GHANA COLLEGE OF PHYSICIANS AND SURGEONS

FACULTY OF ANAESTHESIA

SELECTED ADMISSION SERUM ELECTROLYTE LEVELS AND ASSOCIATED CLINICAL OUTCOMES IN CRITICALLY ILL PATIENTS ADMITTED TO THE KORLE-BU TEACHING HOSPITAL, ACCRA

SUBMITTED TO THE FACULTY OF ANAESTHESIA, IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE CONFERMENT OF FELLOW OF THE GHANA COLLEGE OF SURGEONS (FGCS)

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DECLARATION

I declare that this is my own work produced from research undertaken under supervision at the Korle-Bu Teaching Hospital. This dissertation has not been submitted in any form to another institution for the award of other degrees or diplomas. Authors and publishers whose works have been used in this work have been duly acknowledged in the text and list of references.

Signature……. Date: 15th July, 2023

DR LORRAINE BAFFOUR-AWUAH

SUPERVISOR ATTESTATION PAGE

We certify that this dissertation was carried out by **Dr Lorraine Baffour-Awuah** at the Korle-Bu Teaching Hospital, Accra under our supervision. We supervised the content of the study, data analysis and the write-up of the final dissertation.

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DEDICATION

This book is dedicated to my parents Prof Opoku-Baffour-Awuah and Mrs Felicia Baffour-Awuah (both of blessed memory). My husband and beautiful children: Daniel, Kobby, Awurama and Nhyiraba. My brothers Prof Bernard Baffour-Awuah and Mr Eric Baffour-Awuah and my new mother Mrs Doris Odoi.

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LIST OF ABBREVIATIONS

ICU	Intensive Care Unit
CCU	Critical Care Unit
CICU	Cardiac Intensive Care Unit
PICU	Paediatric Intensive Care Unit
MICU	Medical Intensive Care Unit
HDU	High Dependency Unit
ESRD	End stage renal disease
MODS	Multiple Organ Dysfunction Score
AKI	Acute Kidney Injury
ABG	Arterial blood gas
SOFA	Sequential Organ Failure Assessment
APACHE	Acute Physiology and Chronic Health Evaluation
SAP	Simplified Acute Physiology
COVID-19	Corona Virus disease-19
EEG	Electroencephalogram
ECMO	Extracorporeal membrane oxygenation
ICF	Intracellular fluid
ECF	Extracellular fluid
LOS	Length of stay

ABSTRACT

INTRODUCTION

Electrolytes are minerals that carry an electric charge when dissolved in body fluids (serum) such as blood. Disturbances in serum electrolyte levels are associated with multiple organ system dysfunction; cardiac, respiratory, neuromuscular, immunologic and haematologic function. It is therefore important for clinicians to understand the electrolyte pathophysiology in critical illness. This study therefore seeks to determine some selected serum electrolyte (Phosphate, Magnesium, Calcium, Sodium, Potassium and Chloride) levels and their effect on critically ill patients.

AIM

To determine the admission levels of selected serum electrolytes (Phosphate, Magnesium, Calcium, Sodium, Potassium and Chloride) and their association with clinical outcomes in critically ill patients at the Korle-Bu Teaching Hospital (KBTH), Accra.

METHODOLOGY

This was a longitudinal study involving 26 critically ill patients admitted to the Surgical Ground Floor Intensive Care Unit (ICU) and High Dependency Units (HDUs) of KBTH. Laboratory determination of serum electrolytes (Phosphate, Magnesium, Calcium, Sodium, Potassium and Chloride) of the critically ill patients was done at admission and their SOFA scores calculated. Clinical outcomes such as Length of ICU stay (LOS), duration of mechanical ventilation, duration of inotropic support and mortality were measured upon follow up of the patients. The relationship between the measured electrolytes and their association with clinical outcomes was determined using the Pearson correlation co-efficient. Fisher's Exact test was used to determine the effect of the measured serum electrolytes on mortality.

RESULTS

The mean admission serum electrolyte levels were: Phosphate (1.35(± 0.84) mmol/l), Magnesium (0.83 (± 0.25) mmol/L), Calcium (1.12 (±0.12) mmol/l), Sodium (139 (± 5.3) mmol/L), Potassium (4.32 (±1.06) mmol/L) and Chloride (104 (±6) mmol/L).

