fluid overload: ≥10% increase in body weight.

Daily input: calculated as the sum of total parenteral/enteral fluids, medications, blood, and blood products.

Daily output: calculated as the sum of daily urine output and other body fluids output [drains, naso-orogastric aspirates].

Daily fluid balance: daily difference in all intakes and all outputs which exclude insensible losses.

Cumulative fluid balance: the sum of each day's fluid balance over a period.

Shock: a state of inadequate tissue perfusion causing inadequate oxygen delivery to meet cellular metabolic needs and oxygen utilization or a combination of both.

Fluid bolus: administration of an amount of fluid intravenously often ranging between 10-20mls/kg per episode in a time frame of 30 minutes or less.

Septic shock: a potentially fatal condition that occurs when sepsis leads to dangerously low blood pressure and abnormalities in cellular metabolism despite initial fluid resuscitation.

Euvolemia- volume status allowing adequate filling in cardiac chambers, arteries and capacitance vessels

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ABSTRACT

Background

For critically ill pediatric patients, fluid therapy plays a pivotal role in resuscitation. Adequate intravascular volume re-establishment using timely fluid management may be crucial in saving lives. Nevertheless, pediatric patients also receive varying amounts of fluid beyond resuscitation e.g., via medication, food, or routine fluid administration. The total fluid intake can exceed fluid output leading to a positive water balance. Pediatric practitioners experience challenges regarding the kind of fluid, and volume of intake, besides the timing of intravenous fluid administration.

Fluid buildup following early resuscitation might worsen the condition and increase the risk of death, hence it is imperative to monitor fluid status and ensure close assessment of very ill pediatric patients.

Broad Objective

To determine the relationship between fluid balance and clinical outcomes among critically ill pediatric patients admitted to the Pediatric Intensive Care Unit/Main Intensive Care Unit (PICU/main ICU), Kenyatta National Hospital.

Study design and site

This was a prospective observational study that was conducted at Kenyatta National Hospital. It was carried out in adult and paediatric ICUs.

Participants and methods

Study participants were children aged 1 month to 12 years admitted to the two ICUs.

Consecutive sampling method was used to recruit a total of 81 children.

A standardized questionnaire was used to collect patient data from admission throughout the PICU/ICU stay.

Data management

The data that was collected included continuous, categorical, and discrete data. Data entry was done using excel spreadsheets and then exported to R software.

Data was cleaned, coded, and analyzed using R Studio version 4.0.2. The first analysis included descriptive statistics i.e., median age and weight with their interquartile ranges, frequencies, and proportions for categorical data such as gender and fluid overload. Binary logistic regression was used to determine the association between the independent variables e.g., gender, weight, age

and dependent variables e.g., mortality. On the other hand, Poisson regression was used to determine the relationship between the factors associated with length of ICU stay and days on mechanical ventilation. The results were evaluated at 5% significance level. Tests were interpreted using odds ratios and P-values.

Results

This study sampled a total of 81participants. The prevalence of fluid overload was 74% (95% CI 62%, 83%). There was a mortality rate of 51.0%. Mortality in those with fluid overload was 47.1% (95% CI 33.2%, 61.4%) while mortality in those without fluid overload was 38.9% (18.3%, 63.9%).

There were no factors associated with mortality, fluid overload OR 1.28 (95% CI 0.36, 4.68), p-value 0.70, inotropic use OR 0.84 (95% CI 0.27, 2.69), p-value 0.78. Inotropic use and mechanical ventilation were significantly associated with the length of ICU stay p-values 0.004 and <0.001 respectively.

Conclusion

Mortality and fluid overload in this study were above fifty percent. This study did not find any significant association between ICU mortality and the factors that were investigated among the study participants. Inotropic use and mechanical ventilation were associated with the length of ICU stay. There is need for more studies with larger sample sizes to further investigate the factors studied under this study.

1.0 CHAPTER ONE: INTRODUCTION

Among critically ill pediatric patients, fluid therapy remains pivotal when it comes to resuscitation. Adequate intravascular volume re-establishment using timely fluid administration may be lifesaving. However, children also receive a variable amount of fluid intake beyond resuscitation e.g., via medication, food, or routine fluid. When water intake is more than output, a positive water balance occurs.[1]

Fluid balance may be regarded as absolute or relative. Absolute water balance denotes the cumulative aggregate water input less the aggregate water loss in a specified duration. Relative water balance is the total water balance (in liters) divided by the patient's weight (in kilograms). This is presented as per cent water balance. Significant fluid overload is equal to a ten per cent or more increase in body weight.[2]

Non-experimental studies in sick children requiring renal replacement therapy [RRT] have shown an association between fluid overload and an increase in the risk of death.[3] Careful fluid administration approaches have proven helpful by decreasing morbidities such as ARDS following major surgery.[2]

Sick children with water excess have expressively more respiratory failure, need artificial ventilation and experience increased sepsis.[4] Wiedemann et al. 2006 randomized 1000 patients into a conservative or liberal approach to water administration. Those managed conservatively did not have an increase in the occurrence of shock or necessity for kidney dialysis.[5]

In a study that found a cumulative water excess of more than 15% in 62% of the sample that was studied, mortality in the overload group stood at 40.5% as opposed to 34% in the group that did not have fluid overload. In this study water excess was linked to organ dysfunction, patients remaining on mechanical ventilation longer and spending more days in pediatric ICU.[6]

Secondary analysis of data from the Fluids and Catheters Treatment Trial [FACTT] by Grams et al. 2011showed that patients treated with water restraint took a shorter duration in the intensive care unit and fewer days of mechanical ventilation as opposed to those treated with the unrestricted fluid regimen.[7]

2.0 LITERATURE REVIEW

Fluid resuscitation is crucial in the treatment of critically ill pediatric patients admitted to the intensive care unit. Uncontrolled administration of therapeutic water can cause an imbalance in fluid regulation and cause fluid excess. Among seriously ill pediatric patients according to Weiss et al. 2020, fluid overload can cause a horde of untoward effects and increase the risk of disease worsening and death.[1]

2.0.1 Physiology of body fluids

The human body is 50-60 per cent water for adult men and women, about 75% for infants and reduces to as low as 45 per cent in old age. Body water is reduced by factors such as ageing, obesity, dehydration, and changes at various stages of development. These body fluids are distributed in various compartments of the body.[8] The highest percentage of body fluids is in the kidneys and brain and makes up to 85% of their total mass. Body fluids are distributed in organs and blood vessels.

Blood vessel endothelium permits restricted interchange of fluid, electrolyte, glucose, and other nutrients in and out of tissues autonomously due to their permeability to these constituents. According to Chen et al. 2016, this trans-capillary constituent movement ability is influenced by features such as sterling forces and an intact endothelial glycocalyx.[9]

2.0.2 Body fluid compartments

Willock and Jewkes (2000) state that body fluids are divided into two compartments i.e., the intracellular (55%) and extracellular (45%) compartments (intravascular: 15%, trans-cellular: 45% and interstitial 40%). The intracellular compartment refers to the fluid that is inside the cells and takes the largest quantity of the body water.[10] The intracellular fluid also called cytosol is key when it comes to cellular metabolic activities.[11] As indicated earlier, children have a higher percentage volume of water in their body as compared to adults hence they need more water.

The intravascular compartment refers to the fluid flowing within blood vessels and the cardiac chambers. This is mainly blood and contains blood cells such as reticulocytes, neutrophils, platelets, and plasma. Plasma is fluid containing mainly salts and protein. Blood cells float in the plasma.[10] This fluid plays a key role in transporting oxygen from the lungs to other body parts and carbon (IV) oxide out of the tissues to the lung alveoli, movement of body nutrients and pressure homeostasis.[12]

The interstitial compartment according to Tobias and Mohiuddin (2020) consists of fluid that surrounds body cells. This space provides a connection between the fluid inside cells and the

vascular space. The function of this compartment is to facilitate the exchange of nutrients, oxygen and waste products between the cells and the vascular system.[13]

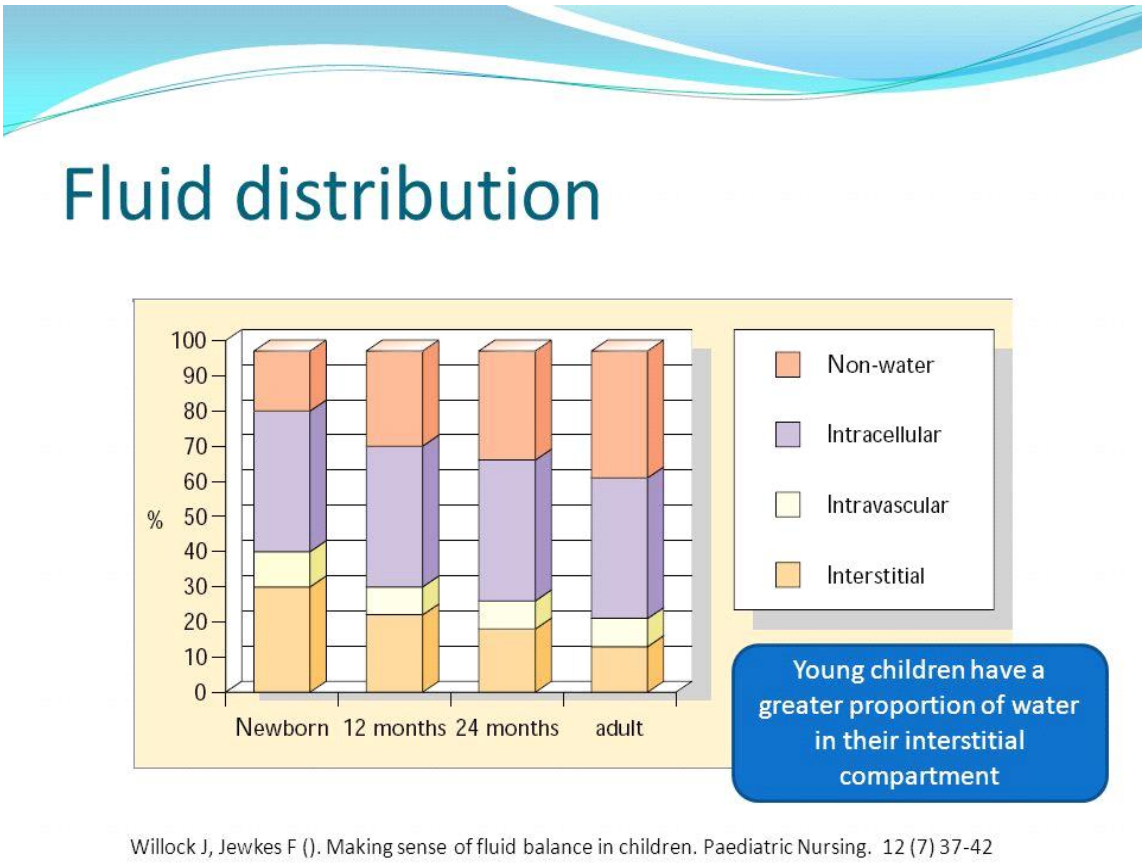

Figure1: Body fluid compartments

Body fluid composition

The components of body fluid differ from one compartment to another according to Jain A. The composition of body water, in general, includes proteins, electrolytes, glucose, creatinine, lipids and urea.[14] Body electrolytes include but are not limited to potassium, which is mainly an intracellular cation, sodium which is an extracellular cation, chloride, calcium and phosphate.

2.0.3 Volume status

There are three states of fluid balance in the body namely: euvolemia, hypovolemic state and fluid overload. The three states of fluid load occur under different circumstances. Euvolemia or normovolemia according to the "Current Cardiology Reviews", is the volume status allowing adequate filling in cardiac chambers, arteries and capacitance vessels.[15] The normal volume of blood differs among the various ages i.e., adults have a larger absolute volume of blood as compared to children.

Hypovolemic state refers to low fluid capacity in the extracellular compartments according to Rivera and Anjun (2021). This is triggered by the loss of sodium and water. Low volume upsets body homeostasis leading to low blood pressure, dizziness, shock, and even acute renal failure. This is associated with tissue hypo-perfusion, hypoxia and organ failure.[16]

Fluid overload is also known as hypervolemia. On the other hand, according to a document reviewed by Brennan, D. MD (2021) it refers to excessive fluids in the body. Major causes include over-replacement of fluids, especially in pediatric patients, renal failure coupled with active fluid management and congestive heart failure. Excessive fluid manifests through oedema, rise in body weight and respiratory distress, especially in patients with pulmonary oedema.[17]

Fluid overload in seriously sick children is considered a trigger for poor respiratory outcomes due to reduced oxygenation index and fewer ventilator-free days due to slow weaning from pulmonary oedema according to Wiedemann et al.[5] 2006. This is due to compromised gas exchange, reduced compliance and increased respiratory work. Acute renal injury may be result from abdominal hypertension and abdominal compartment syndrome which compromises renal blood supply leading to fluid overload.[5] There is reduced renal perfusion, increased tissue pressures, reduced glomerular filtration rate, urea, salts and water retention. Creatinine tends to be low due to increased volume of distribution delaying diagnosis of AKI (PICARD trial-programme to improve care in renal disease).[4] Vaara et al. 2012 studied the role of fluid overload in 90-day mortality and concluded that children with more cumulative water in the 7days of paediatric ICU admission had more deaths, despite receiving diuretics, RRT and inotropes.[18] The increased capillary leak of intravenous solutions is due to distribution to the extracellular compartment from circulation, causing oedema which in turn leads to compromised exchange of gaseous and metabolic products, distorted tissue structure, impairment of capillary blood flow and lymphatic drainage with an upset in cell-to-cell interactions and progressive organ failure. Multiple organ dysfunction results from severe sepsis due to complement factors, cytokines and prostaglandin products altering tissue circulation. Myocardial oedema causes conduction disruption, impairs contraction and diastolic dysfunction. Hepatic fluid overload causes impaired synthetic function and cholestasis. Gut oedema is associated with poor absorption and ileus. Tissue oedema causes poor wound healing, wound sepsis and pressure sores.[18]

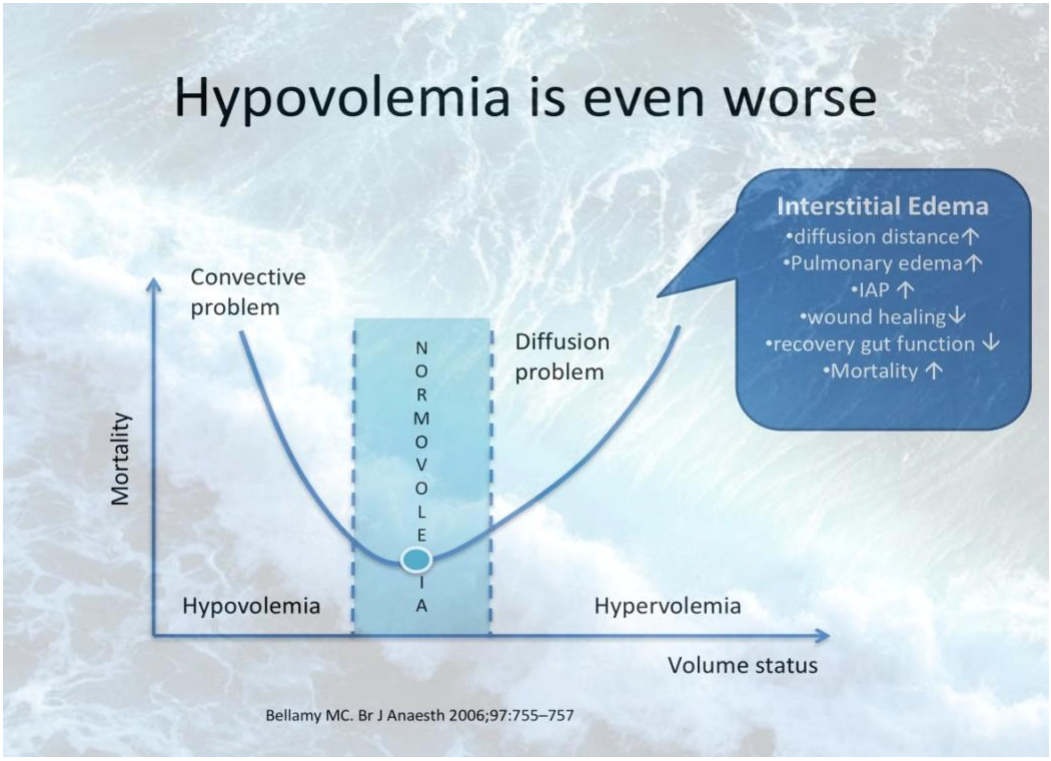

Figure2: Bellamy curve

You have not explained what this diagram shows.

2.0.4 Indications for fluid therapy

Oral intake of fluids is often recommended for patients. For those who cannot tolerate oral intake, fluid management is done intravenously. Parenteral administration of fluids is mostly done in patients admitted to the hospital according to Slattery and Lobaz (2019). These two authors suggest that a careful examination through vital signs should be carried out to determine a patient's need for fluids.[19]

Fluid therapy is a very important aspect of treatment for critically ill patients especially children who present in the hospital with dehydration. Replacement of fluids is recommended in volume depletion among children. Management varies depending on the patient's condition.[19]. Before administering fluids, clinicians usually check capillary refill time; delayed capillary refill suggests low volume and impaired perfusion, blood pressure, heart rate, peripheral pulses and laboratory tests e.g., creatinine and urea which can indicate dehydration.

Another indication for fluid administration is electrolyte replacement. Children who present with diarrhoea, and vomiting tend to have deranged electrolytes due to loss in vomit and stools.[20] Potassium and bicarbonate levels are highly affected among these children. Normal potassium values in the human body range from 3.5 to 5 mEq/L. Hypokalemia refers to potassium levels

below 3.5 mEq/L.[20] Any potassium level less than 2.5 mEq/L is considered detrimental according to a document by Cleveland Clinic (2018).[20] These low levels affect the functioning of the heart and can result in cardiac arrest. The normal bicarbonate levels range from 22-27mEq/L. Low bicarbonate levels induce metabolic acidosis which in turn impair cell metabolism, worsen kidney disease and induce osteoporosis according to the National Kidney Foundation.[21] These two electrolytes are replaced in fluids either in net form or diluted forms. Sodium is another electrolyte that can necessitate replacement especially when it is low. Normal sodium values range from 135-150mEq/L. Low sodium can result from an accumulation of water in the body such as in congestive heart failure and kidney failure. According to Mayo Clinic, sodium is important as it helps in water reabsorption and blood pressure homeostasis.[22]

2.0.5 Fluid administration in critically ill children

Children in the ICU require less standard volume of fluid. This is due to higher ADH levels, and if ventilated, use of humidified gases. They also have reduced BMR if sedated and paralyzed. This reduces maintenance fluids by 30%. SAFE trial (Saline versus Albumin Fluid Evaluation) showed that 4% albumin or normal saline for intravascular volume resuscitation of ICU patients had equivalent mortality rates and ICU outcomes. SALTED trial in 2018 showed no difference in hospital-free days between treatment with balanced crystalloids and saline.

Jayashree et al. 2019 concluded that in pediatric patients with diabetic ketoacidosis, normal saline is the preferred resuscitation fluid. When significant hyperchloremic acidosis develops, the fluids can be switched to hypotonic alternatives e.g., half-normal saline. More physiological alternatives with less chloride but higher sodium content e.g., Lactated Ringer's or plasmalyte.[23] are also an alternative. In paediatric acute respiratory distress syndrome, the Paediatric Acute Lung Injury Consensus Conference (PALICC) endorses observing and adjusting water balance to preserve sufficient vascular volume, while targeting to avert fluid excess.[24] According to Weiss et al. 2020 in cases of pediatric sepsis, diverse studies have shown variable evidence on the fluids that deliver satisfactory recovery while avoiding an increase in the risk of mortality.[1] The surviving sepsis campaign guidelines (SSCG) endorse crystalloids as the early resuscitation fluid. Albumin can be added when significant quantities of crystalloids are required[1]. In a clinical trial conducted on children with complicated malaria and metabolic acidosis, Maitland et al. 2005 concluded that the outcome established a death advantage in malarial septic shock with albumin as opposed to crystalloids.[25] However, Raina et al. 2018 suggest that evidence strongly recommends against the use of hydroxyethyl starch in grown-ups and children. This is as a result

of an increase in the need for kidney dialysis and packed red blood cell transfusion. [26] In a cohort study on paediatric sepsis Raina et al. 2018 stated that Lactated Ringer's (LR) resuscitation was not linked to a reduction in deaths, acute renal disease, or dialysis after matching by water volume and comparable lactated ringer's use. Deaths rose with higher water amounts and reduced with a higher volume of water administered as lactated Ringer's. There was no deviation between LR and NS cohorts following control by volume quartiles, proportional lactated Ringer's use, or in the other group that received lactated Ringers' only. Nevertheless, LR was preferred as the initial fluid in patients with less severe disease or as an adjunct fluid in patients who got higher volumes of water.

2.0.6 Monitoring fluid status

For effective fluid management strategies in critically ill children, strict input and output monitoring are paramount to avoid any untoward effects of fluids. Most hospitals have standard input and output charts that help in monitoring fluid status in patients. With the proper balancing of daily input and output, it is easy to tell at a glance whether the patient has had a negative or positive balance.

Masaki and Manhendiran (2015) studied fluid monitoring in a district general hospital in the United Kingdom. They found that only 50% of fluid monitoring charts were effectively completed. They also noted that about 47% of input/output monitoring was not clinically indicated.[27] Inability to monitor fluid input and output in paediatric ICUs is especially detrimental as sick children may not be able to effectively handle fluids in their bodies. To be able to administer fluids in their required amounts, the use of fluid infusion pumps is highly recommended to deliver the exact volumes as prescribed.

Malbrain et al. 2018 came up with the ROSE concept which entails Resuscitation, Optimization, Stabilization and Evacuation. Resuscitation entails bolusing which is the administration of a specific amount of fluid within a predetermined period. It aims at restoring intravascular volume. Patients in the Ebb phase of shock have low Mean Arterial Pressures (MAPs), cardiac output and small vessel circulatory impairment causing a reduction in tissue blood supply and oxygenation. Rescue fluid administered at 4mls/kg over 10-15 minutes achieves early goal-directed therapy. The optimization phase is maintenance fluid given to provide the everyday requirement for water and electrolytes that occur within 48-72 hours and is the period of ischemia with reperfusion. Boluses may be required in this phase to maintain the same targets as resuscitation. The stabilization period occurs in days and water is needed to maintain and cater for normal losses.

Observing fluid balance, weight and organ function is required during the stabilization period. Innocuous or negative fluid balance is the target. Intravenous fluids should be replaced with total parenteral nutrition or nasogastric feeds. The evaluation phase is for patients who do not shift from Ebb to Flow phase and require de-resuscitation to achieve a negative balance. Diuretics, renal replacement therapy (RRT) and albumin are required here. The goal is a negative fluid balance by day 3. Cordemans et al recommend a PAL approach i.e., high PEEP > 30min to drive fluid from alveoli to the interstitium, Albumin over 60 minutes per day followed by Lasix according to need.[28]

2.0.7 Effect of negative and positive fluid balance

A negative fluid balance commonly known as dehydration occurs when fluid output is more than input. Children are at a greater risk of being dehydrated because of higher fluid requirements. Other causes may be the inability to self-hydrate and verbalize the need for water. They also have higher metabolic rates.[29] Negative fluid balance can be caused by the inability to take enough fluids or fluid loss in large amounts.

According to a document titled 'Assessing Dehydration and Fluid Management', dehydration can manifest in several ways e.g., impaired alertness, sunken eyes, decreased skin turgor, increased heart rate and tachypnoea.[29] In addition to the above, when more water is lost than sodium, a state known as hypernatremic dehydration ensues. This manifests through but is not limited to skittish movements, amplified muscle tone, hyperreflexia, and lethargy.

If there is severe negative fluid balance, dehydration and shock may occur leading to low blood pressures and hence impaired perfusion. The body cells and organs lack enough blood supply and are deprived of oxygen and nutrients resulting in deranged activity. The body in the absence of nutrients cannot generate heat hence impairment in metabolism. The heart and brain will lack the energy to function optimally further deranging their functions. Blood flow to the kidneys will be severely reduced resulting in acute kidney injury and accumulation of toxic materials in the body.[29]

A positive fluid balance on the other hand denotes more input than output. When there is an excess accumulation of fluid, a condition known as hypervolemia or fluid overload occurs.[30] This condition manifests through but is not limited to general body oedema, excessive fluids in the lungs and rapid weight gain. The main causes of hypervolemia are kidney injury leading to reduced output, heart failure impeding venous return and uncontrolled fluid administration.

Persistent positive fluid balance leads to accumulation of fluids in critically ill children and it has been linked to increased risk of mortality.[31] This has therefore brought the need for controlled and careful fluid administration among critically ill patients.

2.0.8 Fluid management strategies

Early Goal-Directed Fluid Therapy

Different approaches exist when it comes to fluid management. The approach and amount of fluid to be administered depend on the severity of the disease, amount of deficit and comorbidities. Fluid administration can be viewed in three spheres: **deficit therapy** to replace what the patient has lost before presenting to the hospital, **maintenance therapy** to meet the daily fluid requirement for the patient and **replacement therapy** to cater for the daily fluid and electrolyte losses. The last therapy can be catered for by increasing the amount of maintenance fluids.[32] The recommendation provided by Synder et al. 2021 is 100ml/kg per day for children weighing up to 10kgs, for those weighing between 10-20 kgs it is 1000ml/day for the first 10kgs plus 50ml/kg for the remaining 10kgs while for those weighing above 20kgs it is 1500ml per day plus 25ml per kg per day for the rest of the weight above 20kgs.

Andre and Pinsky recommend a crystalloid infusion of 30ml/Kg over 30-60 minutes when resuscitating children with septic shock.[33] They add that in case of failure to restore blood pressure after the fluid bolus, inotropic support should be provided through a central line.

Early goal-directed therapy (EGDT) has been researched extensively since the groundbreaking; Rivers' study was published. In this study, a death benefit was sought using a protocol in fluid resuscitation in the first six hours when managing patients with sepsis.[34] Moreover, Rivers proposed that prompt resuscitation was beneficial, while delayed and undue water management was linked to poorer outcomes. The crucial variation highlighted by this tool was the time at which fluids were administered since the amount of water given was the same in the two cohorts studied.[35] The same findings were corroborated by Virk and Arikan (2018) who assessed results in a controlled before and after study using a protocol-driven resuscitation in children with septic shock.[36] Considerate water administration in the early phase of the illness reduced deaths, the occurrence of acute renal injury, and the requirement for renal replacement therapy in contrast to other controls.[36]

Local management strategies

Locally, the ‘Basic Paediatric Protocol’ (2016) developed by the ministry of health (MoH) Kenya provides guidelines for the treatment of dehydration and shock in children. This management is divided into four categories:[37]

- Children with shock are given a bolus of Ringer’s Lactate (RL) 20mls/kg.
- The second step is plan C-step1 where children are given 30mls/kg of Ringer’s Lactate over 1 hour for those less than 12 months and over half an hour for those above 1 year.
- The third step is plan C- step 2 where children are given 70mls/kg of either Ringer's Lactate intravenously or oral rehydration salts (ORS) over five hours for those less than 12 months of age and over two and a half hours for those above one year.
- The fourth step is 75mls/kg of oral rehydration salts given per oral over four hours.

The management regimen above depends on the level of fluid deficit. The protocol also provides that those children with a haemoglobin level of <5g/dL should be considered for immediate blood transfusion.

Another document titled ‘Assessment and management of dehydration’[29] provides management guidelines as shown in the flow chart below.

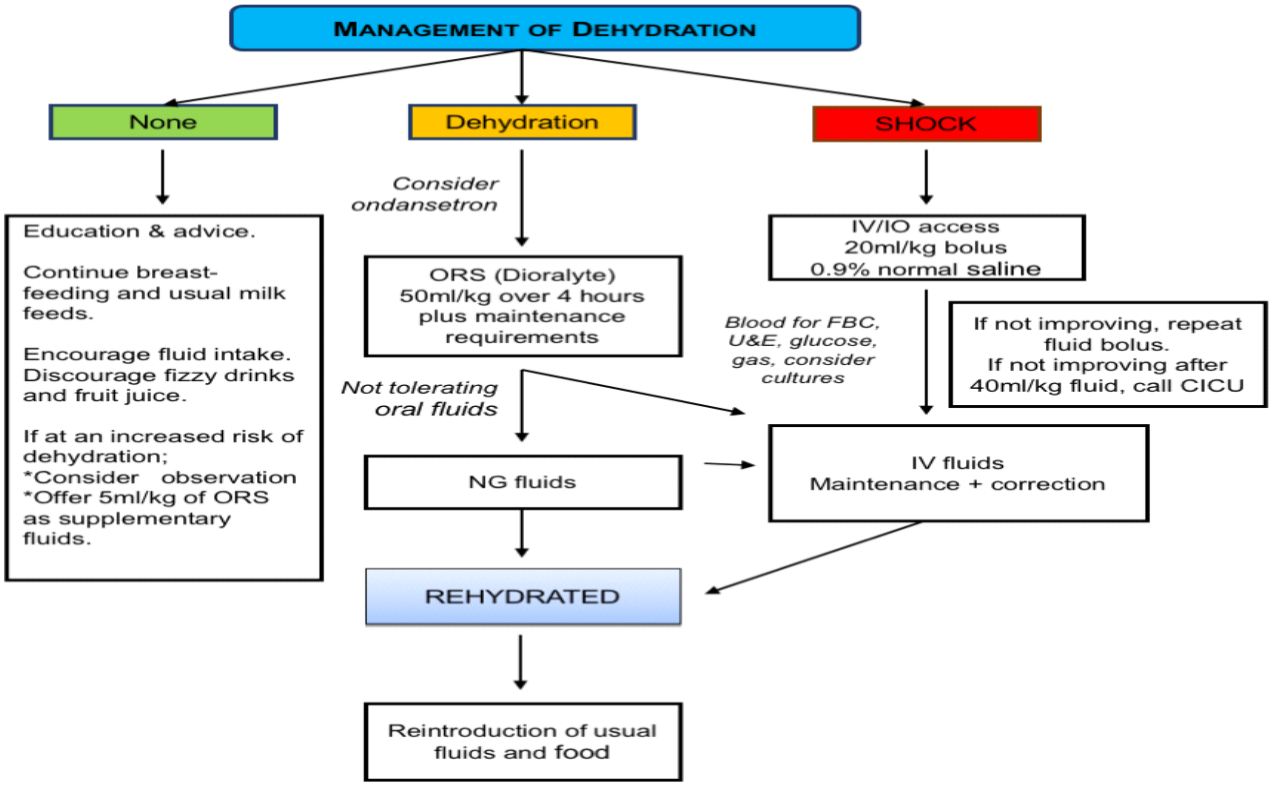

Figure3: Management of dehydration

Positive and negative fluid balances are easily identified from the fluid management charts. While a positive fluid balance may not necessarily have detrimental effects, a negative fluid balance means the body may not be able to function optimally.

Fluid excess can be caused by too much administration of water, kidney injury, congestive heart failure and fluid resuscitation.[27] According to Granado and Mehta (2016), a positive fluid balance in excess can result in gross oedema, pulmonary oedema leading to impaired gaseous exchange in the lungs, congestive heart failure for the critically ill and rapid weight gain.[2] In the event of complications of positive fluid balance, consider diuresis by use of diuretics for those with functioning kidneys, peritoneal or hemodialysis for those with impaired kidneys, closely monitor heart rate and blood pressure, provide supplemental oxygen in case of respiratory complications.[30]

2.0.9 Consequences of fluid overload

Fluid overload as defined by Granado and Mehta (2016) is a ten per cent or more rise in body weight following administration of fluids.[2] This is accompanied by gross body oedema which

usually begins with periorbital oedema. Literature shows that fluid overload has detrimental effects on critically ill pediatric patients.

Common issues observed in pediatric ICUs are water disparities and hemodynamic volatility as shown by Raina et al. 2018. In their study of fluid overload in critically ill children, they concluded that unguarded water administration can lead to fluid excess.[26]

Samaddar et al.2018 suggest that fluid overload in the pediatric ICU is a cause for multi-organ derangement.[6] In particular; patients with acute renal failure are likely to develop tissue oedema, leakage of fluid from the capillaries and fluid overload. Favia et al. 2010 also reviewed several studies and concluded that there was a statistical significance in mortality between those with overload and those without.[38]

For critically ill patients, appropriate fluid balance is vital in managing and maintaining the stability of the body according to Rowe N. (2014). Resuscitation is carried out with fluids to preserve satisfactory intravascular volume. Resuscitation has been linked to a host of untoward effects which can further worsen the patient's status[39].

Fluid overload is not a pointer of death; [26] the adversarial effect of fluid excess on critically ill patients puts them at a higher risk of morbidity and mortality as shown by Raina et al. 2018. Evidence according to Wati et al. 2016 has shown that unwarranted fluid management is closely linked with poor outcomes for critically ill children.[40] Flori et al. 2011 carried out a study on the relationship between excess fluid and poor clinical results in children with Acute Lung Injury. The study concluded that an increment of at least 10 ml/kg/day fluid excess was linked to increased deaths. Furthermore, the increases were also related to fewer ventilator-free days.[41] Boyd et al. 2011 in; "The Vasopressin in Septic Shock Trial (VASST)" with a sample of 778 patients with septic shock post-resuscitation established that fluid excess increased up to two times the death rate.[42] According to Bagus et al. 2016 in their study on the relationship between water excess and death in the pediatric intensive care unit, fluid overload was linked to higher mortality.[43]

Virk and Arikan (2018) concluded that fluid excess had harmful effects on all organs, especially the renal system. They added that fluid excess predisposed an individual to acute renal failure.[36] Mohmand and Goldfarb (2011) suggested that the development of abdominal hypertension and abdominal compartment syndrome impeded renal blood flow and could lead to acute kidney injury (AKI) and more fluid overload.[44] Deferral of AKI diagnosis according to Shen et al. 2017 relates to the degree of water excess.[45]

Raina et al. 2018 in the Re-analysis of FACTT (Fluid and Catheter Treatment Trial) demonstrated that the occurrence of concealed acute kidney injury was individually linked to a greater possibility of death.[26] According to Hazle et al. 2013 fluid treatment is of specific significance in neonates with congenital cardiac disease undergoing heart surgery. Water overload in this cohort was related to an increase in in-hospital deaths, longer ICU and hospital stay, prolonged inotropic use and artificial ventilation, and delayed sternal closure.[46] Innovative fluid overload alleviating approaches, namely passive peritoneal drainage and modified ultrafiltration techniques are increasingly being used.[46]

2.1.0 Pediatric logistic organ dysfunction score

The pediatric logistic organ dysfunction score (PELOD score) is a useful tool, especially during admission of children to the pediatric ICU (PICU). The PELOD score was developed primarily to predict mortality among critically ill children through organ dysfunction.[47] A score above 10 on admission predicts poor outcome even with admission to the ICU. Through PELOD score, clinicians can admit children who are most likely to benefit from ICU care since it helps measure outcomes.[47]

Table1: PELOD SCORE (Adapted from Leteurtre et al.[48])

Organ dysfunction and Variables	**Points by severity level**			
	0	**1**	**10**	**20**
Neurologic				
Glasgow coma scale	**12-15**	**7-11**	**4-6**	**3**
or	Both reactive		**Both fixed**	
Pupillary reaction				
Cardiovascular				
Heart rate				
<12 yrs	**<=195**		**>195**	
≥12 yrs	**<=150**		**>150**	
Systolic blood pressure				
<1 month	**>65**		**35-65**	**<35**
≥1month- <1 yr	**>75**		**35-75**	**<35**
≥1 year-<12 yrs	**>85**		**45-85**	**<45**

≥12 yrs	**>95**		**55-95**	**<55**
Renal				
Creatinine, µm/L(mg/dL)				
<7d	**<140(<1.59)**		**≥1409(≥1.59)**	
≥7d-<1yr	**<55(<0.62)**		**≥55(≥0.62)**	
≥1yr-<12yrs	**<100(<1.13)**		**≥100(≥1.13)**	
≥12 yrs	**<140(<1.59)**		**≥140(≥1.59)**	
Respiratory				
PaO2:FiO2(P:F) ratio, mmHg	>70		≤70	
PaCO2, mmHg(kPa)	≤90(≥11.7)		>90(>11.7)	
Mechanical ventilation	No ventilation		Ventilation	
Hematologic				
Leucocyte count, *10^9/L	**≥4.5**	**1.5-4.4**	**<1.5**	
Platelet count, *10^9/L	**≥35**	**<35**		
Hepatic				
Glutamic oxalate transaminase, IU/L	**<950**	**≥950**		
Prothrombin time, %standard (INR)	**>60(<1.40)**	**≤60(≥1.40)**		

Note: FiO2 = fraction of inspired oxygen, PaCO2 = partial pressure of carbon dioxide in arterial blood, PaO2 = partial pressure of oxygen in arterial blood. *For the Glasgow coma score, use the lowest value. If the patient is sedated, record the estimated coma score before sedation. Assess the patient only with known or suspected acute central nervous system disease. For pupillary reactions, nonreactive pupils must be > 3 mm; do not assess after iatrogenic pupillary dilatation. †The use of mask ventilation is not considered to be mechanical ventilation.

2.2 STUDY JUSTIFICATION

Fluid input frequently exceeds output leading to clinically significant fluid overload (weight gain equal to or above 10% of initial body weight). This results in increased ICU utilization and morbidity, organ injury and probably mortality. There is a lack of consensus on fluid dosing leading to variability in practice and outcomes. This study sought to associate fluid status with clinical outcomes of children in the PICU/ICU.

No local study of the same nature has been conducted to establish the practice of fluid therapy, the relationship between fluid balance and clinical outcomes, the extent of fluid excess in KNH Pediatric Intensive Care Unit/main ICU and the effects associated with it. The results of this study will help inform the practice of fluid management at Kenyatta National Hospital.

2.3 Research Question

What is the relationship between fluid balance and clinical outcomes in seriously ill children admitted to KNH PICU/main ICU?

Null Hypothesis: Fluid balance does not affect clinical outcomes in critically ill children.

2.4 Broad objective

To determine the relationship between fluid balance and clinical outcomes; mortality and length of ICU among critically ill children admitted to KNH PICU/ICUs.

2.5 Specific Objectives

1. To establish the distribution of cumulative fluid balance in pediatric critically ill patients during their ICU stay.
2. To determine the proportion of patients with clinically significant positive fluid balance during their ICU stay.
3. To establish the relationship between clinically significant fluid balance and clinical outcome (length of ICU stay, days on MV, whether dead or alive), at the end of ICU stay

3.0 CHAPTER 3: METHODOLOGY

3.0.1 Design of the study

This was a prospective single-center observational study.

3.0.2 Study Site

The study was conducted at the Kenyatta National Hospital. KNH is a tertiary level referral and teaching hospital in Nairobi, Kenya. The hospital has over six thousand staff and about two thousand five hundred beds. There are six Critical Care Units with a capacity of up to sixty critically ill patients: The main ICU has a bed capacity of 21, Medical ICU has 8, Neonatal ICU has 8, Pediatric ICU has 5 beds, Private Wing/9A HDU (5), neurosurgical ICU (5) and the Cardio-thoracic ICU has 4 beds. In addition to these, emergency critical care services can provide 4 additional beds to critical patients if need be.

The patients were followed up during their admission period. The average time of stay for one patient was estimated to be 10 days. In one month the two ICUs would admit approximately 32 patients. In the four months of this study, the two ICUs would have admitted 128 patients.

3.0.3 Study population

The study population included all critically ill children admitted to Kenyatta National Hospital pediatric and adult intensive care units requiring fluid therapy.

3.0.4 Eligibility

Inclusion Criteria

All children admitted to KNH PICU and main ICU, aged between 1 month and 12 years, and requiring fluid administration whose parents/guardians gave consent for the study.

Exclusion Criteria

-Children who were in multiple organ dysfunctions on admission

-Children with fluid overload on admission (Acute kidney injury, Congestive heart failure or liver failure)

-Children whose parents/guardians declined to give consent

3.0.5 Sampling Procedure/Selection of study participants

A consecutive sampling method was employed until the required sample size was achieved.

3.1.6 Study period

The data was collected over a period of three and a half months.

3.1.7 Calculation of sample size

We used the study by Samaddar et al. 2018 as a reference for sample size calculation:[6]

- Proportion overload, P=62%, Mortality = 40.5%
- Mortality in non-overload group = 34%

Difference in effect = [40.5-34%] =6.5%

- Confidence level = 95%; $Z_{\alpha/2} = 1.96$

Formula (**Adapted from Chow and Liu, 2020**)[49]

$$n = Z^2_{\frac{\alpha}{2}} * p(1-p)/d^2$$

$$n = 1.96^2 * 0.405 * 0.595/0.065^2$$

$$n = 220$$

Sample adjustment

$$\boldsymbol{n_1 = \frac{n * N}{n + N}}$$

N=128; the number of patients admitted in four months (approximation).

$$\boldsymbol{n_1 = 81}$$

Where:

n_1 = sample size with finite population correction

N = size of target population

Z = Z statistic (critical value) for 95% confidence level

d = effect size

P = proportion of patients with positive fluid balance

3.0.8 Recruitment and Study Procedure

Patients were evaluated for suitability for recruitment upon admission. Once inclusion criteria were met, informed consent was obtained.

On admission, the following clinical information was obtained: age, gender, weight, diagnosis, and PELOD score.

Subsequently, the following information was obtained daily until the end of ICU stay: Net fluid balance (daily fluid input minus output), ventilation status, diuretic use, need for RRT, whether on inotropes and signs of significant fluid overload, and 3 daily cumulative fluid balance (sum of net fluid balance) and PELOD score. Outcome and Length of Stay (LOS) were recorded at the end of the ICU stay.

Information on fluid balance was extracted from daily fluid charts which are a strict PICU/ICU practice.

3.1.0 Data Collection

A standardized questionnaire via a mobile App was used to collect patient data from admission throughout ICU stay.

3.1.1 Variables

Independent variables: Age, gender, PELOD score, admitting diagnosis, degree of fluid balance (absolute/relative)

Dependent variables: ICU stay in days, days on mechanical ventilation and outcome at the end of ICU stay (dead/alive).

3.2 Quality Assurance Procedures

The questionnaire was checked to remove any repetitive and unnecessary questions. The research assistant was dully trained on the data collection tool. All the records were checked for completeness after data collection. Merging of the different parts of the questionnaire was done using the serial numbers to avoid mixing records.

3.3 Ethical Consideration

Permission to conduct the study was sought from KNH/UON Research and Ethics committee. Involvement was by choice; removal of oneself from the study was allowed at any point. The anonymity of the participants was ensured by coding the observations. No use of names or subject identifiers. The cost of the study was NOT transferred to the patient. Study results were availed to the KNH Ethics and Research Committee and the UON Department of Anaesthesia. Data collection in PICU/ICU was carried out only after the acceptance of a formal request to collect data by the KNH Research and Programs department.

3.4 Data Management and Analysis

The data was imported into R version 4.0.2 for cleaning and analysis. Data cleaning was carried out before analysis. Statistical analysis was performed using R version 4.0.2.

Categorical variables e.g., gender and diagnosis were analyzed and presented using frequency tables and bar charts. Normality test was conducted for continuous variables e.g., for age and weight after which their medians and interquartile ranges were computed. Continuous variables were also presented using density plots.

The relationship between categorical independent variables and categorical outcome variables were examined using chi-squared tests e.g., the association between overload (yes/no) and risk of mortality. Multivariable analyses [binary logistic regression] was used to assess the association between independent variables e.g., gender, age, fluid overload and weight with categorical outcomes e.g., mortality. Poisson regression was used to assess the factors associated with the length of ICU stay (outcome).

3.5 Dissemination of study results

The study results were disseminated through the presentation of a report to the department of anaesthesia of the University of Nairobi/KNH. The same report was to be published in the University of Nairobi repository for public use. The findings of the study were also availed to the pediatric intensive care unit/main intensive care unit at KNH for further action.

CHAPTER 4: RESULTS

A total of 81 participants who met the inclusion criteria were included in this study. The youngest participant was 1 month while the oldest was 12 years old. The minimum weight of the participants was 3.5 kilograms while the maximum weight was 28 kilograms.

Table 2: Demographic and clinical characteristics of the participants

Variable	**Category**	**Frequency N = 81**	**Percentage (%)**
Age (Median = 0.8 years, IQR = 0.42 years)			
Weight (Median = 7.5 kgs, IQR = 1.7 kgs)			
Gender	Female Male	40 41	49.6 50.4
Clinical characteristics			
Peripheral oedema	No Yes	46 30	60.5 39.5
Pulmonary oedema	No Yes	60 16	78.9 21.1
Hepatomegaly	No Yes	63 13	82.9 17.1
Mechanical ventilation	No Yes	12 64	15.8 84.2
Children on diuretics	No Yes	47 29	61.8 38.2
Inotropic support	No Yes	29 47	38.2 61.8

The above table shows the distribution of demographic and clinical characteristics. Of the total sample, the majority of the patients were males 50.4% (n = 41) while the rest were females.

39.5% of the patients had peripheral oedema, 20.1% had pulmonary oedema and 17.1% had hepatomegaly. 84.2% (n = 64) had been on mechanical ventilation while the rest were ventilator-free. Regarding the use of diuretics, only 38.2% (n = 34) needed diuretics.

Age distribution of the participants

H_0: Age distribution = normal distribution

H_1: Age distribution ≠ normal distribution

Shapiro-Wilk normality test

W = 0.49334, p-value = 9.157e-15

The age of the children was not normally distributed, Shapiro test p-value<0.05.