There was a positive significant association between serum phosphate and serum magnesium (p-value=0.011) and a non-significant positive association with serum calcium levels (p-

value=0.748). There was however a non-significant negative association between serum calcium and serum magnesium levels at admission (p-value=0.175).

There was a significant positive correlation between serum phosphate and SOFA scores (p-value=0.041) and mortality (p-value=0.110). A non-significant negative correlation was found between serum phosphate and duration of ventilatory support (p-value=0.638), inotropic support (p-value=0.718) and LOS (p-value=0.683).

There was a non-significant positive correlation between serum magnesium and SOFA scores (p-value=0.912) and mortality (p-value=0.199). A non-significant negative correlation was noted between serum magnesium levels and duration of inotropic support (p-value=0.655) and LOS (p-value=0.772).

There was a non-significant positive correlation between serum calcium levels and SOFA scores (p-value=0.912), LOS (p-value=0.439), and duration of inotropic support (p-value=0.333). A non-significant negative correlation was found between serum calcium levels and mortality (p-value=0.240). Hypernatraemia and hypophosphataemia were associated with high mortality, though not statistically significant.

CONCLUSION

Derangements in admission serum electrolyte levels had an effect on SOFA scores, LOS, duration of inotropic support, duration of ventilatory support and mortality in critically ill patients. Hypernatraemia and hypophosphataemia were associated with hundred percent mortality.

KEYWORDS:

Intensive care unit, Phosphate, Calcium, Magnesium, Admission, Electrolytes, critically ill

patients

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CHAPTER ONE

INTRODUCTION

1.1 BACKGROUND

Critical illness is a life-threatening multisystem process that can result in significant morbidity or mortality[1] usually requiring support of one or more organ systems. Critical care medicine specialises in treating patients who are extremely ill most often in an intensive care unit (ICU). This is a facility manned by experienced specialists and personnel (including intensive care physicians, nurses, respiratory therapists, dieticians etc) with advanced supportive care, such as the ability to offer significant organ system support for high-risk patients. A number of hospitals and centers dedicate separate units for groups of patients with special needs of care (e.g., cardiac, neurologic, paediatric, trauma, surgical, obstetric or neonatal patients). ICUs have a high nurse to patient ratio to provide the necessary high intensity of service, including treatment and monitoring of physiologic parameters.

Electrolytes are minerals that dissolve in body fluids and carry an electric charge. They play a crucial role in many biochemical processes and are involved in but not limited to cardiac activity, nerve excitability and signal transduction, energy production, immune function and acid-base balance.

Disturbances in fluid and electrolytes are among the most common clinical problems encountered in the intensive care unit. Literature has reported that fluid and electrolyte imbalances are linked to an increased risk of morbidity and mortality among patients who are critically ill[2]. Electrolyte disturbances are involved in many disease processes, and are an important component of patient management.

Acute phase responses to critical illness have been linked to several metabolic disturbances such as hypo/hyper- calcaemia, phosphataemia and magnesaemia[3]. Disorders of these electrolytes are common in patients admitted to the ICU, however, continuous observation and replacement of electrolytes is still suboptimal [4]. Most research focuses on individual electrolytes without considering their associations with particular deficiencies [3]. Since calcium, magnesium, and phosphate are vital for human physiological functions, a change in their normal levels can cause clinical illness and potentially fatal consequences. For instance, calcium and phosphate are interdependent, and when either is out of balance, the other is frequently impacted. Due to the diverse physiological relevance of the study electrolytes, it is

imperative for clinicians to have a thorough understanding of the factors affecting their homeostasis. Furthermore, knowledge of the above electrolytes and their functions highlights the need for routine monitoring and correction of derangements if any are present; especially in the management of the critically ill population.

1.2 PROBLEM STATEMENT

According to ICU protocols in the Korle-Bu Teaching Hospital, Serum Calcium and Magnesium levels are routinely assessed and corrected in the critically ill. However, the inter-relation between Calcium, Magnesium and Phosphate necessitates that Phosphate levels be measured and corrected at the same time. Presently, Phosphate levels are not routinely measured or corrected in critically ill patients in the intensive care unit at the Korle-Bu Teaching Hospital. In a study by Baker et al it was discovered that hypophosphatemia was the most frequent and under estimated electrolyte imbalance in the ICU. Occasionally, Phosphate is added to the patients' routine drugs without any empirical evidence of phosphate deficiency. Prevalence for derangements in serum levels for all study electrolytes in critically ill patients was 31%, 34% and 47% for Magnesium, Calcium and Phosphate deficiency respectively[3] . Derangements, especially deficiency of Phosphate, have been shown to be associated with prolonged ICU and hospital stay, prolonged duration of mechanical ventilation and increased mortality[5]. This further elucidates the need to ensure phosphate homeostasis in the critically ill patient. In relation to critical care in Ghana and the West African sub-region, there is a paucity of data in relation to these serum electrolyte levels and their influence on patient outcomes, thus increasing the importance of this study.