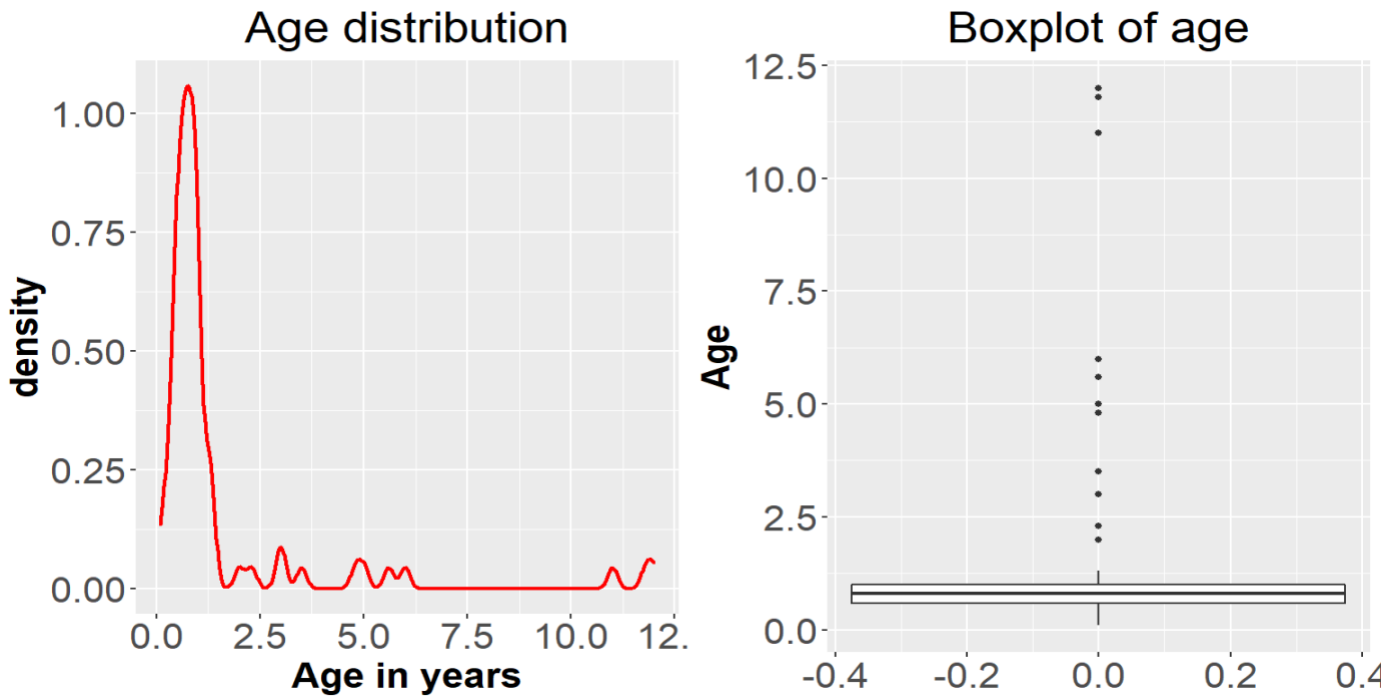

Figure 4: Density and boxplot showing age distribution

The age of the children was right skewed (density plot in figure 4). The median age was 0.8 years with an interquartile range of 0.42 years. The mean age was 1.5 years.

Weight Distribution

H_0: Weight distribution = normal distribution

H_1: Weight distribution ≠ normal distribution

Shapiro-Wilk normality test

W = 0.67374, p-value = 1.04e-11

The weight of the children was not normally distributed, Shapiro test p-value < 0.05.

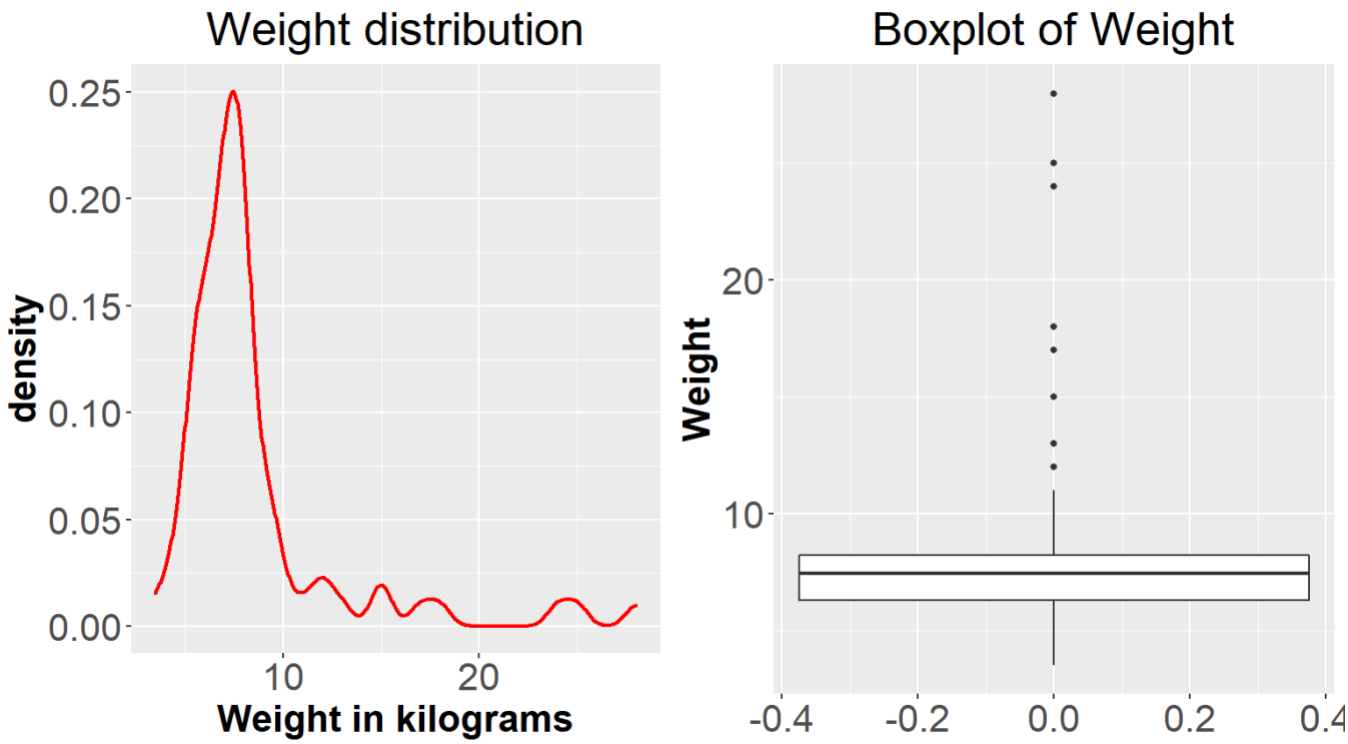

Figure 5: Density and boxplot of weight distribution

Weight is skewed to the right (density plot, figure 5). The median weight was 7.5 kilograms with an interquartile range of 1.7 years. The mean age was 8.5 kilograms.

Distribution of PELOD score

H_0: PELOD score distribution = normal distribution

H_1: PELOD score distribution ≠ normal distribution

Shapiro-Wilk normality test

W = 0.956, p-value = 0.01413

Reject null hypothesis, p-value for Shapiro test < 0.05. PELOD score was not normally distributed.

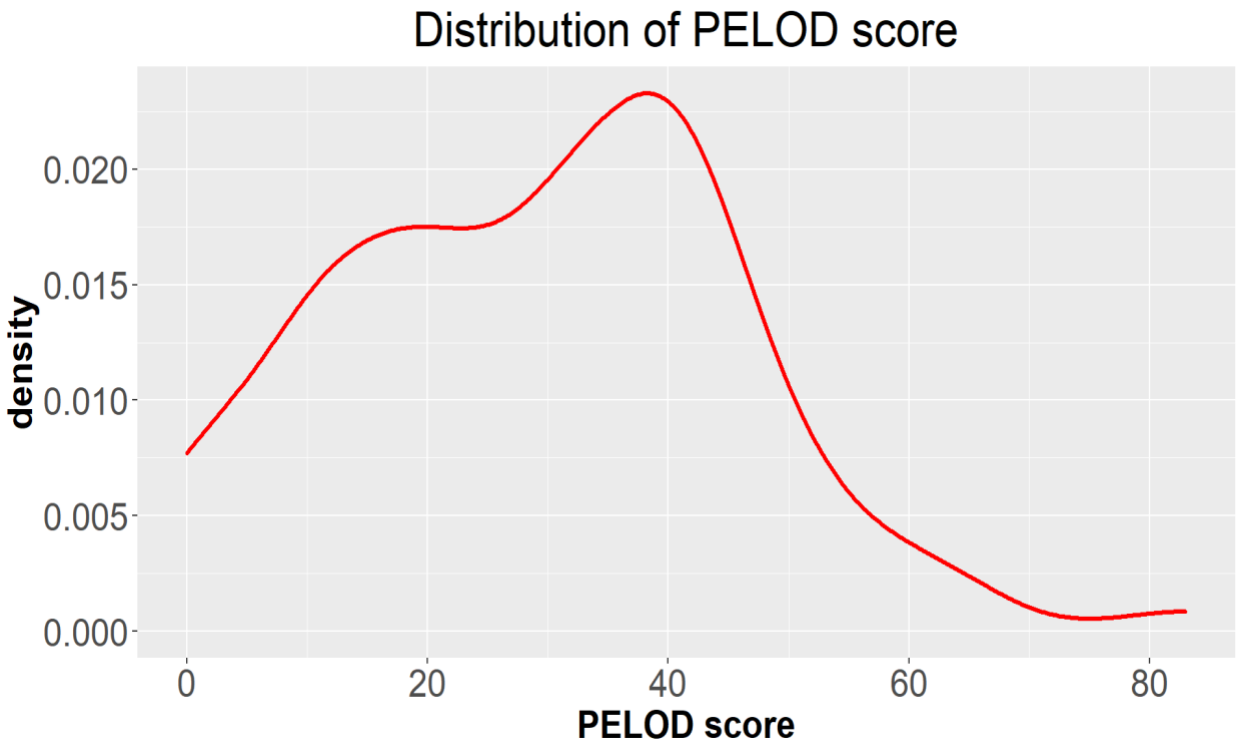

Figure 6: Density plot of PELOD score

The PELOD score was positively skewed with a median of 31 and an interquartile range of 21. The mean PELOD score was 29.2.

Objective 1: To establish the distribution of cumulative fluid balance in pediatric critically ill patients during their ICU stay

H_0: cumulative fluid balance distribution = normal distribution

H_1: Cumulative fluid balance distribution ≠ normal distribution

Shapiro-Wilk normality test

W = 0.90238, p-value = <0.001

Reject null hypothesis, Shapiro test p-value <0.05. Cumulative fluid balance was not normally distributed.

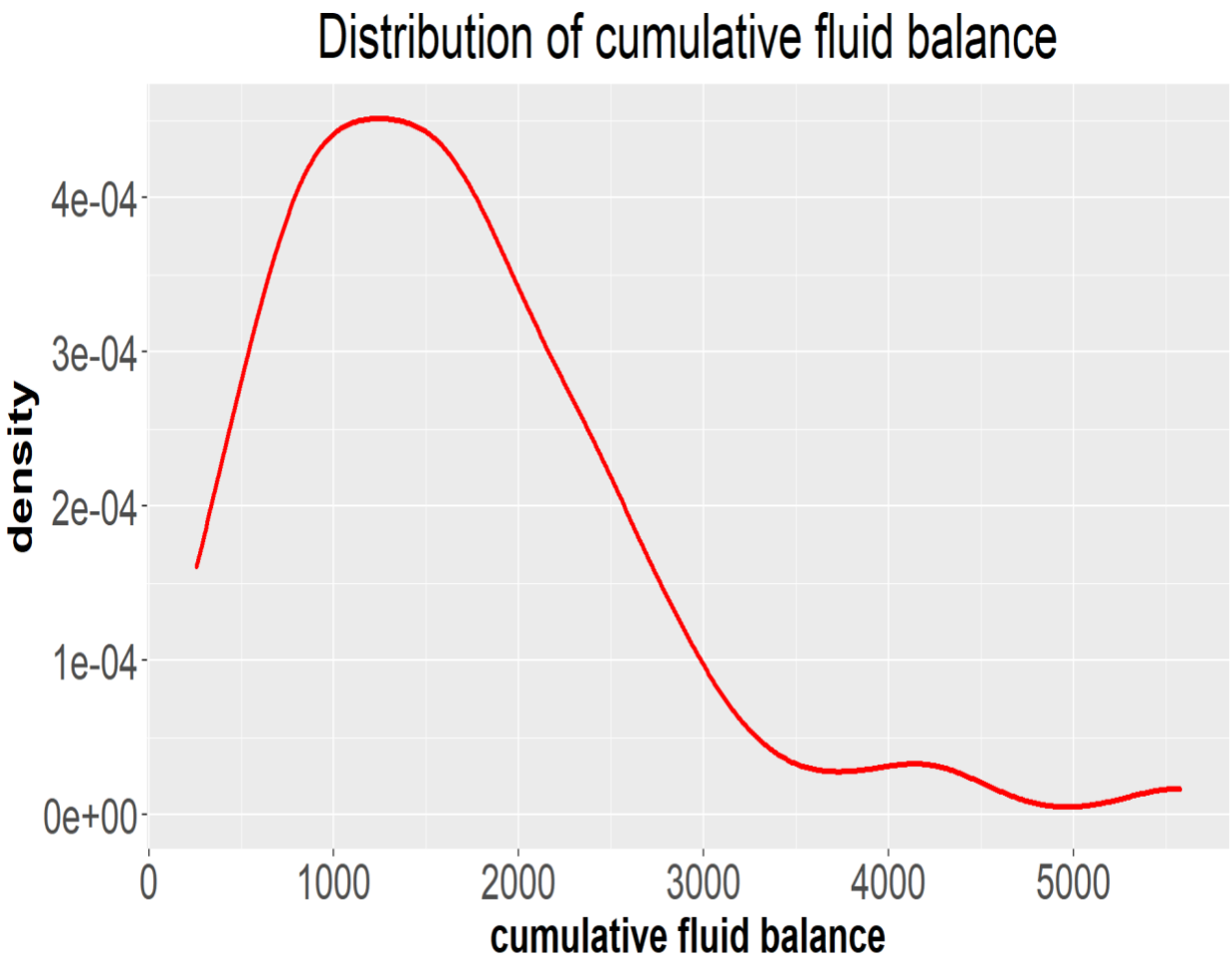

Figure 7: Density plot showing the distribution of cumulative fluid balance

The distribution of cumulative fluid balance was positively skewed. The maximum cumulative fluid balance was 5578.0 MLS while the minimum was 255.2 MLS. The median cumulative fluid balance was 1459.0 MLS with an interquartile range of 1111.9 MLS.

Percentage positive fluid balance

H_0: Percent fluid balance distribution = normal distribution

H_1: Percent fluid balance distribution ≠ normal distribution

Shapiro-Wilk normality test

W = 0.92016, p-value <0.001

Reject null hypothesis, Shapiro test p-value < 0.05. Percent fluid balance was not normally distributed.

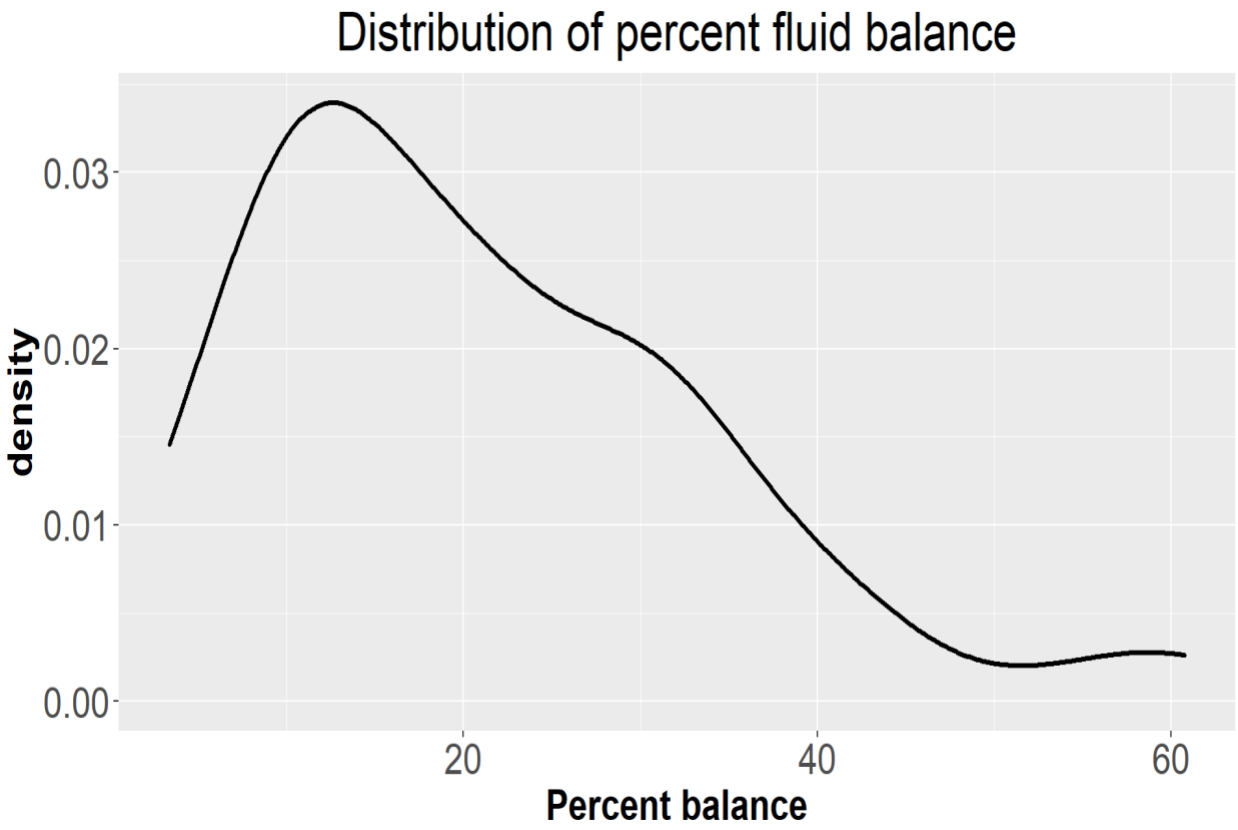

Figure 8: Density plot of percent fluid balance

The percent fluid balance was positively skewed with median 19.1% and interquartile range 17.9%. The mean percent fluid balance was 21.2%.

Days on inotropic support

H_0: Distribution of days on inotropes = normal distribution

H_1: Distribution of days on inotropes ≠ normal distribution

Shapiro-Wilk normality test

W = 0.85093, p-value <0.001

Reject null hypothesis, Shapiro test p-value <0.05. Days on inotropic support were not normally distributed.

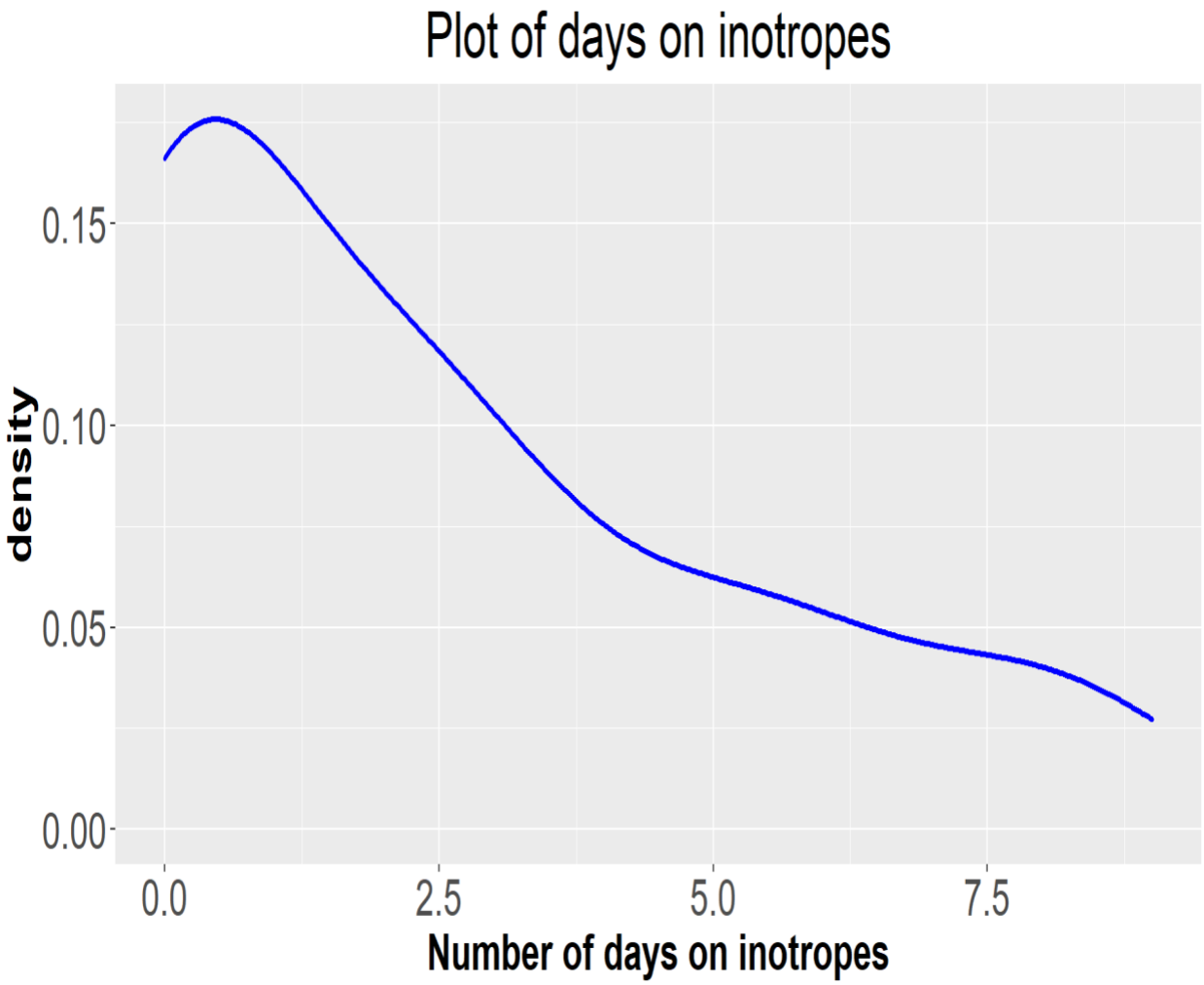

Figure 9: Density plot showing distribution of days on inotropic support

The number of days on inotropic support was right skewed with median 2.0 days and an interquartile range of 4 days. The mean days on inotropes was 2.6 days. Maximum days on inotropes were 9.0 days with a minimum of 0 days.

Distribution of days on mechanical ventilation

H_0: Distribution of days on mechanical ventilation = normal distribution

H_1: Distribution of days on mechanical ventilation ≠ normal distribution

Shapiro-Wilk normality test

W = 0.63142, p-value <0.001

Reject null hypothesis, Shapiro test p-value <0.05. Days on ventilator support were not normally distributed.

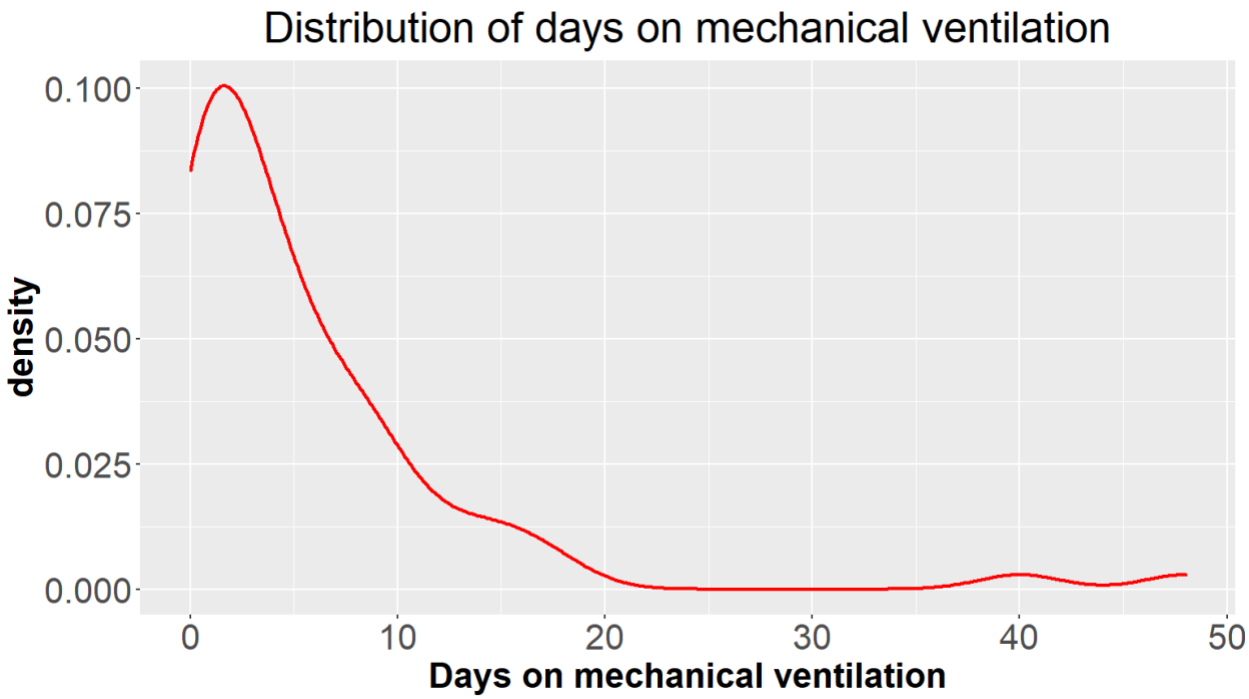

Figure 10: Density plot of days on mechanical ventilation

Days on mechanical ventilation were right skewed with median 3.0 days and an interquartile range of 7.0 days. The mean days on mechanical ventilation was 5.6 days. The maximum number of days on mechanical ventilation was 48 days and minimum were 0 days.

Distribution of length of ICU stay

H_0: Length of ICU stay = normal distribution

H_1: Length of ICU stay ≠ normal distribution

Shapiro-Wilk normality test

W = 0.63978, p-value <0.001

Reject null hypothesis, Shapiro test p-value <0.05. Length of ICU stay was not normally distributed.

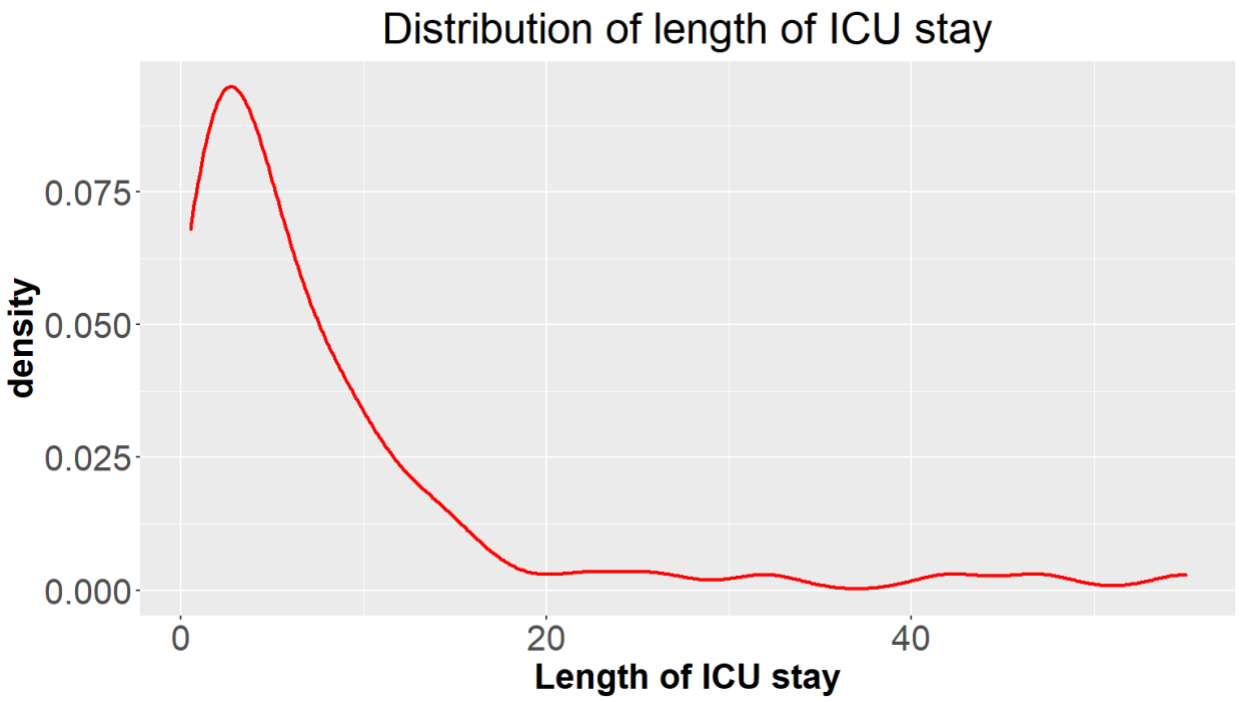

Figure 11: Distribution of days on mechanical ventilation

The length of stay in ICU was right skewed with median of 5 days and an interquartile range of 7 days. The mean length of stay was 8 days. The maximum length of stay was 57 days with a minimum of 1 day.

Correlation between the numerical variables

Correlation between the variables

Figure 12 below shows that days on mechanical ventilation and length of ICU had a high positive correlation, r = 0.94.

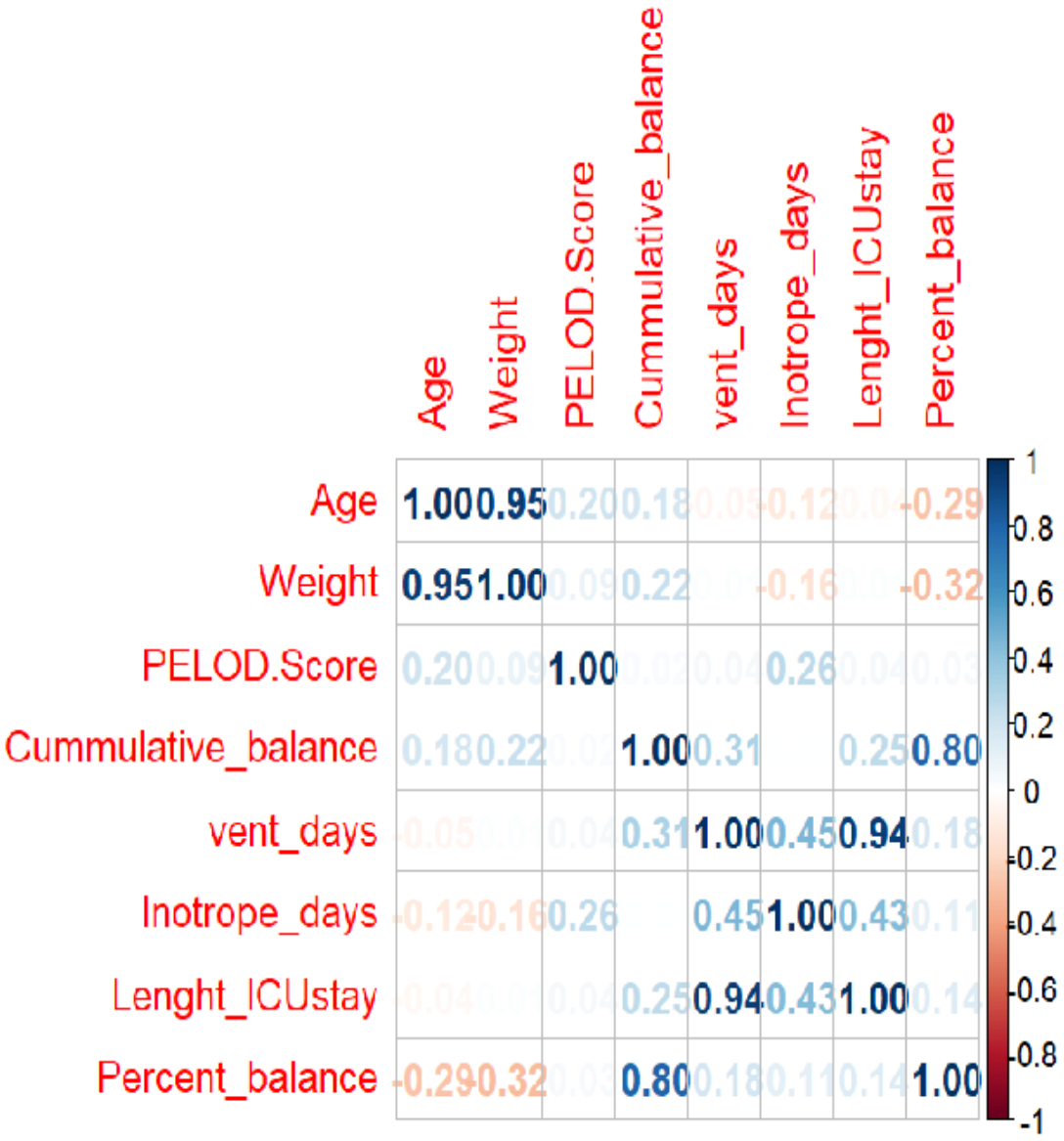

Figure 12: Correlation matrix among the numerical variables.

Diagnoses of the admitted patients

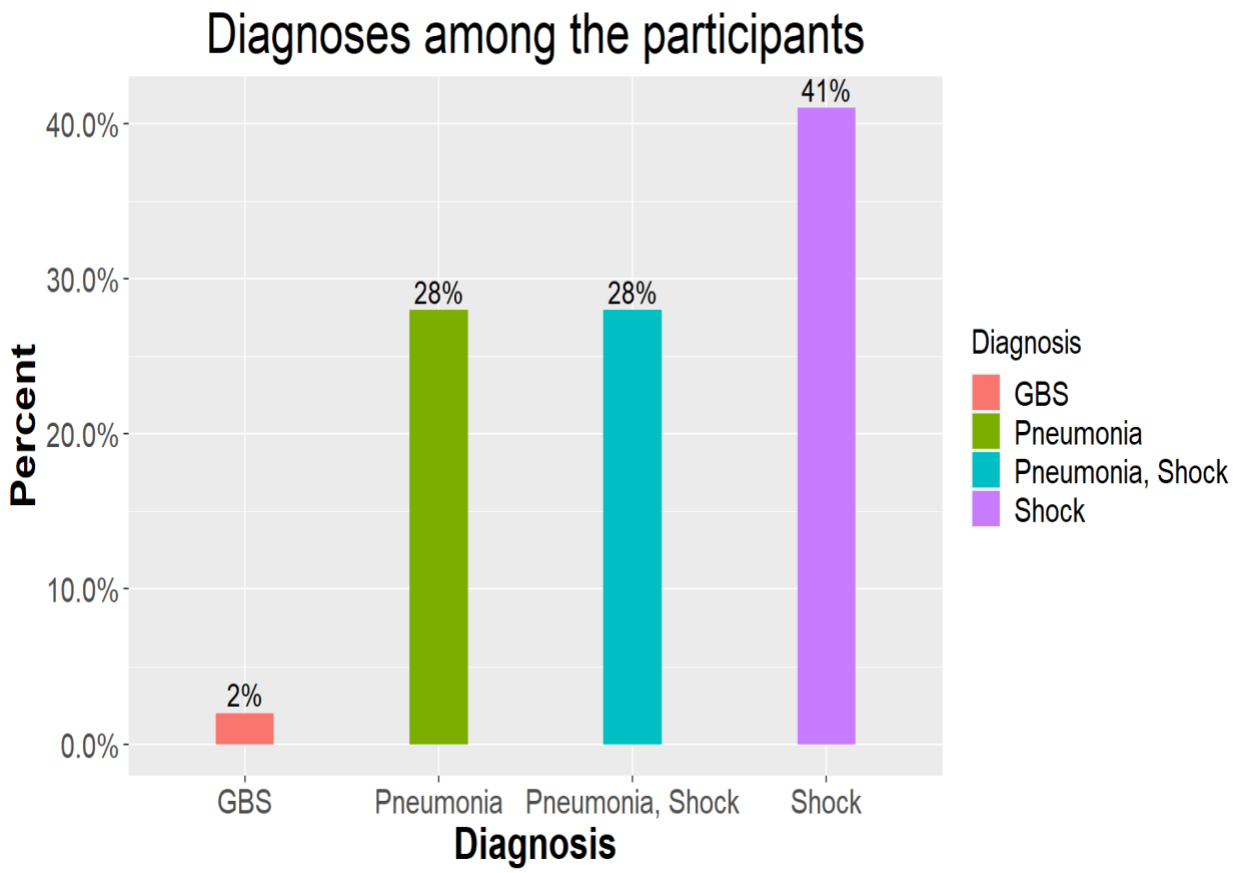

Figure 13: Bar graph showing the various diagnosis among the participants

Majority of the patients i.e., 41.0% were admitted with a diagnosis of septic shock. 28.0% had a combination of shock and pneumonia. Equally, those with pneumonia were 28.0% while the rest had GBS as shown in figure 13.

Intensive care outcomes

This study found a mortality rate of 51.0% as shown in figure 11 below. A study published by Kumar and Canarie, 2019 estimated that mortality in paediatric and adult ICUs was 37.5%.[50]

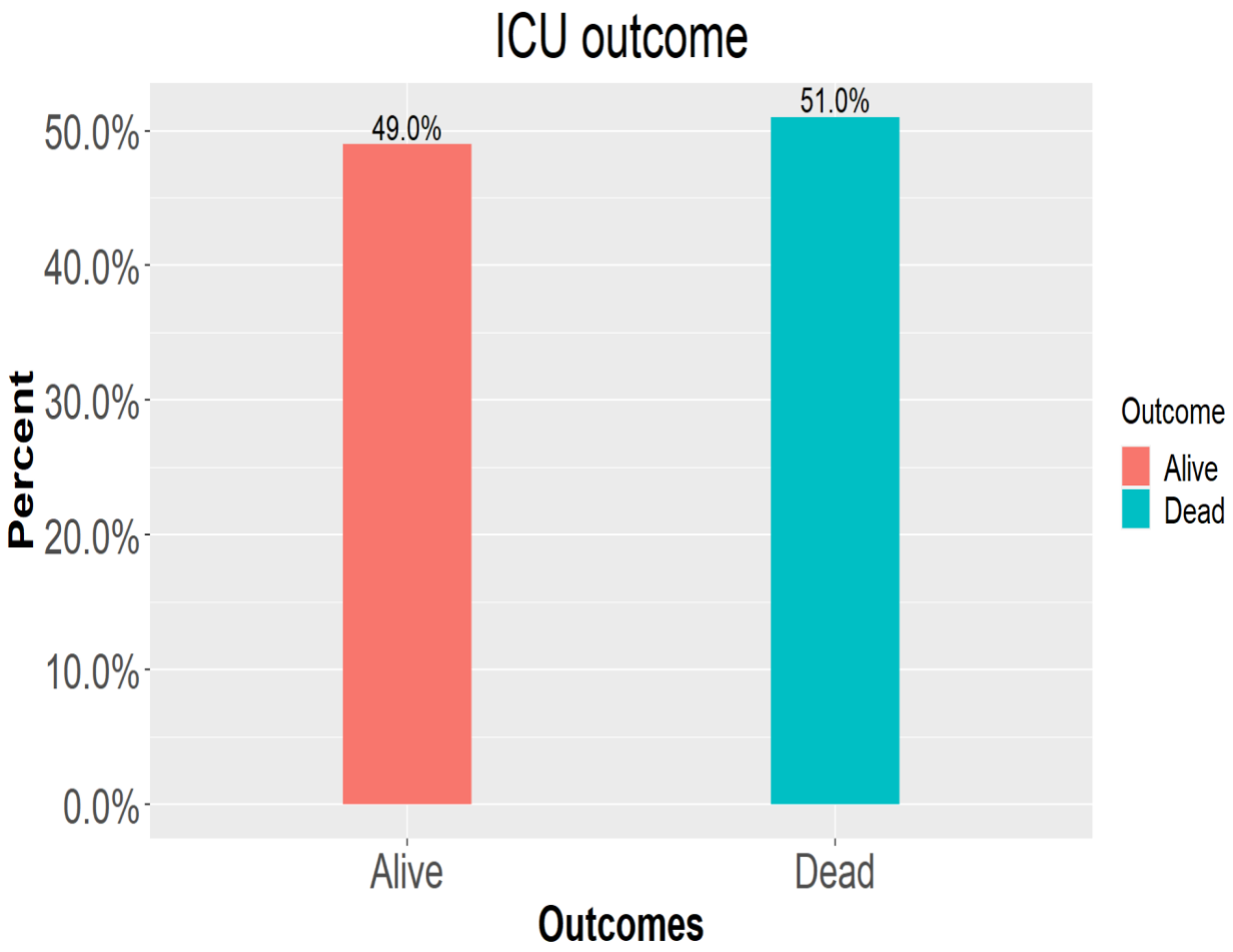

Figure 14: Bar graph showing mortality at the end of ICU stay

Mortality and gender

Overall, out of the 51.0% of the patients who died, 32.0% were females while the rest were males as shown in figure 15 below.

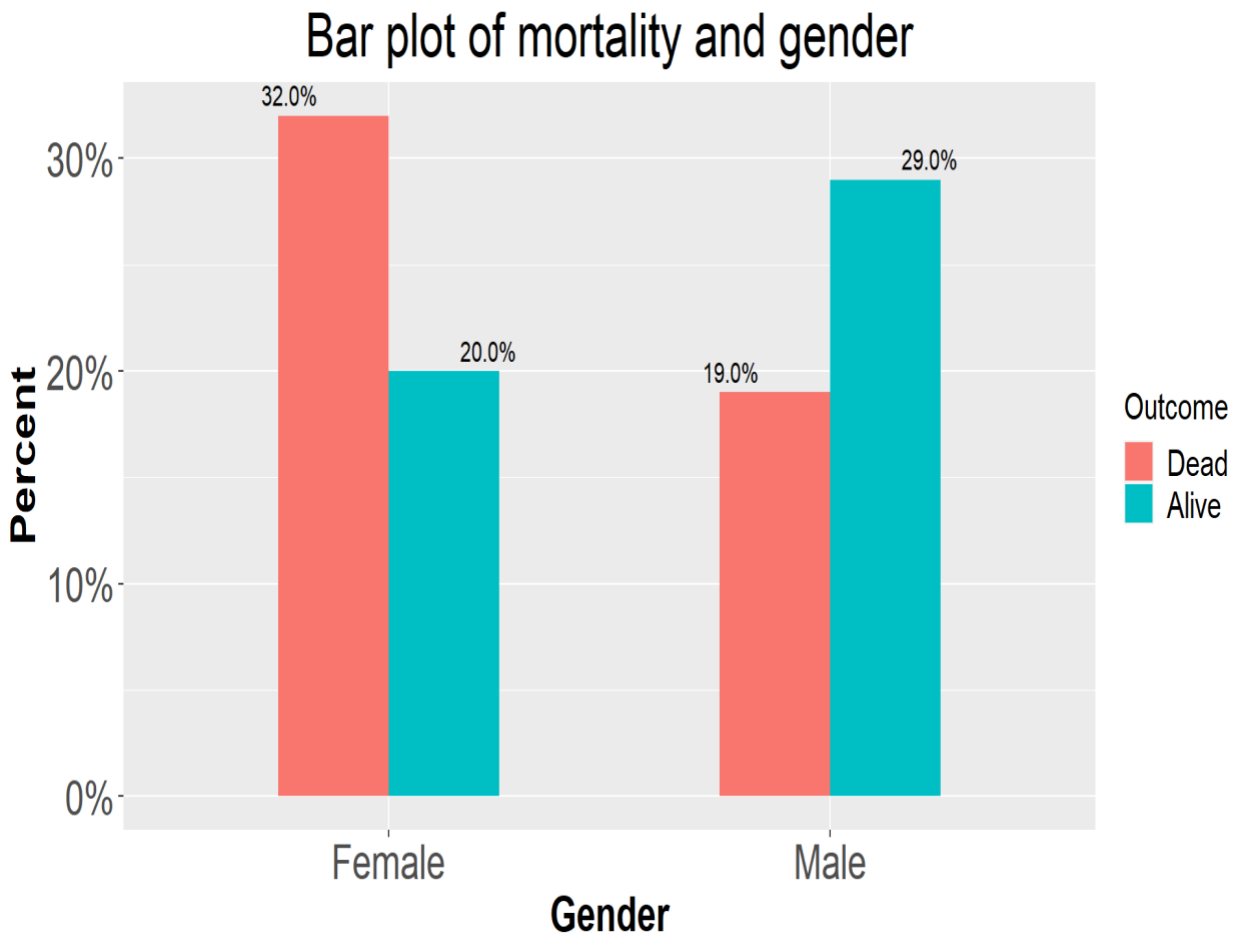

Figure 15: Bar graph showing mortality in terms of gender

Bivariate analysis

Difference in mortality between males and females

$$Ho: Male\ deaths = female\ deaths$$

$$H1: Male\ deaths \neq females\ deaths$$

A Chi square test of association between gender and mortality yielded a Chi squared value 2.44 and a p-value 0.12 at significance level 0.05. The p-value is greater than 0.05 hence we fail to reject the null hypothesis. There is no difference in deaths between males and females.