1.3 JUSTIFICATION

As a middle- income sub-Saharan country, the enormous cost of ICU care is often crippling to the health sector. Ghana suffers from a severe scarcity of staff and critical care beds in ICUs, which are unevenly dispersed around the nation [6]. Many individuals admitted to the ICU cannot afford the care rendered. Even if financial issues are not taken into account, ICU bed availability is a severe drawback. A study by Siaw-Frimpong et al revealed that there was a total of 113 adult and 36 paediatric ICU beds for a population of 30 million, (working out per capita as 0.5 ICU beds per 100,000 people). Countries like United States of America and Spain have 34.7 and 9.7 ICU beds per 100,000 people respectively. Due to the constraint of limited availability of ICU beds it is imperative to institute measures that can potentially enhance patient recovery and shorten duration of ICU stay. Thus, factors contributing to the prolongation of ICU stay must be investigated and avoided. Phosphate plays a vital role in

many biochemical processes crucial for cardiac, respiratory, immunologic, haematologic and neurological function.[7] Some studies have shown that derangements of Serum phosphate leads to prolongation of duration of ventilatory support and longer ICU stays[5]. The colossal impact that this electrolyte and its derangement has or could have on patient outcomes have been somewhat ignored in the institution's protocols in the management of the critically ill patient. Homeostasis of Phosphate, Magnesium and Calcium are inter-related hence they should not be studied in isolation. Most studies focus on individual electrolytes without taking the inter-relationship between specific deficits into account[3]. There are very few studies of disorders of calcium, magnesium, and phosphate among adult critically ill patients[4]. In critical illness in which a myriad of processes already leads to depressed immunity, portals of possible improvement of immune status should be looked at. This is because the presence of a strengthened immunity could expedite recovery and hence equate to shorter ICU stays. Paucity of data pertaining to Serum Phosphate, Magnesium and Calcium levels in the critically ill patient in our setting has necessitated this study.

1.4 HYPOTHESIS

NULL HYPOTHESIS

Admission Serum levels of Phosphate, Magnesium, Calcium, Sodium, Potassium and Chloride will not have any impact on patient outcome in the ICU.

ALTERNATE HYPOTHESIS

Admission Serum Levels of Phosphate, Magnesium, Calcium Sodium, Potassium and Chloride will have an impact on patient outcome in the ICU.

1.5 AIM

To determine the admission levels of selected serum electrolytes (Phosphate, Magnesium, Calcium, Sodium, Potassium and Chloride) and their association with clinical outcomes in critically ill patients at the Korle-Bu Teaching Hospital (KBTH), Accra.

1.6 SPECIFIC OBJECTIVES

1. To determine the admission levels of some selected serum electrolytes (Phosphate, Calcium, Magnesium, Sodium, Chloride and Potassium) of critically ill patients admitted to KBTH adult surgical ICUs.
2. To determine the relationship between the admission levels of some selected serum electrolytes (Phosphate, Calcium and Magnesium) in critically ill patients admitted to KBTH adult surgical ICUs.

3. To determine the effect of admission levels of some selected serum electrolytes (Phosphate, Calcium and Magnesium) on SOFA scores at admission, duration of ICU stay and duration of inotropic support in critically ill patients admitted at KBTH adult surgical ICUs.
4. To determine the effect of admission Serum Phosphate levels on duration of mechanical ventilation.
5. To determine the effect of admission Sodium, Chloride and Potassium levels on the SOFA score and mortality.