Effect of weight on ICU outcomes

$$Ho: Mean\ weight\ among\ deaths = Mean\ weight\ among\ alive$$

$$H1: Mean\ weight\ among\ deaths \neq Mean\ weight\ among\ alive$$

The box plots in figure 13 below displays median weights in ICU outcomes. The Wilcoxon test (figure 16) yielded a p-value of 0.14 at significance level 0.05 which led to the conclusion that that was no significant difference in mean weights between the patients who died and those who survived and we therefore fail to reject the null hypothesis.

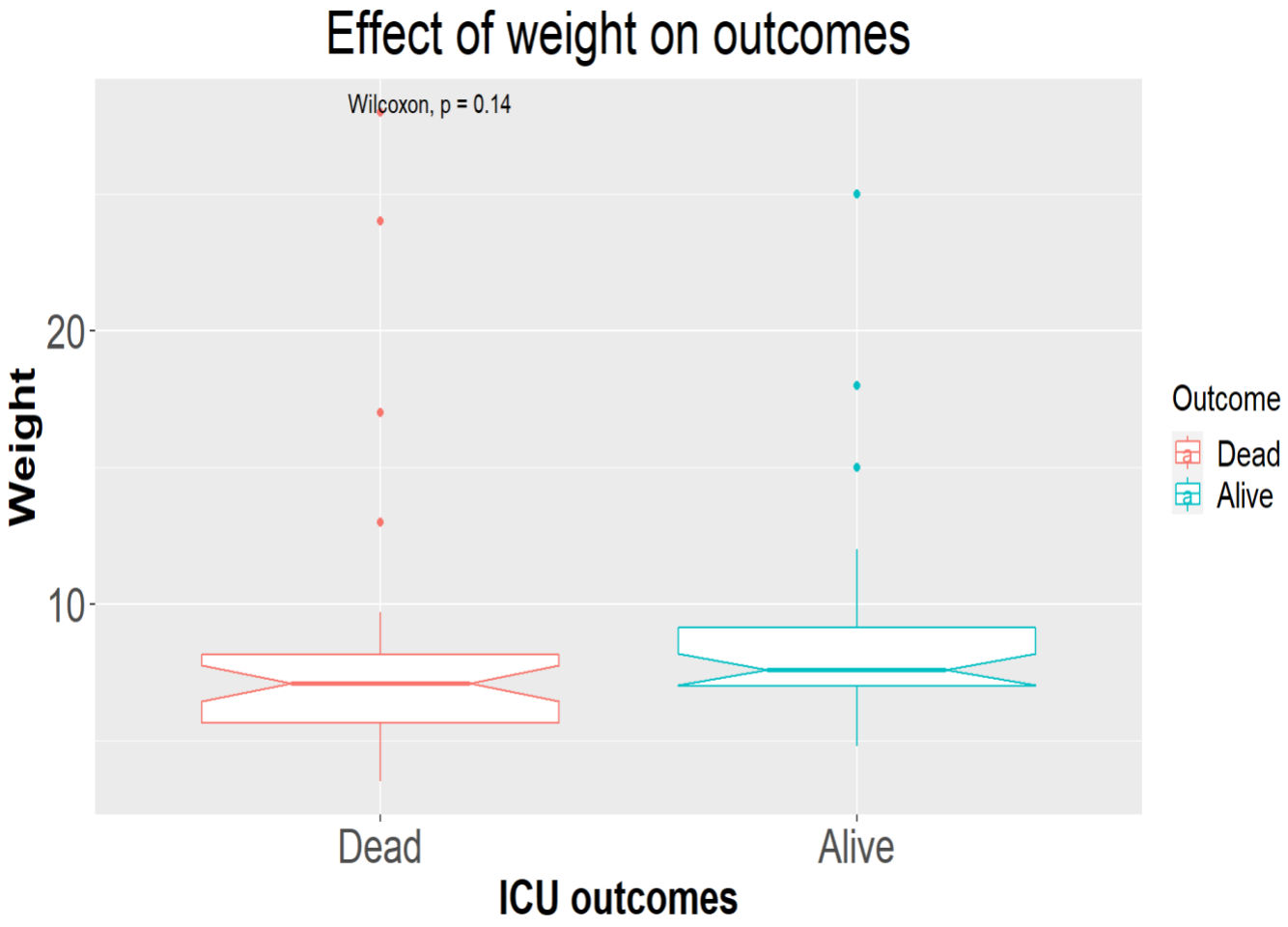

Figure 16: Box plots showing ICU outcomes and weights

Age and ICU outcomes

$$Ho: Mean\ age\ among\ deaths = Mean\ age\ among\ alive$$

$$H1: Mean\ age\ among\ deaths \neq Mean\ age\ among\ alive$$

The box plot in figure 14 below shows how ICU outcomes varied according to the participant's age. A test of mean age difference in the two outcomes using Wilcoxon test yielded a p-value of 0.74 (figure 14). At significance level 0.05, we fail to reject the null hypothesis that there was no

age difference between the children who died and those who survived because the p-value is greater than 0.05.

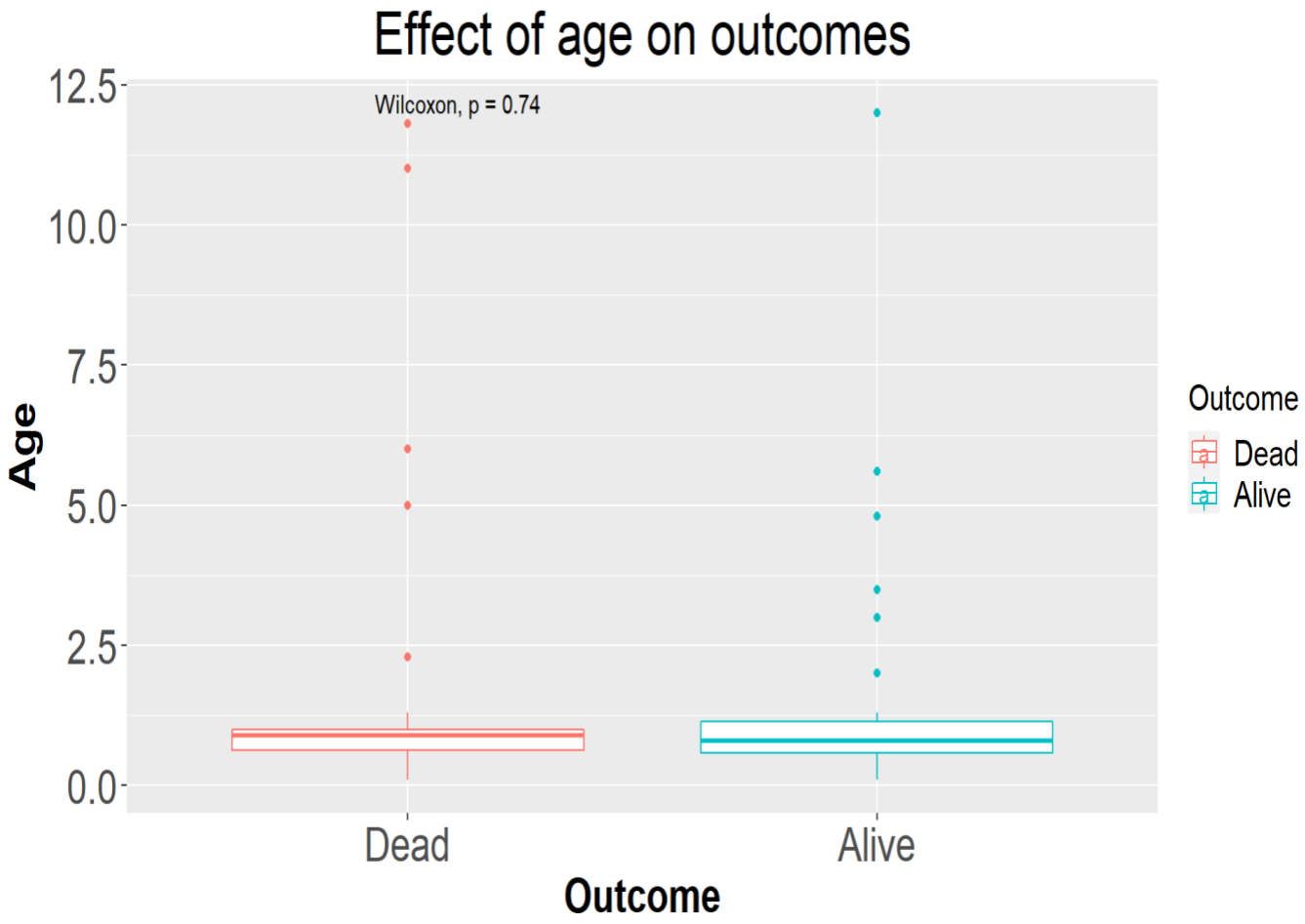

Figure 14: Box plot showing how outcomes varied according to age

PELOD score and outcomes

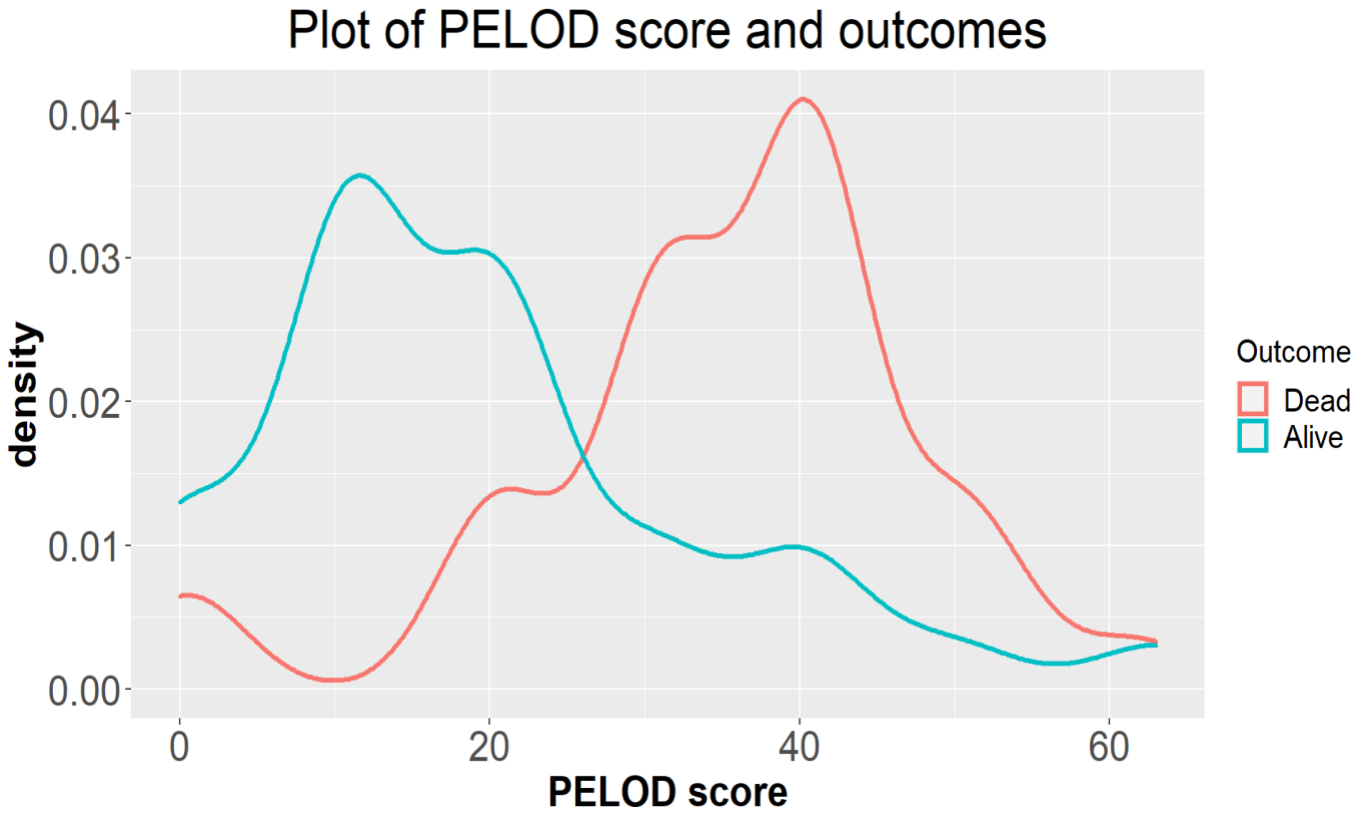

Figure 17: Density plot of PELOD score ant ICU outcomes

From the density plot in figure 17 above, the curve for the patients who survived is skewed right meaning that there were fewer survivals with larger PELOD scores. The curve for the patients who died is negatively skewed meaning that fewer patients died with smaller PELOD scores.

$$Ho: Mean\ PELOD\ score\ among\ deaths = Mean\ PELOD\ score\ among\ alive$$

$$H1: Mean\ PELOD\ score\ among\ deaths \neq Mean\ PELOD\ score\ among\ alive$$

The box plots in figure 16 compared mean PELOD scores between the patients who died and those who survived. The Wilcoxon test produced a p-value <0.01. At 95% confidence level, we reject the null hypothesis and conclude that there was a statistically significant difference in mean PELOD score between the patients who died and those who survived because the p-value is less than 0.05.

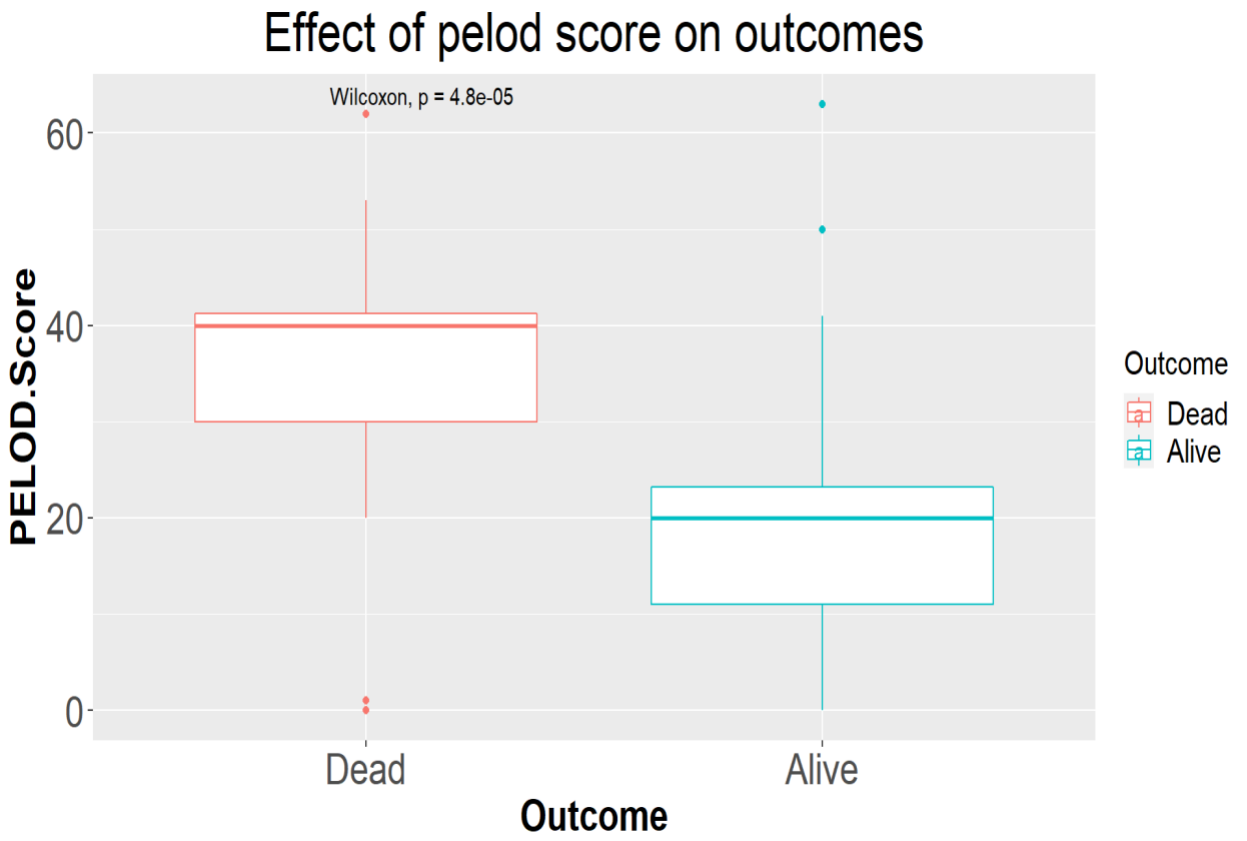

Figure 18: Box plots showing the effect of PELOD score on ICU outcomes

Objective2: To determine the proportion of patients with clinically significant positive fluid balance during their ICU stay

Significant positive fluid balance was capped at 10% and above which is also described as fluid overload[2] according to Granado et al. 2016. The proportion of the participants with a significant positive fluid balance in this study was 0.74 (0.62, 0.83) as shown in figure 19 below.

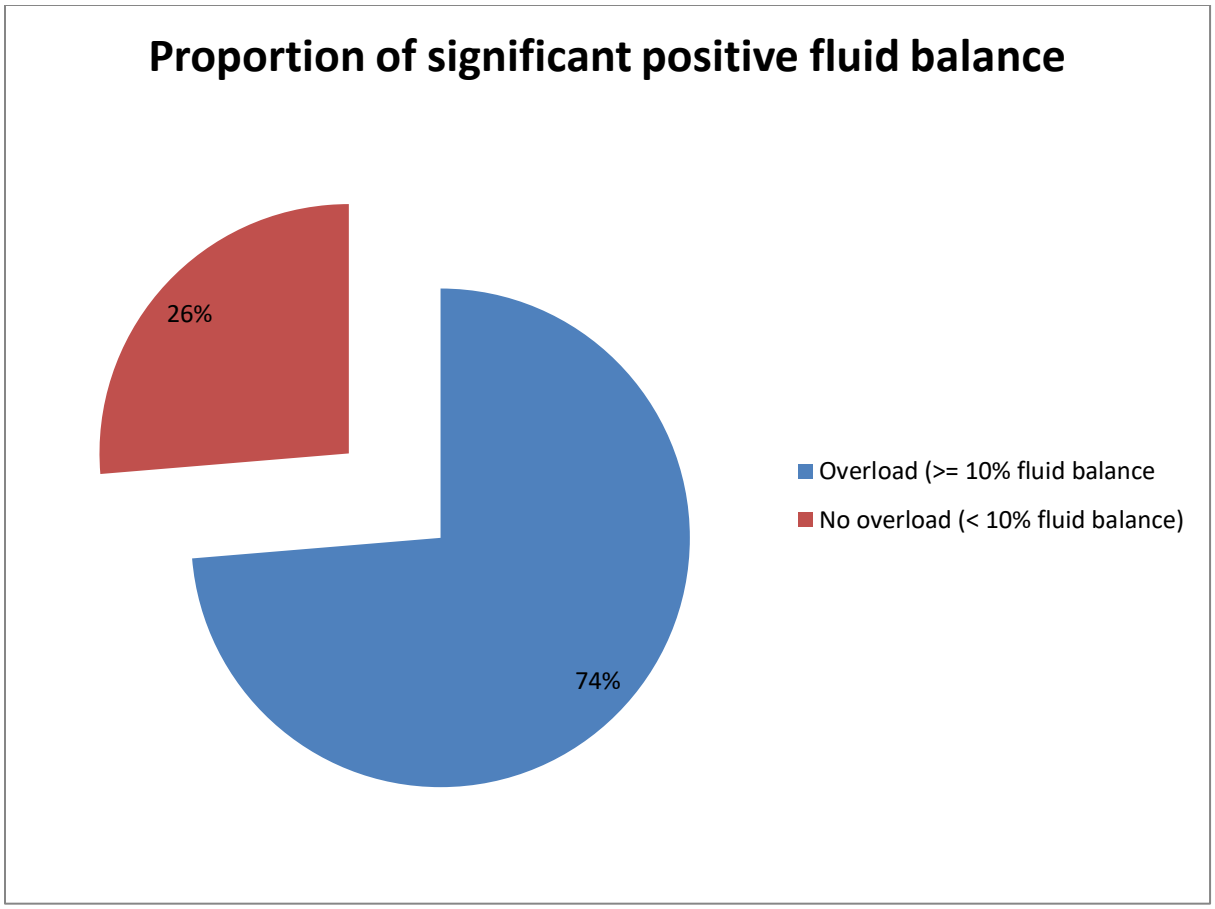

Figure 19: Proportion of significant positive fluid balance

Table 3: Proportion of mortality in the overload and non-overload groups

Fluid balance	Outcome		Proportion of mortality (%) (95% CI)
	Dead	Alive	
Overload	24	27	47.1 (33.2, 61.4)
No overload	7	11	38.9 (18.3, 63.9)

The table 3 above shows that 47.1% (n = 24) died in the overload group while 38.9% (n = 7) died among those who did not get fluid overload. A study by Samaddar et al. 2018 found mortality of 40.5% and 34% in the overload and non-overload groups respectively.[6]

Objective 3: To establish the relationship between clinically significant positive fluid balance and clinical outcome (length of ICU stay, days on MV, whether dead or alive), at the end of ICU stay

Effect of clinically significant positive fluid balance on mortality

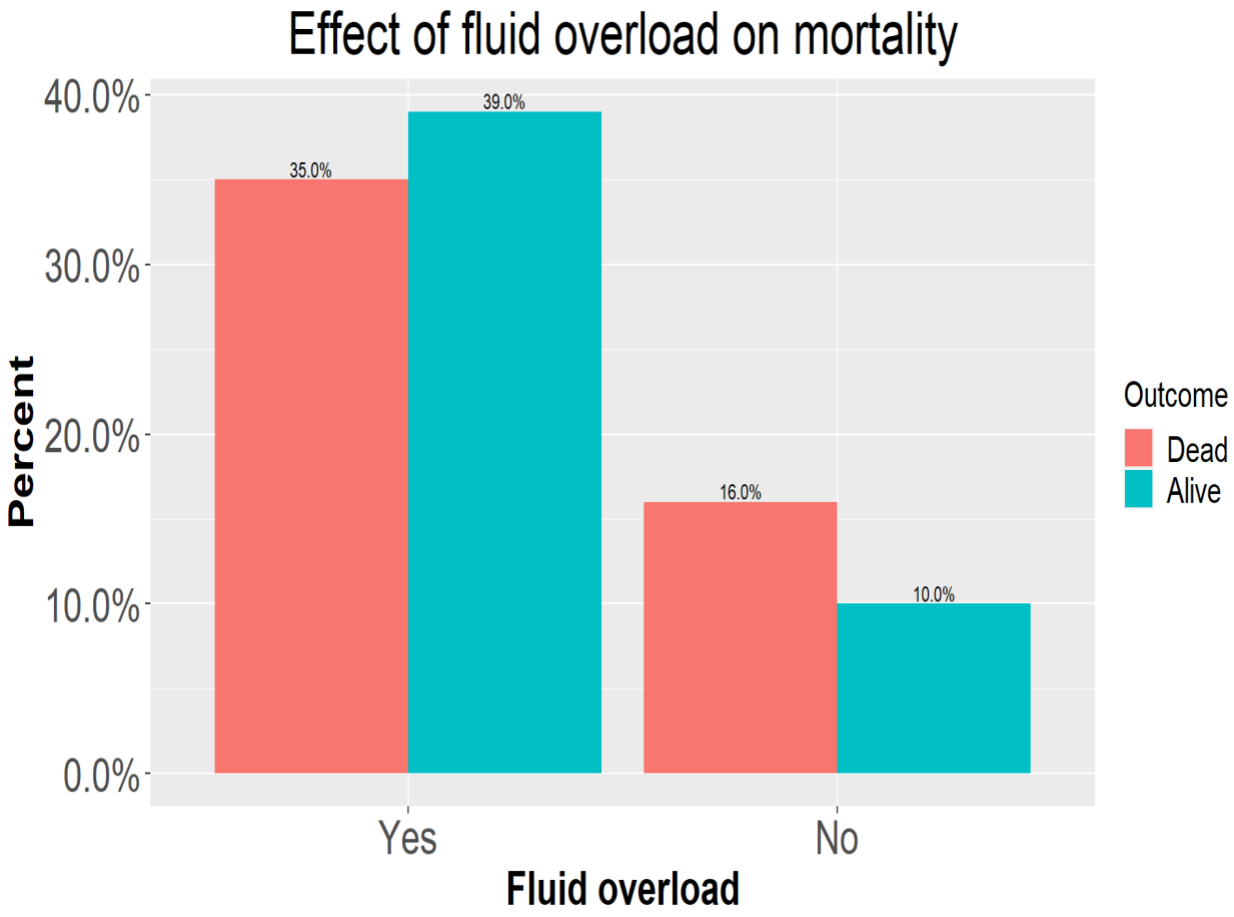

Figure 20: Bar graph showing the effect of fluid overload on mortality

Figure 20 above shows that of the 51% of the patients who died, 35.0% of them had received fluid overload. The remaining 16% had not received fluid overload.

$$Ho: Fluid\ overload\ among\ deaths = Fluid\ overload\ among\ alive$$

$$H1: Fluid\ overload\ among\ deaths \neq Fluid\ overload\ among\ alive$$

On whether there was an association between fluid overload and mortality, Pearson's chi square test yielded a p-value 0.45. We fail to reject the null hypothesis and conclude that there was no difference in mortality between the patients who received fluid overload and those who did not because the p-value is greater than 0.05.

Days on ventilation and outcomes

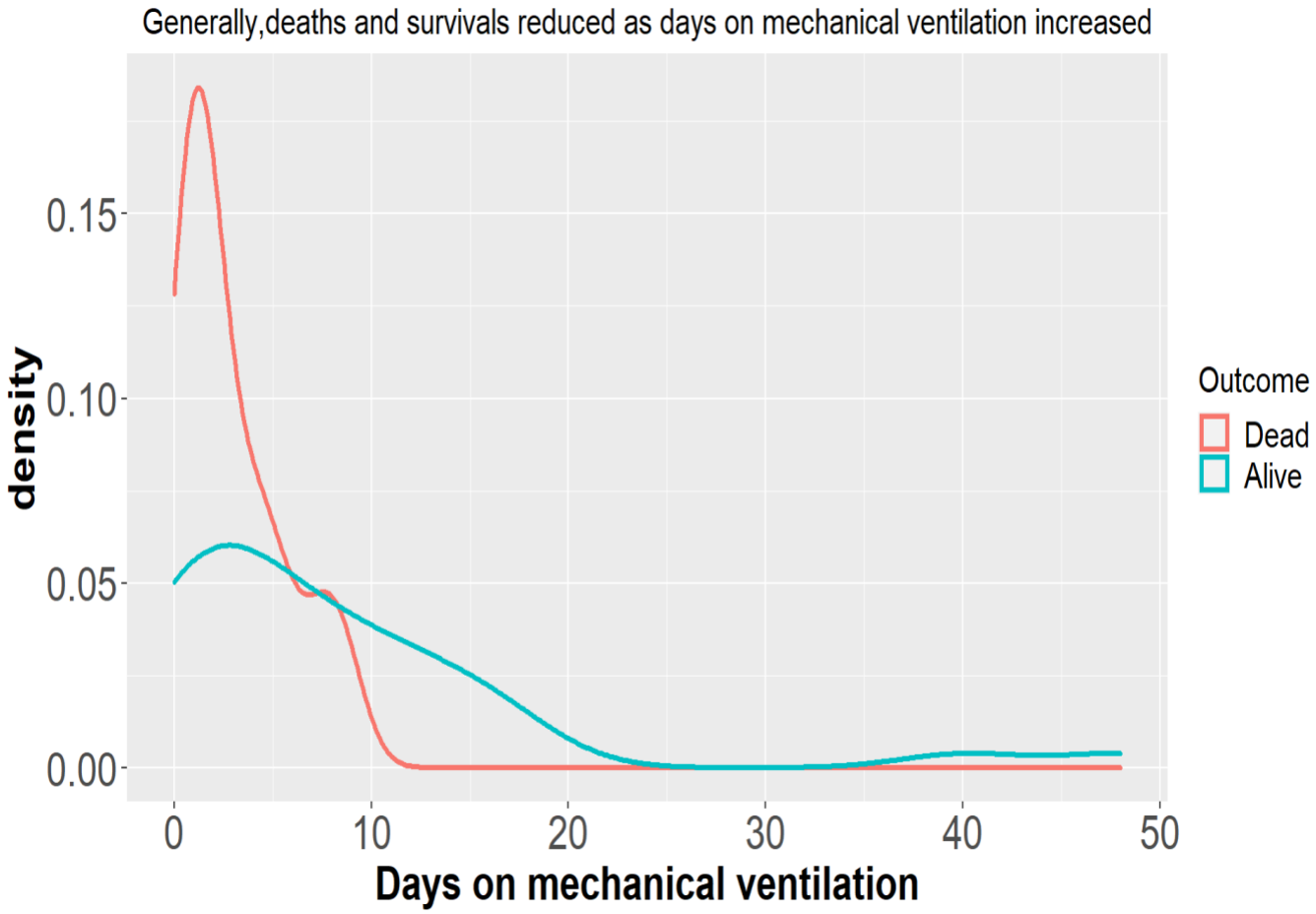

Figure 21: Density plot of days on mechanical ventilation and ICU outcomes

The density plot in figure21 above shows that more deaths occurred in the early days of mechanical ventilation. Generally, days on mechanical ventilation were left skewed both for those who died and those who survived.

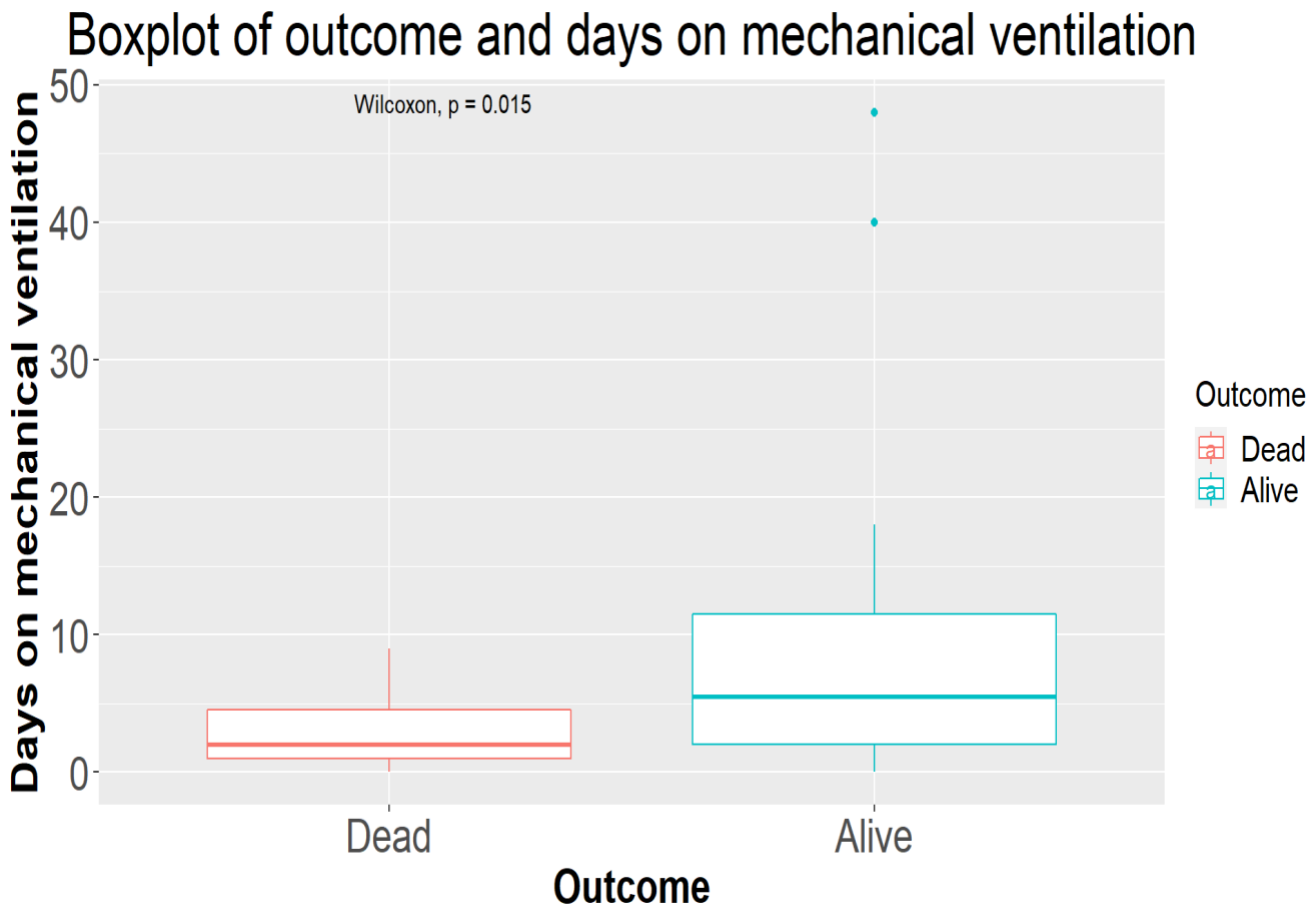

Figure 22: Box plot showing how outcomes varied with days on mechanical ventilation.

The median days on mechanical ventilation were higher for those who survived as opposed to those who died as shown in figure 22 above. This shows that patients who spent a few more days on mechanical ventilation had better chances of survival.

$$Ho: Mean\ days\ on\ mechanical\ ventilation\ among\ deaths = Mean\ days\ on\ mechanical\ ventilation\ among\ alive$$

$$H1: Mean\ days\ on\ mechanical\ ventilation\ among\ deaths \neq Mean\ days\ on\ mechanical\ ventilation\ among\ alive$$

A comparison of survival using Wilcoxon test for mean mechanical ventilation days yielded a p-value 0.015. We therefore reject the null hypothesis and conclude that there was a significant difference in mean days on mechanical ventilation between the patients who died and those who survived.

Days on inotropic support and outcomes

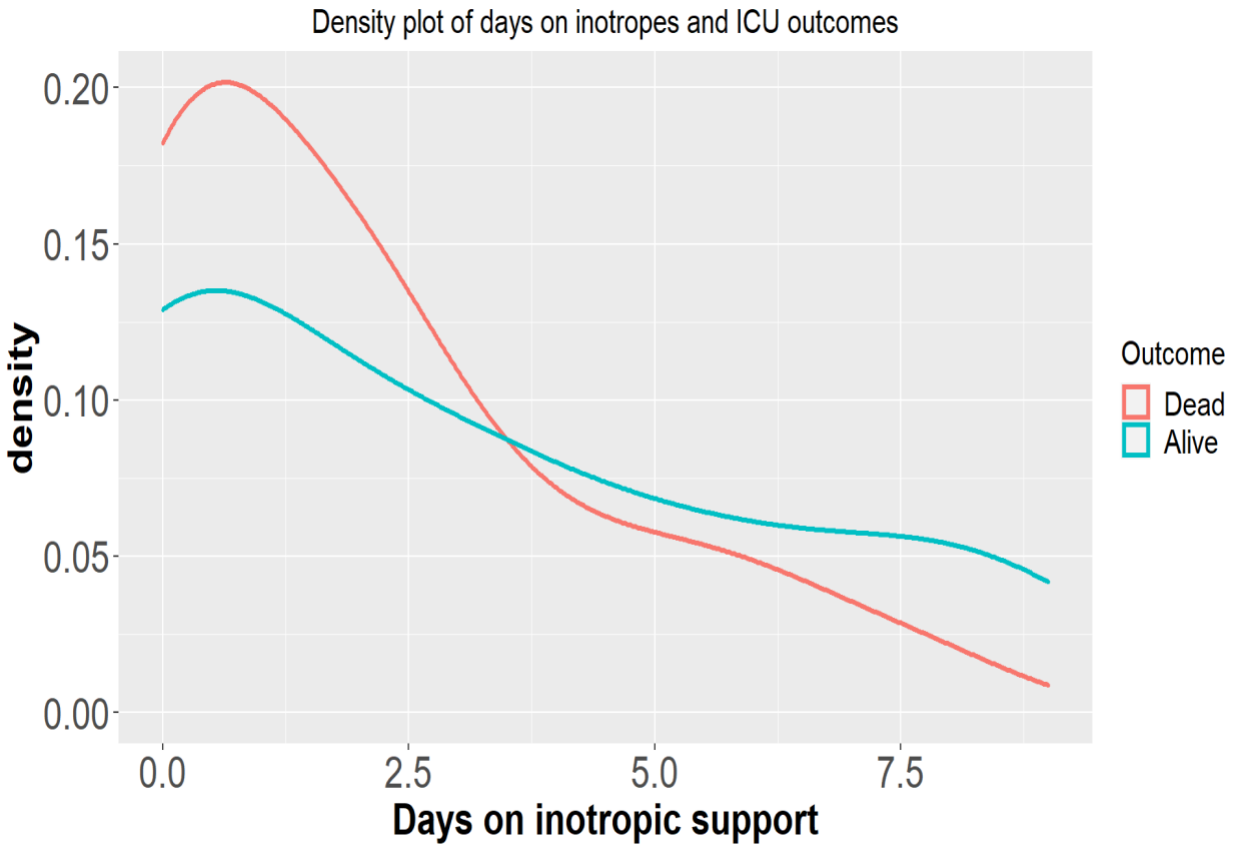

Figure 23: Density plot showing how mortality varied with days on inotropes

The density plot in figure 23 above shows that deaths were high with fewer days and sharply decreased with more days on inotropic support.

$$Ho: Mean\ days\ on\ inotropic\ support\ among\ deaths = Mean\ days\ on\ inotropic\ support\ among\ alive$$

$$H1: Mean\ days\ on\ inotropic\ support\ among\ deaths \neq Mean\ days\ on\ inotropic\ support\ among\ alive$$

We fail to reject the null hypothesis because Wilcoxon test yielded a p-value of 0.34. There was no significant difference in mean days of inotropic support between the patients who died and those who survived (figure 24).

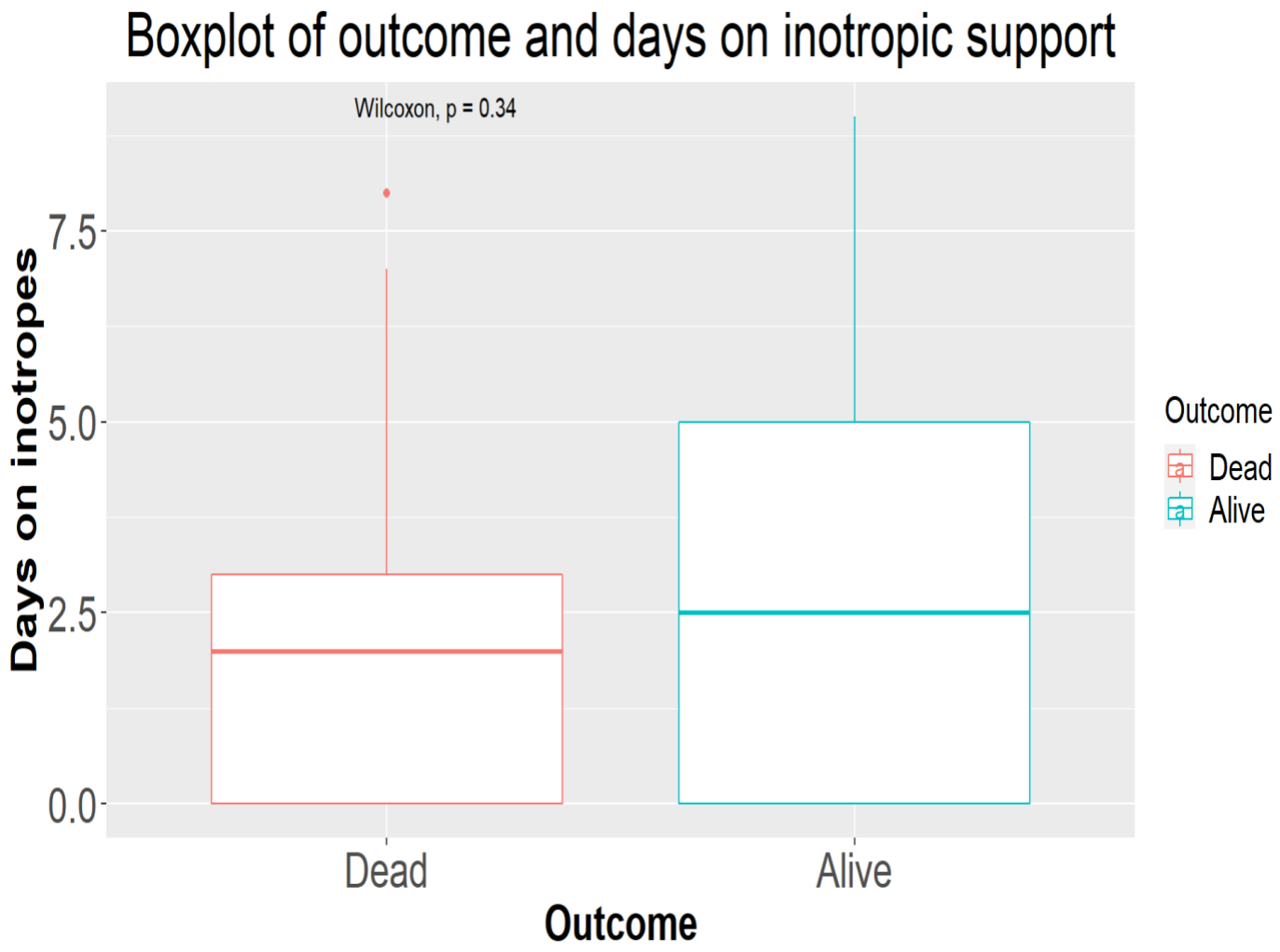

Figure 24: Box plot showing how outcomes varied with inotropic support

Predicting mortality using PELOD score

Figure 25 below shows a logistic regression curve fitted to predict mortality using PELOD score. The figure shows that the probability of death is approximately 20% for PELOD scores of 0 and more than 90% for PELOD scores of 80 and above.

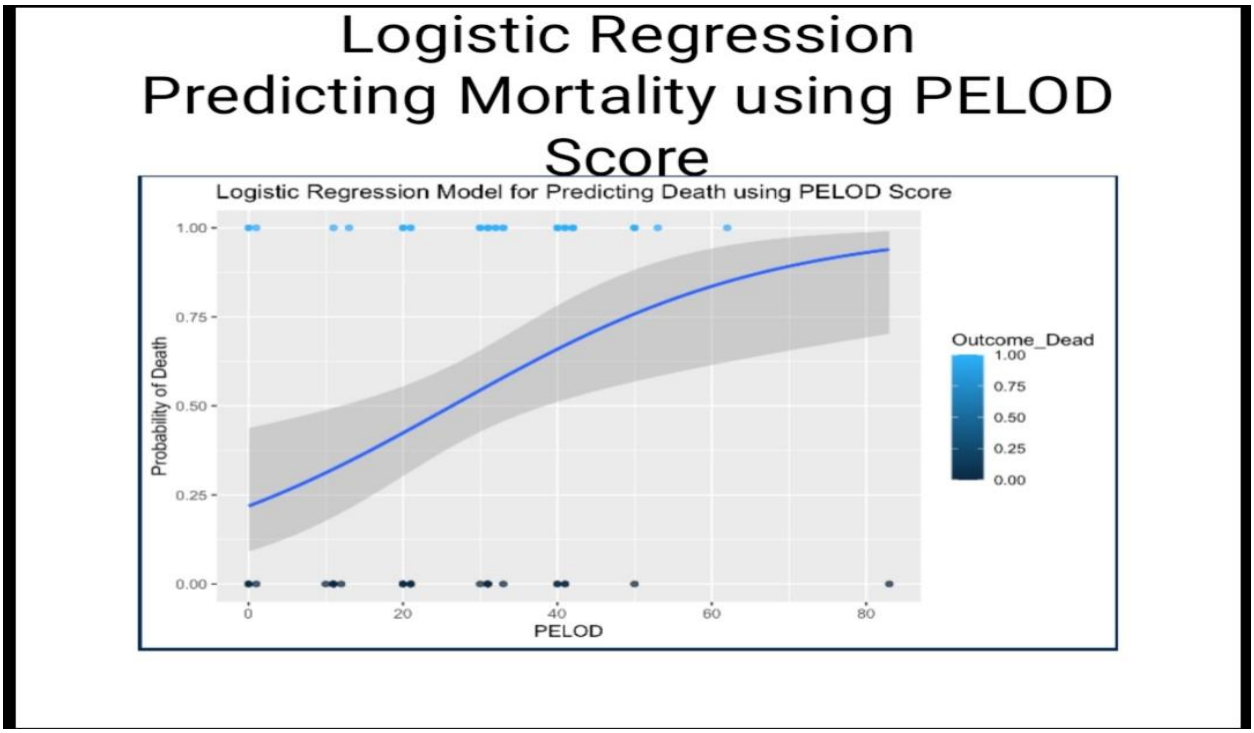

Figure 25: Predicting mortality using PELOD score

Table 4: Confusion matrix for predicting mortality

PELOD >26 is Critical
Confusion Matrix

		Predicted		
		Dead	Alive	
Situation on the Ground	Dead	32	10	42
	Alive	24	15	39
				81

$$\text{Sensitivity} = \frac{32}{42} * 100\% = 76.2\%$$

$$\text{Specificity} = \frac{15}{39} * 100\% = 38.5\%$$

$$\text{Accuracy} = \frac{47}{81} * 100\% = 58\%$$

Multivariable analysis

Table 5: Factors associated with ICU mortality

Variable	**Category**	**Outcome N = 74**			
		Dead	**Alive (ref)**	**Adjusted OR (95% CI)**	**P-value**
Gender	Female Male (ref)	20 11	16 22	2.53 (0.86, 7.85)	0.10
Fluid overload	Yes No (ref)	24 7	27 11	1.28 (0.36, 4.68)	0.70
Inotropic use	Yes No (ref)	18 11	26 11	0.84 (0.27, 2.69)	0.78
PELOD score	>=10 <10 (ref)	30 2	28 4	5.52 (0.73, 62.01)	0.12
Weight in kilograms	NA	NA	NA	0.52 (0.27, 0.89)	0.03

On the factors affecting mortality, we found that no factor was significantly associated with mortality when adjusted for the other factors. This is because all the p-values are above 0.05 at 95% confidence level.