CHAPTER TWO

LITERATURE REVIEW

The Critically Ill Patient

Intensive care, commonly referred to as critical care, is a branch of medical care that is in charge of managing patients who have acute, life-threatening organ malfunction or who are in danger of developing multiple organ dysfunction. The approach, more often than not is a team approach involving multiple disciplines in the management of these patients requiring Intensive care.[8]

In clinical practice, the critically ill patient is qualified as one who has multi-system dysfunction requiring support for the organs that have already failed or are failing. These processes pose an extreme morbidity or mortality threat to the patient.[1] The critical illness is usually preceded by an injury/trauma, noxious insult or infection. When the physiological deterioration exceeds the capacity of the body to recover or if the appropriate therapies are not instituted in a timely manner after prompt diagnosis, then the cascade begins. Though quite a challenging task, when acutely ill patients or patients who have decompensated are identified early outcomes are potentially better.[9]

Care for extremely unwell patients is the specialty of critical care medicine. These patients are most effectively cared for in an ICU staffed by trained professionals. Some intensive care units in hospitals have separate facilities for particular populations (e.g., cardiac, trauma, surgical, neurologic, paediatric, obstetric or neonatal patients). ICUs have a high nurse-to-patient ratio (1 nurse per 2 patients) in order to offer the required high level of care, including therapy and advanced monitoring of physiologic parameters.[9] These units specialise in providing advanced organ support where required whilst identifying and treating any pathological processes precipitating the critical condition of the patient. Optimisation of the patient's physiological state is pivotal to patient management and improving outcomes and survival.[1] It is essential to understand that the identification and subsequent management of the underlying pathology whilst concurrently providing the patient with the required advanced organ support are the mainstays of critical care.[9] A multi-disciplinary team is usually responsible for the care of these extremely ill patients often led by the critical care physician. A key member of the management team is also the primary care physician who plays a role in the treatment process as they usually are essential to managing the primary pathology leading to the deterioration of the physiological state of the patient.

The ICU Structure

Critical care has evolved significantly since its inception in the 1950s in Denmark when individuals inflicted with poliomyelitis required assistance with breathing due to the effects of the disease. Negative pressure ventilation was the employed method of respiratory support at that time, however due to its association with significant mortality rates positive pressure ventilation was developed[10].

Patients were often aggregated at a common location receiving heightened nursing care with ventilatory support from hand-held devices powered by students. It was then observed that the mortalities were on a downward trend.[10] Since this time, more than seven decades ago, critical care provision has become an integral part of healthcare delivery.

An ICU can be defined as an organized system responsible for the provision of intensive specialised medical and nursing care to the critically ill. The ability to provide sophisticated monitoring and numerous physiologic organ support modalities during periods of life-threatening organ failure or insufficiency is a crucial component of an ICU.[8] Categorisation of ICUs are varied depending on how it is run by the medical personnel. A numerical grading system exists that stratifies ICUs from 1 to 3 depending on the intensity of the care they provide.

A level 1 ICU facility is one that has the ability to provide non-invasive monitoring coupled with oxygen and more advanced nursing care compared to the general ward. An ICU qualifies to be a Level 2 facility when it provides basic life support for a limited period alongside the ability to monitor patients using invasive methods. A level 3 ICU is specialised enough to provide the full spectrum of monitoring and possesses technologies available for organ and life support. Typically, it plays a crucial role in the development of critical care services through research and education.

An ICU may be also classified according to the pathologies or clinical conditions treated in it (e.g., burns, neurosurgical, trauma, medical or surgical ICUs) or by the age group of the patient admitted into that facility (e.g., neonatal, paediatric, adult). Specialised intensive care units include medical, surgical, paediatric and neonatal intensive care units

The question of who is clinically responsible for the decision-making pertaining to the care of the critically ill patient has also led to another prong for the classification of an ICU. When all major decisions are made by the Intensivist this system is referred to as a closed system. Here the primary care physicians are involved in the care only when specialised procedures such as angiography, endoscopies or surgeries are required or when consultations are required for

specific issues or questions that arise in the course of the patient's care. An open ICU is defined as one where the patient is admitted into the unit by the attending primary care physician. All decisions with regard to the patient's care is taken by the primary care attending and he /she possesses full admitting rights. A trained critical care physician is only involved when a consultation is required. On the other end of the spectrum is the closed system of ICU staffing. In this system a trained Intensivist or a physician trained in critical care medicine is the one whom the end responsibility of all treatment decisions lies. Internationally the debate as to which model has better outcomes speaks more for the closed system[11].