Interpretation of odds ratios

Holding the other factors constant;

A female child was 2.53 times more likely to die compared to a male child. On the other hand, children who got fluid overload were 28% more likely to die compared to those who did not get fluid overload. The odds of dying for children with a PELOD score of 10 and above were 5.52 the odds of children with a PELOD score of less than 10. The odds of dying for the children who were on inotropic support was 0.84 the odds of those who were not on inotropic support (table 5).

Length of intensive care unit stay

Bivariate analysis

Gender and length of ICU stay

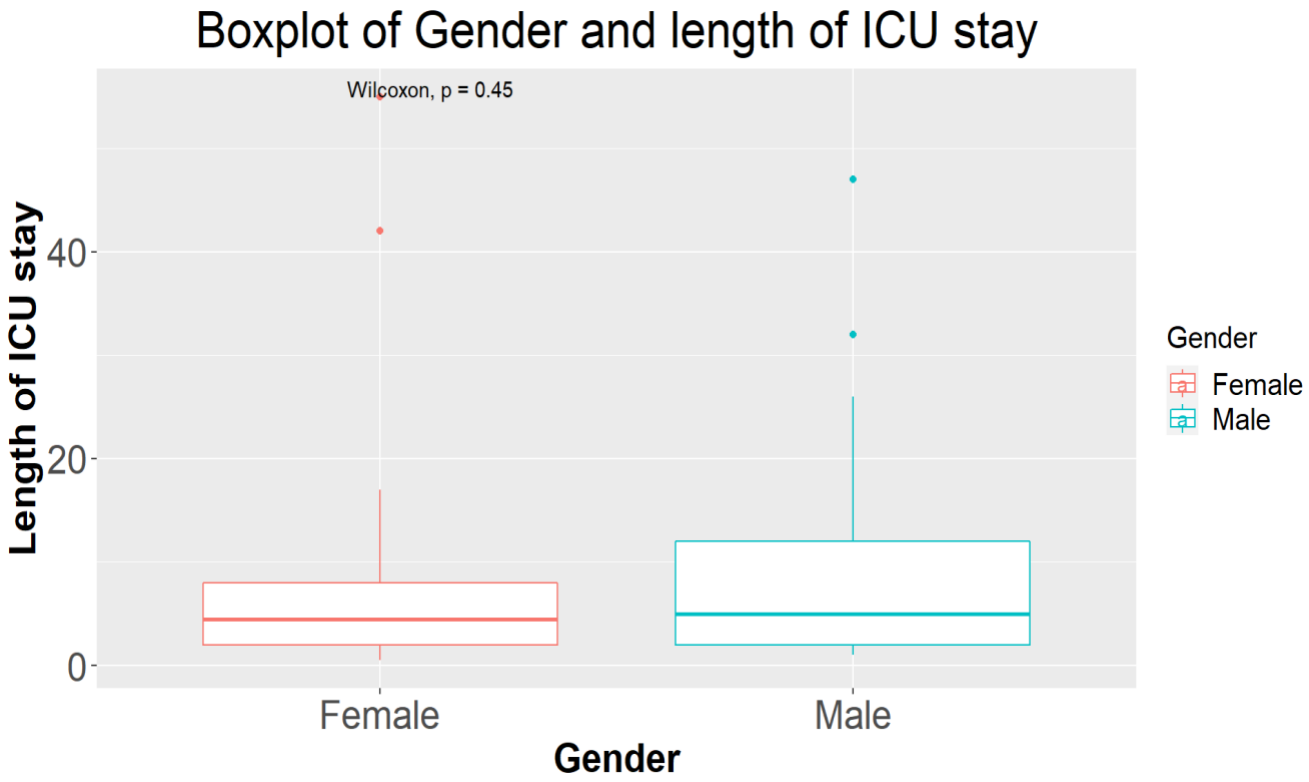

Figure 26: Boxplot showing the effect of gender on length of ICU stay

$$Ho: Mean\ days\ of\ lenght\ of\ ICU\ stay\ among\ males = Mean\ days\ of\ lenght\ of\ ICU\ stay\ among\ females$$

$$H1: Mean\ days\ of\ lenght\ of\ ICU\ stay\ among\ males \neq Mean\ days\ of\ lenght\ of\ ICU\ stay\ among\ females$$

The p-value 0.45 is greater than 0.05. We fail to reject the null hypothesis and conclude that there was no significance difference in mean days of ICU stay between males and females.

Age of the participants and length of ICU stay

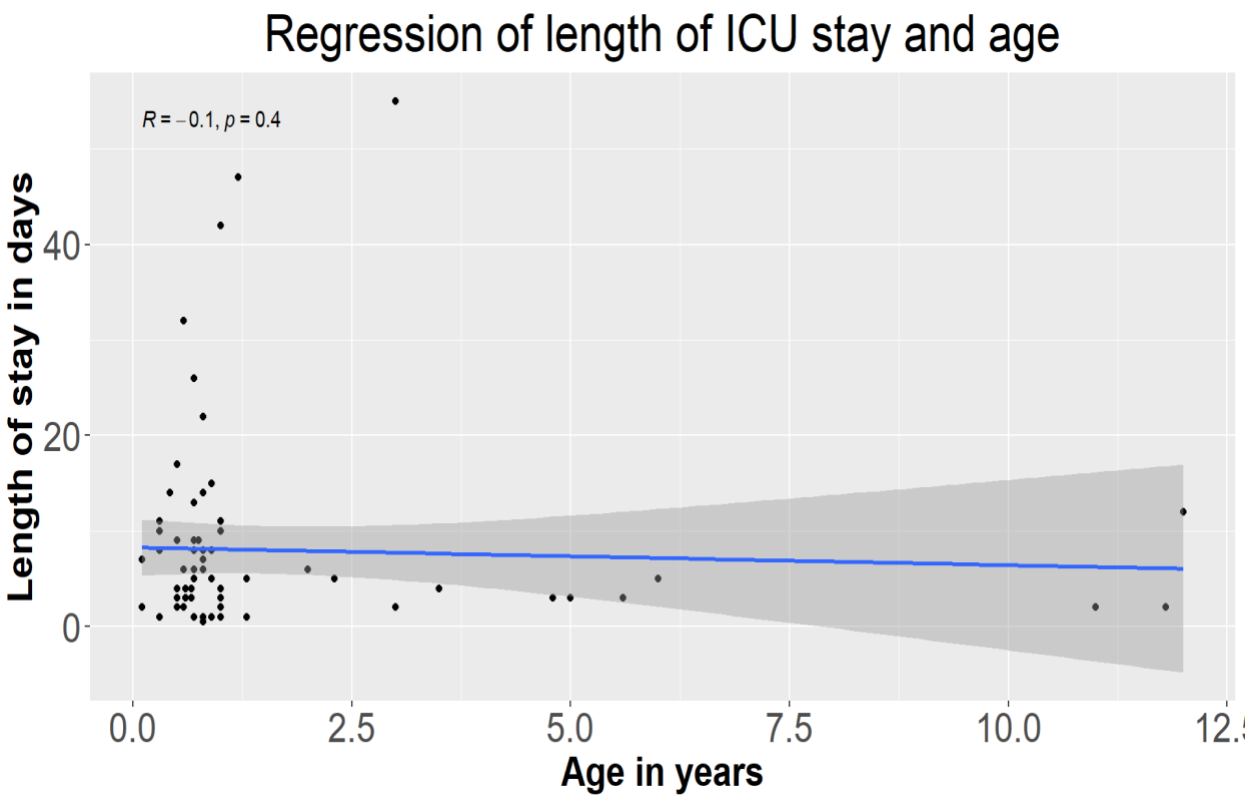

Figure 27: Scatter plot showing regression of days in ICU stay and age in years

$$Ho: There\ is\ no\ relationship\ between\ mean\ age\ and\ mean\ days\ of\ ICU\ stay$$

$$H1: There\ is\ a\ relationship\ between\ mean\ age\ and\ mean\ days\ of\ ICU\ stay$$

Linear regression produced a p-value 0.4 which is greater than 0.05. We therefore fail to reject the null hypothesis. We conclude that there was no relationship between mean age and mean days of ICU stay. The spearman's correlation coefficient of -0.1 indicates a weak negative correlation.

Weight and length of ICU stay

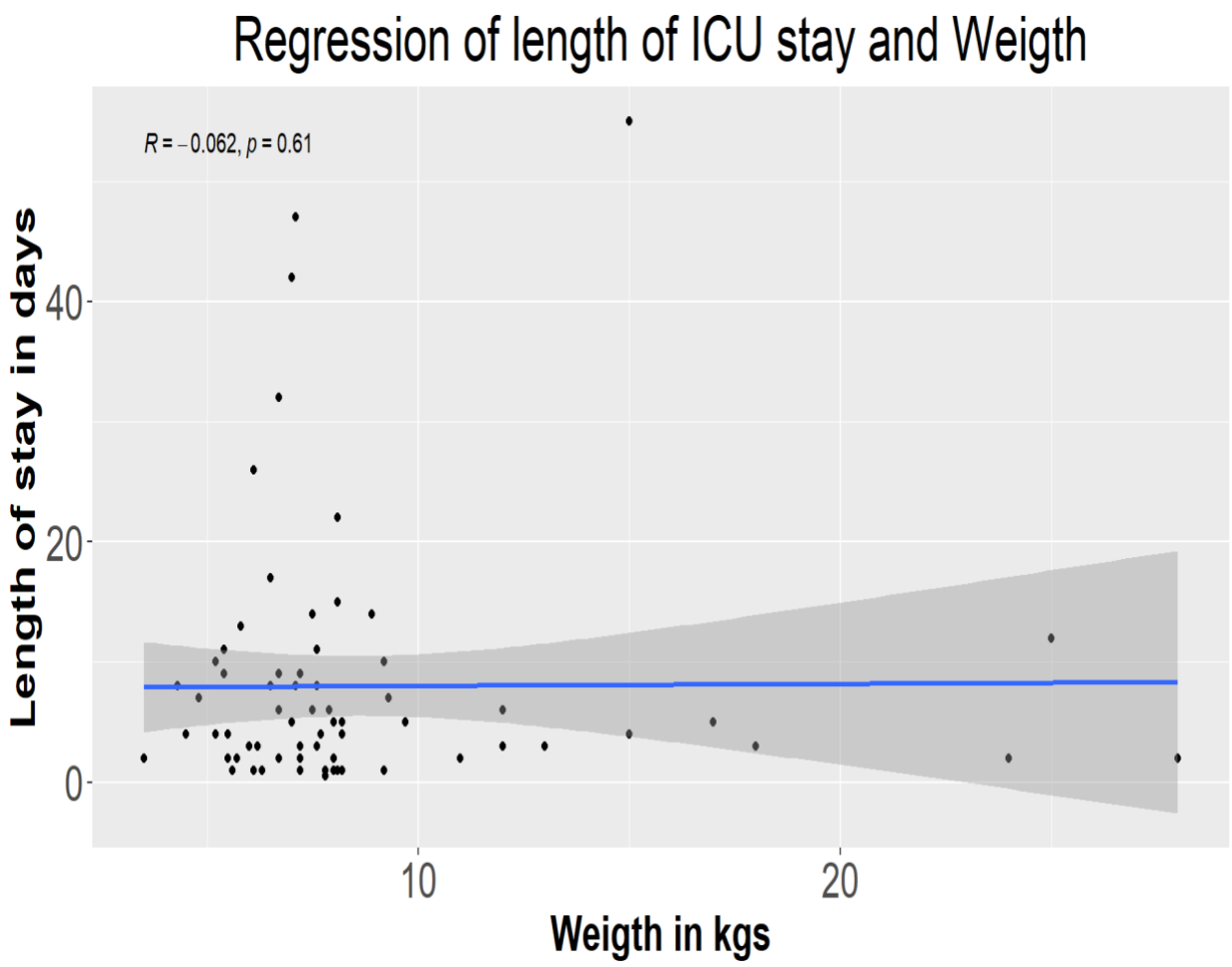

Figure 28: Scatter plot of regression for length of ICU stay and weight

$$Ho: There\ is\ no\ relationship\ between\ mean\ weight\ and\ mean\ days\ of\ ICU\ stay$$

$$H1: There\ is\ a\ relationship\ between\ mean\ weight\ and\ mean\ days\ of\ ICU\ stay$$

Linear regression produced a p-value 0.61 which is greater than 0.05. We therefore fail to reject the null hypothesis. We conclude that there was no relationship between mean weight and mean days of ICU stay. The spearman's correlation coefficient of -0.062 indicates a weak negative correlation.

Length of ICU stay and PELOD score

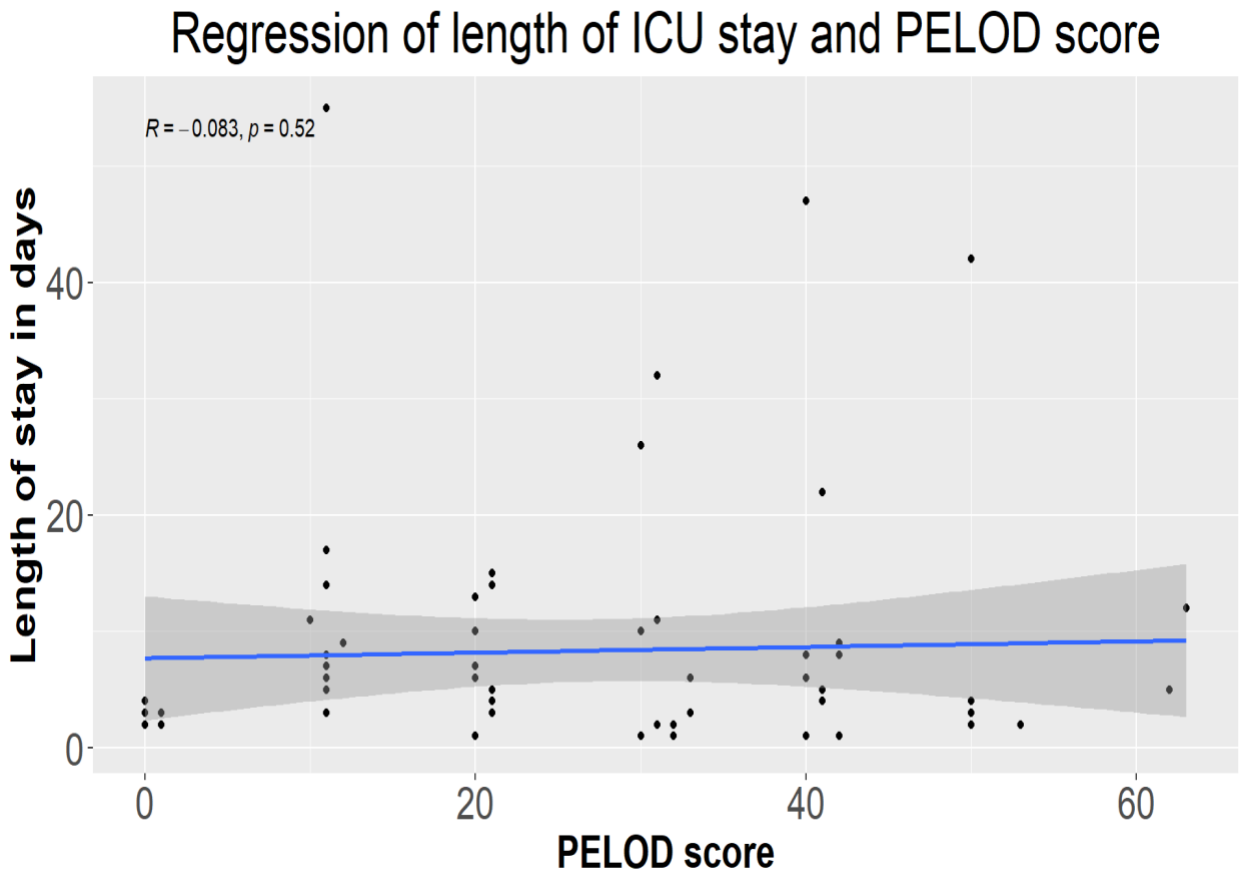

Figure 29: Scatter plot of regression between length of ICU stay and PELOD score

Ho: *There is no relationship between mean PELOD score and mean days of ICU stay*

$H1$: *There is a relationship between mean PELOD score and mean days of ICU stay*

Linear regression produced a p-value 0.52 which is greater than 0.05. We therefore fail to reject the null hypothesis. We conclude that there was no relationship between mean PELOD score and mean days of ICU stay. The spearman's correlation coefficient of -0.083 indicates a weak negative correlation.

Length of ICU stay and days on mechanical ventilation

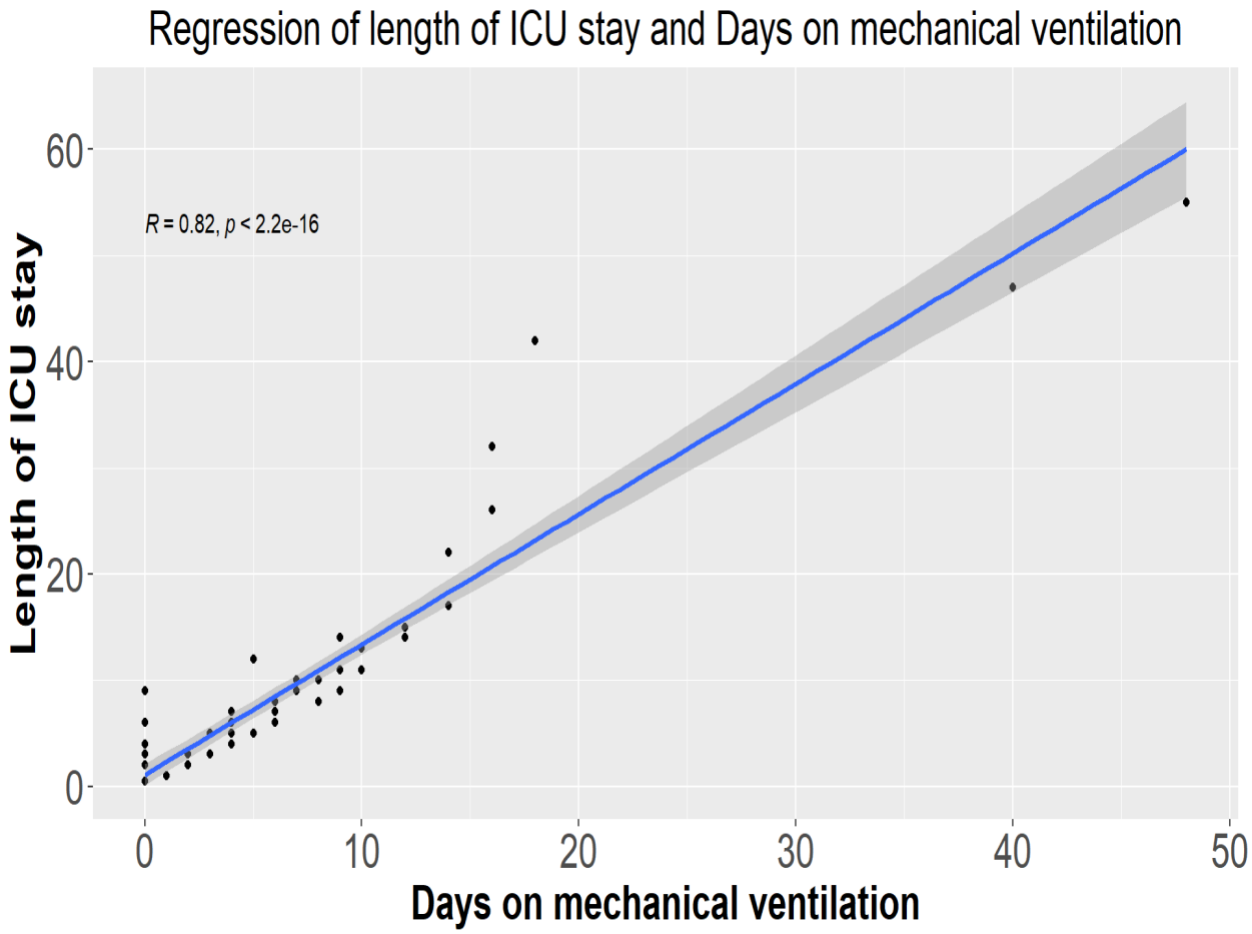

Figure 30: Scatter plot showing regression of length of ICU stay and days on mechanical ventilation

$Ho: There\ is\ no\ relationship\ between\ mean\ days\ on\ ventilation\ and\ mean\ days\ of\ ICU\ stay$

$H1: There\ is\ a\ relationship\ between\ mean\ days\ on\ ventilation\ and\ mean\ days\ of\ ICU\ stay$

The p-value for regression of days on mechanical ventilation and length of ICU stay is <0.01. we reject the null hypothesis because the p-value is less than 0.05. We conclude that there is a

statistically significant relationship between the days on mechanical ventilation and length of ICU stay.

Days on inotropic support and length of ICU stay

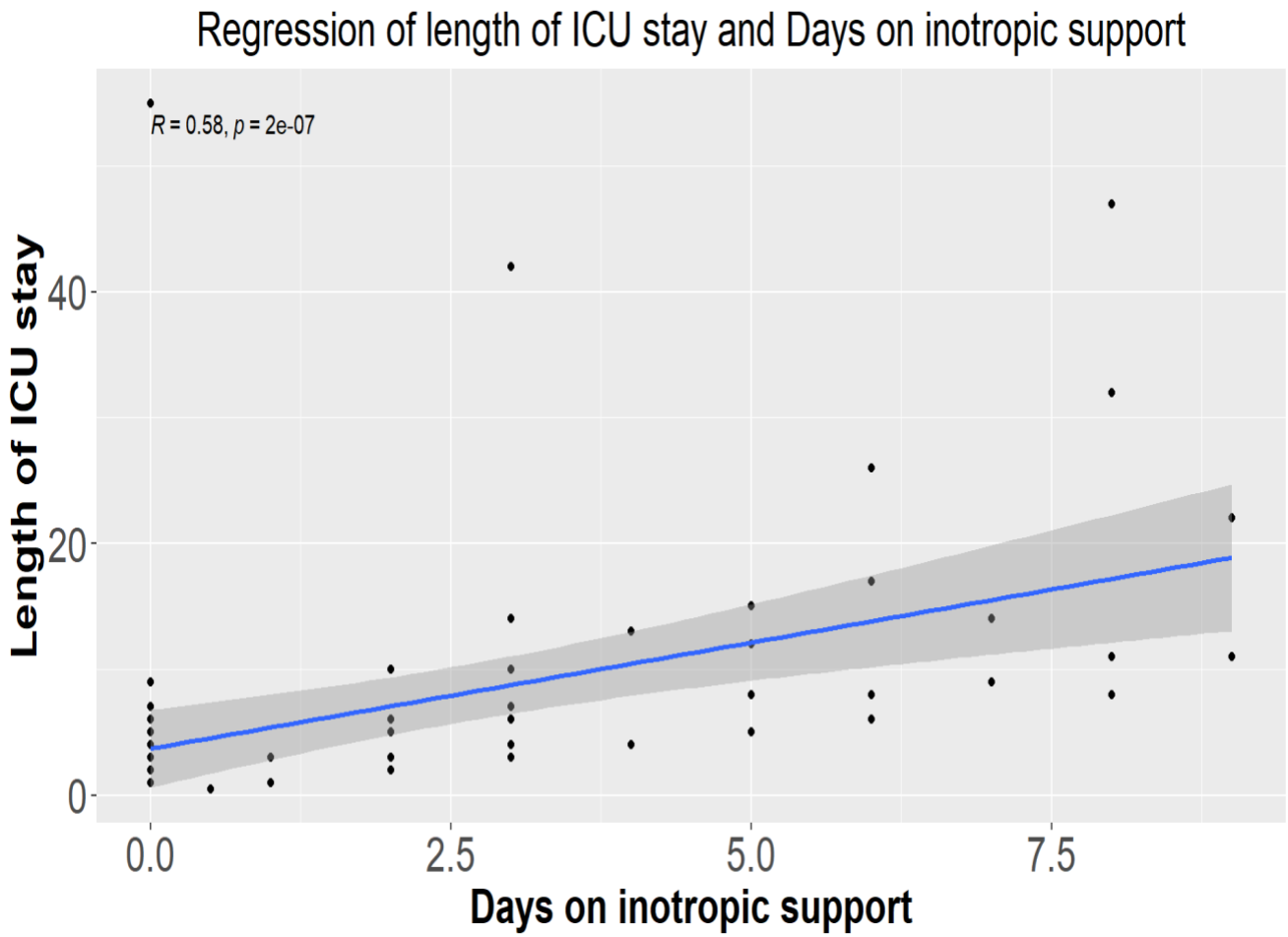

Figure 31: Scatter plot showing regression of length of stay and days on inotropic support

$Ho: There\ is\ no\ relationship\ between\ mean\ days\ on\ inotropic\ support\ and\ mean\ days\ of\ ICU\ stay$

$H1: There\ is\ a\ relationship\ between\ mean\ days\ on\ inotropic\ support\ and\ mean\ days\ of\ ICU\ stay$

The p-value for regression on days on inotropic support and length of ICU stay is <0.01. we reject the null hypothesis because the p-value is less than 0.05. We conclude that there is a

Length of ICU stay and percent fluid balance

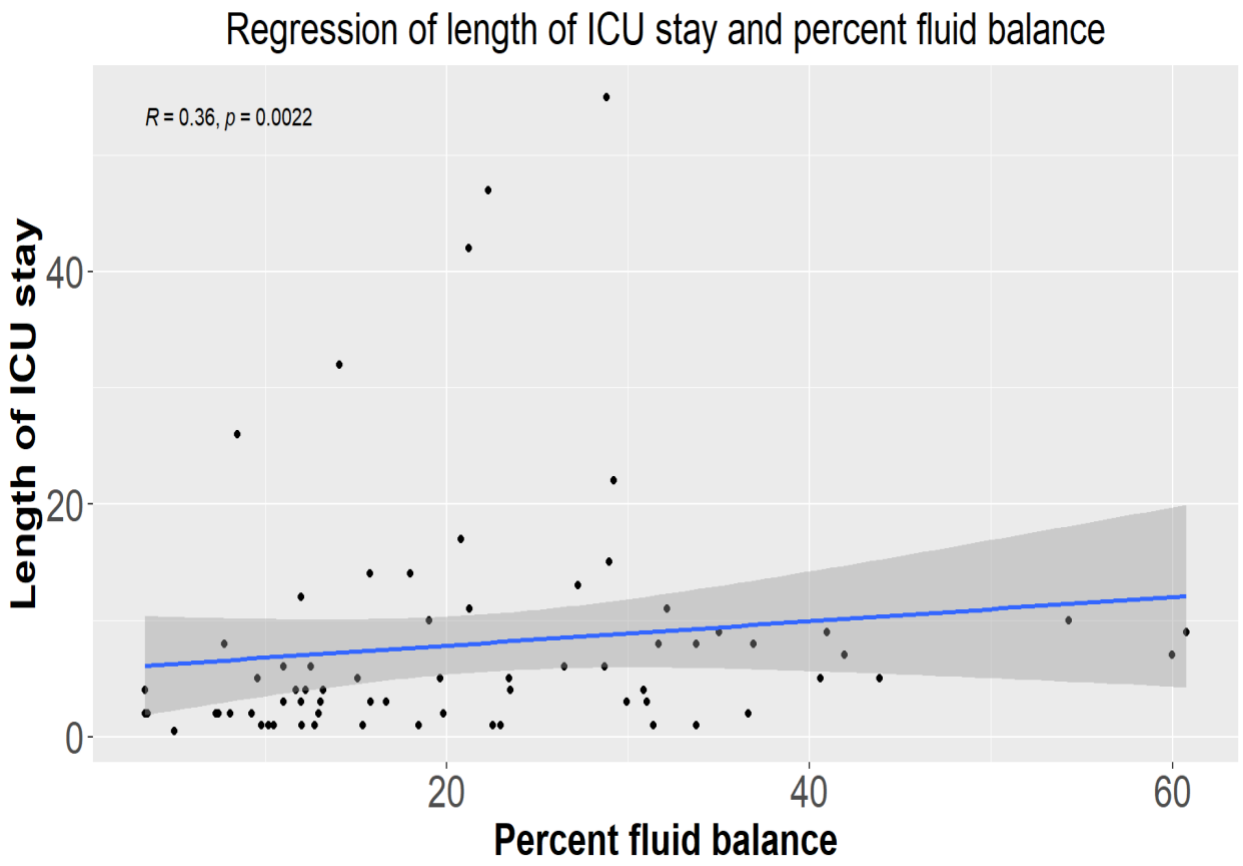

Figure 32: Regression plot of percent fluid balance and length of ICU stay

$Ho: There\ is\ no\ relationship\ between\ mean\ percent\ fluid\ \ balance\ and\ mean\ days\ of\ ICU\ stay$

$H1: There\ is\ a\ relationship\ between\ mean\ days\ on\ inotropic\ support\ and\ mean\ days\ of\ ICU\ stay$

The p-value for regression on days on percent fluid balance and length of ICU stay is 0.002. We reject the null hypothesis because the p-value is less than 0.05. We conclude that there is a statistically significant relationship between precent fluid balance and length of ICU stay.

Multivariable analysis

Table 6: Factors associated with the length of ICU stay in days

Variable	Category	Length of ICU stay		
			Adjusted OR (95% CI)	**P-value**
Gender	Female Male (ref)	NA	1.14 (0.96, 1.37)	0.14
Fluid overload	Yes No (ref)	NA	1.24 (0.99, 1.57)	0.07
Inotropic use	Yes No (ref)	NA	1.36 (1.10, 1.68)	0.004
PELOD score	>=10 <10 (ref)	NA	0.95 (0.46, 1.92)	0.89
Ventilated	Yes No (ref)	NA	2.48 (1.52, 4.45)	<0.001

Two factors were found to have a significant statistical association with the length of ICU stay after adjusting for the other factors i.e., inotropic use, and mechanical ventilation, p-values 0.004 and <0.001 at 5% significance level respectively.

Holding other factors constant;

Children who got fluid overload spent 24% more days in ICU compared to those who did not get fluid overload OR 1.24 (95% CI 0.99, 1.57). The odds for length of ICU stay for the children who were on inotropic support were 1.36 times the odds of those who were not on inotropic support. The odds for length of ICU stay for children who were on mechanical ventilation were 2.48 times the odds of those who were not on mechanical ventilation table (6).

CHAPTER 5: DISCUSSION

5.1 Factors associated with mortality

This study found a significant positive fluid balance of 74% (95% CI 62%, 83%). This finding is supported by Samaddar et al. 2018 who found a fluid overload of 62.7% in a study with 118 participants.[6] In addition, this study found a mortality prevalence of 47.1% (95% CI 33.2%, 61.4%) in the overload group and 38.9% (95% CI 18.3%, 63.9%) in the non-overload group which is also similar to the cited study that found 40.5% and 34% in the overload and non-overload group respectively.[6]

There was no significant association between fluid overload and mortality in this study OR 1.28 (95% CI 0.36, 4.68). A systematic review and meta-analysis by Matsushita et al. 2021with 4772 participants found a significant association between fluid overload and mortality OR 4.95 (95% CI 2.26, 10.87).[51] In support of the findings of this study, Samaddar et al. 2018 in a study of 278 critically ill children did not find a significant statistical association between fluid overload and mortality.[6] Zhu et al. 2021 did not find significant differences in mortality between the overload and non-overload group in a study of critically ill mechanically ventilated children, p-value 0.053.[52]

This study did not find a significant difference in mean age between the patients who died and those who survived. A similar study conducted by Volakli et al., 2011 did not find a significant difference in mean age between those who died and those who survived in paeditric intensive care unit.[53] This finding is in agreement with the present study. Another study by Makrufardi *et al*. reached the same finding as ours where age was not associated with paediatric ICU mortality.[54]

Our study showed that inotropic support among children admitted to the intensive care unit was beneficial despite the lack of significance. The odds of dying for the children who were on inotropic support were 0.84 the odds of those who were not on inotropic support indicating that the children who were on inotropic support were 16% less likely to die compared to those who were not on inotropic support. Overall, this study did not find a significant association between inotropic use and mortality among critically ill children. A meta-analysis of randomized controlled clinical trials conducted by Belletti et al. (2015) did not find a statistically significant difference in risks between the group on inotropic support and the one that was not RR 0.98 (0.96, 1.01).[55] This is in support of the current study.

The present study found a significant association between PELOD score and ICU outcomes p-value <0.01 before adjusting for other factors. After adjustment in the multivariable analysis, we did not find a significant association between PELOD score and mortality but a score of 10 and above had higher odds for mortality than a score of less than 10 OR 5.52 (0.73, 62.01). According to Leteurtre et al. 2010 in their study of 1806 participants, PELOD score of 10-19 was significantly associated with ICU mortality with OR 4.2 (95% CI 2.0, 8.7).[48] The two studies show that a higher PELOD score is linked to higher mortality but the lack of significance can be attributed to the smaller sample size in the current study.

The present study did not find a difference in median age between the patients who died and those who survived. This is supported by Volakli et al. 2011 in their study where they reached a conclusion of no significant difference in median age between survivors and non survivors.[53]

Our study did not find a significant difference in median weight between the children who died and those who survived. Nevertheless, the association between weight and ICU mortality became significant after adjusting for other factors under multivariable analysis. A search of literature did not yield similar studies for comparison.

5.2 Factors associated with the length of ICU stay

In our study, age did not affect the length of ICU stay before adjusting for other factors. However, Pollack et al.,2018 found a significant association between age and length of ICU stay among paediatric patients. [56] In addition, Polito et al. 2019 found a significant association between age and length of stay in paediatric ICU.[57]

This study found a significant association between percent fluid balance and length of ICU stay before adjusting for the other factors. Fluid overload had higher odds for days in ICU OR 1.24 (0.99, 1.57) after adjusting for other factors. Having fluid overload increased the length of ICU stay by 24%.

This finding is supported by Magee and Zbroesk (2010) whose study showed that fluid balance was significantly with the length of ICU stay and that it increased the length of stay by 29%.[58]

A systematic review by Alobaidi et al. also found that fluid overload was associated with longer duration of PICU stay.

We also looked at the effect of inotropic support on the length of ICU stay and it yielded an OR 1.36 (95% CI 1.10, 1.68) with a p-value of 0.004. This shows that the use of inotropes had a statistically significant association with the length of ICU stay in days and that it increased the

length of stay by 36%. In support of the current study, Ravli and Kancherla, (2019) found that the use of noradrenaline was associated with an increase in the length of ICU stay[59].

Conclusion

PELOD score was significantly associated with mortality before adjusting for other factors but became insignificant after adjustment. Weight was significantly associated with mortality after adjusting for other factors.

Despite there being no significance, some factors like fluid overload, female gender and PELOD score of 10 and above were found to worsen mortality among critically ill paediatric patients. On the other hand, some factors e.g., inotropic support reduced the odds of mortality.

The odds for length of ICU stay were increased by gender being female, fluid overload, being on mechanical ventilation and inotropic support. Inotropic use and being on mechanical ventilation were significantly associated with length of ICU stay.

Recommendations

Similar studies with larger sample size need to be conducted in order to get more insight into the relationship between fluid overload and clinical outcomes of children in critical care units.

Fluid balance measurement should be done accurately

Similar multi-site studies should be conducted to compare results

Study limitations

The non-probabilistic, small size sampling method used reduces external validity and would impede the generalizability of the results to other populations. Additionally, it is a single-center study.

Another challenge that this study may have faced was weighing critically ill and unstable children when the need to weigh arose. Such patients were not weighed but instead, this study used the closest estimated weights.

Study Timeline: Gantt chart

Time	March-July/2021	AUG/2021	Sept-Oct/2021	Nov/2021-Feb/2022	March/2022-April/2022
Proposal Development					
Proposal presentation					
Review by Ethics Committee					
Data collection					
Data analysis/Report writing and presentation					

Budget estimate in Kenya shillings

ITEMS	COST (KES)
Weighing scale	15,000
Stationary	30,000
Research assistant	45,000
Statistician	50,000
ERC Fee	2,000
Miscellaneous	20,000
Internet	25, 000
Total	**187,000**

This study will be self-funded.

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APPENDIX 1: INFORMATION FORM FOR THE PATIENTS' NEXT OF KIN

AN OBSERVATIONAL STUDY ON THE EFFECTS OF FLUID BALANCE ON OUTCOMES AMONG CHILDREN IN THE KNH ICU

Background

Fluid therapy plays a pivotal role in resuscitation of critically ill-children. Adequate intravascular volume re-establishment using timely fluid management may be crucial in saving lives. Nevertheless, pediatric patients also receive varying amounts of fluid beyond resuscitation e.g., via medication, food, or routine fluid administration. The total fluid intake can exceed fluid output leading to a positive water balance. Pediatric practitioners experience challenges regarding the kind of fluid, and dose, besides timing of intravenous fluid administration. Fluid buildup following early resuscitation might worsen the condition and increase the risk of death, hence it is imperative to monitor fluid status and ensure close assessment of very ill pediatric patients.

Purpose

This study sought to improve the quality of care and fluid management amongst the pediatric population admitted to Kenyatta National Hospital under intensive care.

Study procedures

Patients were evaluated for suitability for recruitment upon admission. Once inclusion criteria were met, informed consent was obtained. Preliminary data such as age, weight, comorbidities and PELOD score were gathered at the admission stage. The patients were then followed up over the admission period to collect data on their fluid status and the final outcomes.

Voluntary participation

Participation was voluntary. Only those whose guardians agreed to sign the consent were included in the study.

Confidentiality

The data collected was used solely for the purpose of this study. Participants were identified by unique IDs and not by names.

Benefits

There were no financial benefits from participation. Participation did not affect or delay the planned treatment.

Risk of Participation

We did not alter the patient's planned treatment. Measurement of body weight and fluid balance did not add to the risk associated with treatment.

Right of withdrawal

No participant was obligated to remain in the study until the end. Withdrawal was allowed any time and there was punishment whatsoever.

Assenting Form

I …… as a parent or I ……. as next of kin hereby give written consent for the participation in the prospective observational study assessing the effects of fluid practices amongst patients in pediatric intensive care outcomes at KNH

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I have understood the information regarding the study. I have had my questions addressed. I have the right to withdraw at any point.

Signed…… Date……..

I have explained to the patient/next of kin about the study. I have addressed all their questions and concerns to the best of my knowledge.

Signed…….. Date…….

FOMU YA MAKUBALIANO YA KUJIUNGA NA UTAFITI

Fomu hii ya utafiti ya wale wagonjwa ambao wanahudumiwa katika hospitali la Kenyatta na wamealikwa kujiunga na utafiti.

UTAFITI WA KUZINGATIA KUHUSU ATHARI ZA MAJI MINGI KWA MUDA WA KUKAA HOSPITALINI NA VIFO KATI YA WAGONJWA WALIOLAZWA KATIKA CHUMBA CHA WATU MAHUTUTI KATIKA HOSPITALI KUU YA KENYATTA

Jina langu ni Cynthia Achieng Odipo, nafanya utafiti wa shadaha ya juu katika anaesthesia kwenye Chuo kikuu cha Nairobi.

Utafiti huu unalenga kuchunguza athari za maji mengi mwilini mwa Watoto waliolazwa kwenye chumba cha watu wa hali mahututi cha Watoto hapa KNH. Maswali yataulizwa wakati wa kuingia kwenye ICU na wakati wamelazwa huko.

Utafiti utaweza kuboresha jinsi tunavyowatunza wagonjwa wetu. Kujisajili kwa utafiti huu ni kwa hiari yako. Hakuna malipo utakayo lipa Zaidi ya malipo ya hospitali. Hakuna pesa utakayo pewa kwa kushiriki. Hakuna hatari itakayotokana na kushiriki katika utafiti huu. Uko na ruhusa ya kujiondoa kwa utafiti wakati wowote. Majina yako hayatatumika katika utafiti na usiri mkubwa utatumika katika utafiti. Kama jamaa/mgonjwa utahitajika kuelewa kuhusu utafiti na kutia sahihi kibali ili jamaa /wewe usajiliwe katika utafiti.

Baada ya utafiti, uchambuzi wa takwimu utafanywa. Habari itachapishwa katika kitabu kitakachowekwa kwa maktaba ya Chuo kikuu cha Nairobi. Usiri mkuu utatumika kwa kuziweka taarifa hizi. Sasa nitakupa nafasi ya kuuliza maswali yoyote uliyo nayo kuhusu utafiti huu. Ikiwa umekubali kushiriki katika utafiti huu tia sahihi yako kwenye nafasi iliyotolewa. Maswali yoyote kuhusu utafiti huu yanaweza kuelekezwa kwa KNH-ERC, Sanduku la posta 20723, Nairobi.

FOMU YA IDHINI

Nambari ya usajili……

Mimi ni……..... mzazi wa mgonjwa

Ama mimi…….. jamaa wa karibu wa mgonjwa

Nimekubali kushiriki katika utafiti wa :

A prospective observational study on the effects of fluid balance on LOS and mortality amongst patients in PICU-KNH

Naelewa ya kwamba uchunguzi utafanyika bila madhara yoyote kwa mgonjwa. Nina uhuru wa kujiuzulu kutoka kwa utafiti huu wakati wowote.

Sahihi…….. tarehe……..

Nina thibitisha kwamba nimemwelezea mgonjwa/mzazi/mtu wa karibu wa mgonjwa kwa ukamilifu kuhusu utafiti huu na amekubali bila kushurutishwa

Sahihi…… tarehe…….

APPENDIX2: QUESTIONNAIRE

AN OBSERVATIONAL STUDY ON THE EFFECTS OF FLUID PRACTICES ON OUTCOMES CRITICALLY ILL CHILDREN IN KNH ICU

Participant Number

Biodata

- Age……..
- Sex: male ( ) female ( )

Admission Parameters:

- Admission weight……
- Admission diagnosis……
- PELOD Score……..

Patient Management (Daily at 8 am)

- Ventilated: Yes/No
- Diuresis yes/no
- Inotropes: Yes/No

Signs of excess fluids

- Development of oedema:
- Pulmonary oedema (Yes) (No)
- Developed hepatomegaly (Yes) (No)

Fluid Management (3 daily tallies)

- Cumulative fluid input
- Cumulative fluid output
- Cumulative fluid balance
- Cumulative fluid balance per cent [cumulative fluid balance/admission weight*100]…
- PELOD Score

Outcomes

- The patient is discharged: (Yes) (No)
- The patient died: (Yes) (No)
- LOS…

PELOD SCORE (Adapted from Leteurtre et al.[48])

Organ dysfunction and Variables	**Points by severity level**			
	0	**1**	**10**	**20**

Neurologic				
Glasgow coma scale	**12-15**	**7-11**	**4-6**	**3**
or	Both reactive		**Both fixed**	
Pupillary reaction				
Cardiovascular				
Heart rate				
<12 yrs	**<=195**		**>195**	
≥12 yrs	**<=150**		**>150**	
Systolic blood pressure				
<1 month	**>65**		**35-65**	**<35**
≥1month- <1 yr	**>75**		**35-75**	**<35**
≥1 year-<12 yrs	**>85**		**45-85**	**<45**
≥12 yrs	**>95**		**55-95**	**<55**
Renal				
Creatinine, µm/L(mg/dL)				
<7d	**<140(<1.59)**		**≥1409(≥1.59)**	
≥7d-<1yr	**<55(<0.62)**		**≥55(≥0.62)**	
≥1yr-<12yrs	**<100(<1.13)**		**≥100(≥1.13)**	
≥12 yrs	**<140(<1.59)**		**≥140(≥1.59)**	
Respiratory				
PaO2:FiO2 ratio, mmHg	>70		≤70	
PaCO2, mmHg(kPa)	≤90(≥11.7)		>90(>11.7)	
Mechanical ventilation	No ventilation		Ventilation	
Hematologic				
Leucocyte count, *10^9/L	**≥4.5**	**1.5-4.4**	**<1.5**	
Platelet count, *10^9/L	**≥35**	**<35**		
Hepatic				
Glutamic oxalate	**<950**	**≥950**		
transaminase, IU/L	**>60(<1.40)**	**≤60(≥1.40)**		
Prothrombin time, %standard (INR)				

Note: FiO_2 = fraction of inspired oxygen, $PaCO_2$ = partial pressure of carbon dioxide in arterial blood, PaO_2 = partial pressure of oxygen in arterial blood. *For the Glasgow coma score, use the lowest value. If the patient is sedated, record the estimated coma score before sedation. Assess the patient only with known or suspected acute central nervous system disease. For pupillary reactions, nonreactive pupils must be > 3 mm; do not assess after iatrogenic pupillary dilatation. †The use of mask ventilation is not considered to be mechanical ventilation.

15/09/2022
Chairman

EFFECTS OF FLUID BALANCE ON OUTCOMES AMONG CHILDREN IN THE INTENSIVE CARE UNIT AT KENYATTA NATIONAL HOSPITAL

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