In the year 2000, a hospital in the Netherlands converted their surgical ICU model from an open one to a closed one. They found a significant mortality benefit resulting in a reduction in postoperative mortalities among patients for surgical procedures who had high risk .[12] Yang et al. observed that the open model of the ICU structure was related to greater mortality compared to the closed system. Their results elucidated that the intensivist-led management of the critically ill patient is associated with appreciable reduction in mortality rate .[13]This emphasizes the importance of having a trained physician in critical care medicine as the physician in charge of the management of critically ill patients. . Around the world however controversies still exist as to the better of these models in patient management. Worldwide, largely the closed system is in operation except in the United States which implements mainly the open format (Life in the fast lane).

The study sites used for this study, the Ground Floor Surgical ICU, first floor Surgical recovery and the First floor Labour ward recovery operate the closed system.

Table 2. 1 .World Federation Societies of Intensive and Critical Care Medicine (WFSICCM) Classification of Intensive Care Units.

	LEVEL 1	LEVEL 2	LEVEL 3
Unit Design	Dedicated geographic area	Central monitoring in a dedicated geographical area	Dedicated geographical region, specialized patient care zones, and central monitoring station
Treatment	Non-invasive respiratory support	Ventilatory Support, Inotropic Support and Intermittent renal replacement therapy	Ventilatory Support, Inotropic Support and Continuous renal replacement therapy
Capacity	Short-term support of mild organ dysfunction	Basic support of organ dysfunction	Complex support of organ dysfunction
Health Care Personnel	Nurse patient ratio 1:3 or 1:4. Physicians with some critical care experience available during the day	Minimum nurse-to-patient ratio of 1:3. Physicians with skills in critical care available during the day and at night	Nurse patient ratio 1:1 or 1:2 Physicians with ICU training on call 24/7
Monitoring	Non-invasive or minimally invasive	Invasive	Advanced Invasive
Education and Research	Ad hoc educational activities and basic quality improvement programs available	Structured instructional activities for personnel, structured quality improvement program, and ad hoc clinical research participation	Formal educational programs for staff with training for residents and Fellows. Active involvement in clinical research.

Criteria for ICU Admission

Protocols for admission into the ICU varies from institution to institution. The type of ICU structure operated by the facility would determine who has the prerogative to admit into the unit. Although there is not an established criterion that governs the admission of a patient into the ICU, these patients are usually severely ill with existing organ failure or impending organ failure. This is usually in the face of physiological deterioration from a pathological insult.[14] As per the facility, at the Korle-Bu Teaching Hospital (KBTH) the ICU Protocol published in 2017 outlines the following as criteria for admission into the intensive care unit:-

1. The patient's clinical condition or the decompensation process should potentially be reversible.
2. Patients who are critically ill and require ventilatory and/ or haemodynamic support.
3. Patients with airway compromise or at risk of eminent airway compromise
4. Post-operative patients who require ventilatory or haemodynamic support and advanced monitoring. Some patients are declared critically ill as a consequence of intra-operative events either due to the surgical procedure or anaesthetic causes. Many of these patients have a good outcome once they receive adequate , relevant organ support for a limited duration until they are physiologically stable.[15]

Early referral is essential to recovery. If the referral to the ICU is delayed until the patient has decompensated, clinically chances of survival are further narrowed.[16]To curtail this from happening the assessment of patients implementing scoring systems should be executed promptly.

These early warning systems or scores are instruments utilised by healthcare providers to identify the earliest indicators of clinical deterioration in order to initiate the appropriate early intervention and therapy. These include enhancing monitoring and vigilance or deploying a rapid response or medical emergency team.

Care and Organ support in the ICU

ICUs are specialised hospital wards that provide treatment and sophisticated monitoring for severely ill patients. These units are often manned by staff who are specifically trained healthcare professionals to care for very sick individuals. The care of the critically ill is usually a multi-disciplinary team effort consisting of but not exclusive to Critical care Nurses, Surgeons, Nephrologists, Cardiologists, Dieticians, Physiotherapists and Clinical Psychologists.

The intensivist, who is a physician who has been trained in critical care medicine, is the team lead and ultimately the responsibility of all medical decisions made is reposed on the team lead.[17] Studies have shown that a well-co-ordinated and structured multi-disciplinary approach to the critically ill patient leads to a reduction in morbidity and mortality. [18]

The monitoring equipment found in these specialised wards are sophisticated to offer advanced monitoring. Apart from heightened monitoring, a key component of ICU care is often ventilatory support. An unspecified ICU in a sub-Saharan country found that almost half (49.7%) of their critically ill patients required ventilatory support.[19] Intensive Care Units are also referred to as Critical Care Units (CCUs) or Intensive Therapy Units (ITUs). Support for organs that have failed or are failing occurs with heightened monitoring and ideally a 1:2 patient to nurse ratio to enhance care. The level of care and the degree of organ support that can be given is largely determined by whether the establishment is classified as a level 2 or a level 3 ICU. Both levels can offer support to the cardiovascular, respiratory and renal organ systems however to varying extents. A level 3 ICU has the ability to offer more sophisticated and technologically advanced organ support and is able to also offer neurological monitoring.[9]

A level 2 ICU or an HDU has the ability to offer non-invasive and invasive ventilation and arterial blood gases (ABG) in terms of respiratory support. Regarding the cardiovascular support available it involves administration of vasopressors and invasive blood pressure monitoring. In support of the renal system these facilities are able to offer some renal replacement therapies and ensure close fluid balance control.

A level 3 ICU category has the ability to offer all the above as well as invasive ventilation, Extra-corporal membrane oxygenation (ECMO), carbon-dioxide removal in some selected centres, advanced cardiac output monitoring, ventricular assist devices, intra-aortic balloon pumps and renal replacement therapies. Of extreme relevance is the availability of neurological

support and advanced neurological monitoring in the form of encephalograms (EEGS) and intra-cranial pressure monitoring

Electrolytes

Electrolytes are capable of conducting electricity when dissolved in bodily fluids[20]. They provide a variety of key functions in the body and are essential for physiological equilibrium. Some of their functions include acid-base balance, fluid balance, effective functioning of muscles, nerves and cardiac contractility. These chemical substances are found in either the intracellular (ICF) or extracellular (ECF) fluid compartments.

The major cations found in the intracellular compartment are Potassium and Magnesium whilst those that are predominately found extracellular fluid are Sodium and Calcium. When considering anions found in the two fluid compartments: Chloride and Bicarbonate are the electrolytes that dominate the extracellular space and Phosphate does the same in the intracellular fluid compartment.

It is essential to note that these electrolytes may occur in both fluid compartments at the same time but predominate in the compartments in which they originate. For the body's physiological systems to be in equilibrium or homoeostasis said to exist then all these electrolytes should be within their normal levels or ranges. An imbalance is said to occur when these electrolytes have their levels being too high or too low and this may be without any symptom or may lead to life-threatening conditions.[21]

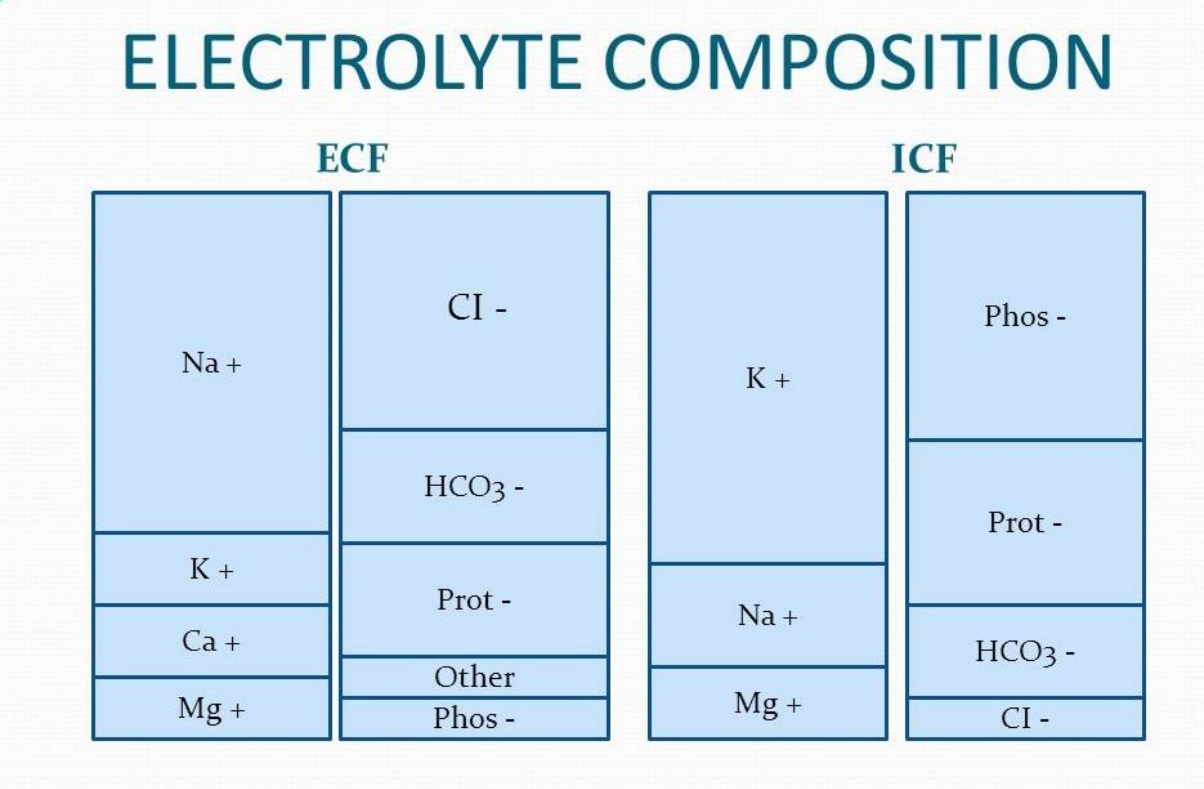


Figure 2. 1. Electrolyte distribution in body fluid compartments

Source:[22] https://slideplayer.com/slide/3786733/

Uses of Electrolytes

These chemical substances are responsible for maintaining the body's state of physiological equilibrium. They do this by playing multiple roles in many daily functions of cell activity, single organ actions and the ability of entire organ systems functioning. These electrolytes are an extremely important component of fluid balance in the body. Some are also cardinal to ensure cardiac contractility. The role played by others are seen in nerve conduction, muscle activity, coagulation of blood, the formation of strong and healthy bones and teeth and cell division. Others are also involved in energy formation, cell membrane and Deoxyribonucleic acid (DNA) formation. In critically ill patients, fluid and electrolyte imbalances or derangements can lead to an escalation in morbidity and mortality rates.[2]

Table 2. 2 Functions of Electrolytes and normal reference ranges

ELECTROLYTE	FUNCTION IN THE BODY	NORMAL ADULT RANGE
Calcium	Required for muscular contraction, neuron function, blood clotting, cell division, bone and tooth health	1.2-1.4mmol/L
Chloride	Regulates fluid balance within the body	95-110mmol/L
Potassium	Regulates heart contractions, helps maintain fluid balance	3.5-5.5mmol/L
Magnesium	Essential for muscular contraction, neuron function, heart rhythm, bone density, energy production, and protein synthesis	0.7-1.00mmol/L
Sodium	Regulates fluid balance, muscular contraction, nerve function	135-150mmol/L

Sodium

Sodium is the most abundant cation in the extracellular fluid compartment. It is a crucial electrolyte in the body due to its function in fluid balance, conduction of nerve impulses and muscle contractility. Sodium is key in the maintenance of normal cellular homeostasis, fluid and electrolyte balance and blood pressure (BP) regulation. Sodium regulation in the body is ensured by body mechanisms such as thirst (leading to an increase in water intake), sweating through the skin and by the action of the kidneys(excretion and reabsorption).[23]

The homeostasis of sodium is a complex process involving also hormonal input. The average male adult has a total sodium content of 92g, distributed throughout the body, half of it being in the ECF, 11g in the ICF and 35g in the bony skeleton. ATP provides the energy for the sodium-potassium pump to maintain the concentration gradient between the ICF and ECF. This energy is needed because the shift of sodium and potassium is usually against the gradient.[24]

Absorption of sodium occurs in the intestinal wall (primarily in the distal small bowel and the colon) and in the renal tubular epithelium. This is through transport mechanisms or via specific channels. The transport of sodium mostly occurs in association with that of other substrates, e.g. amino acids, glucose, phosphates and galactose. The balance of sodium and water are closely inter-connected and regulated by the kidneys.

In the kidneys up to 100% of all filtered sodium via the glomeruli can be reabsorbed. Sodium reabsorption is stimulated by substances such as norepinephrine, aldosterone, insulin and angiotensin II. Conversely a natriuretic effect is elicited by cAMP, dopamine, cardiac natriuretic peptides and prostaglandins. Trace amounts of sodium are excreted through sweat and faeces.

Derangements in serum sodium (hypo and hypernatraemia) levels are linked with a high risk of morbidity and mortality and, when present at admission, are independent risk factors for a poor prognosis.[25]This finding was also established by Breen et al in a study amongst patients admitted to a cardiac ICU.[26]

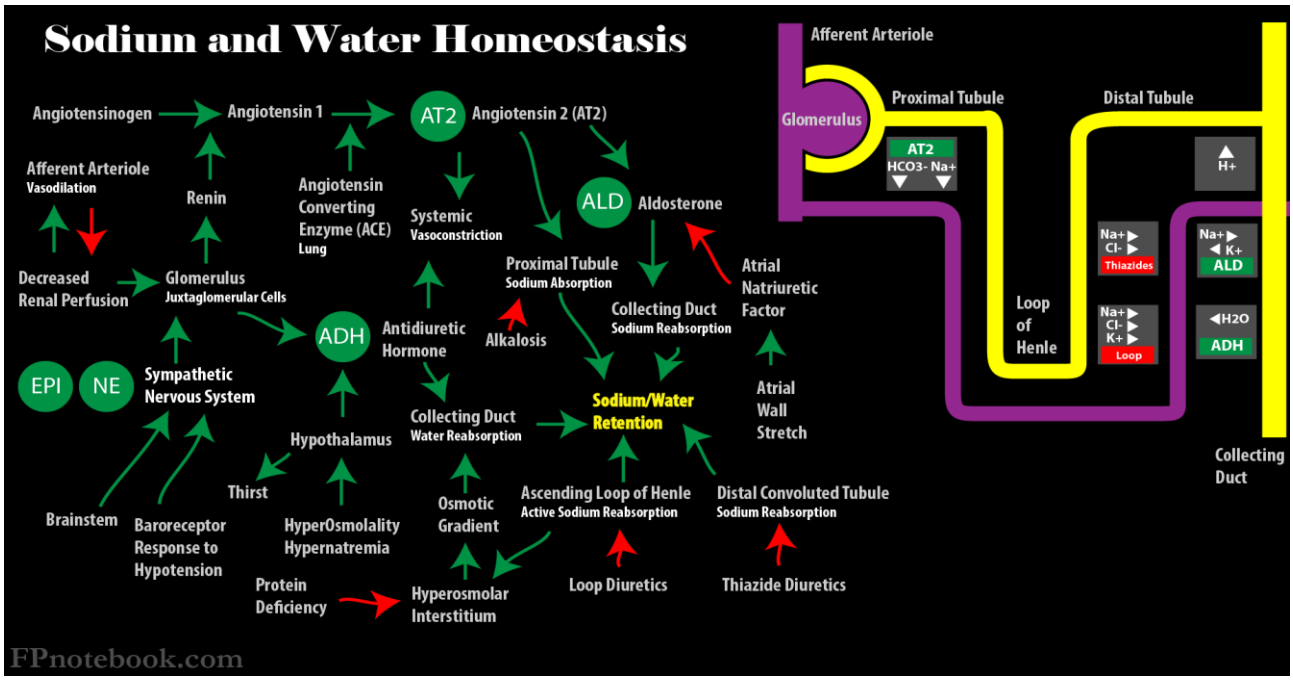


Figure 2. 2. Salt and Water homeostasis

Source: [27] https://fpnotebook.com/renal/Lab/SdmAndWtrHmsts.htm

Hyponatraemia

Hyponatraemia, which is a serum sodium concentration <135 mmol/l is the most prevalent disorder of electrolytes in clinical practice.[28] Rostami et al when they randomly sampled 300 patients hospitalized on account of COVID-19 ,found it to be the most frequently observed electrolyte imbalance their facility in Tehran,Iran.[29] It accounted for a significant 42% of all admitted patients followed by hypomagnesaemia which was present in 35% of admissions. Spasovski et al. discovered hyponatraemia in 15 to 20% of all emergency department admissions.[28] This was in their guidelines for the diagnosis and treatment of hyponatraemia which was written by a collaboration of European clinical groups including the European Society of Intensive Care Medicine (ESICM). It manifests as a wide spectrum of clinical symptoms, from asymptomatic to severe or even life threatening. This frequently occurring electrolyte imbalance may lead to increased mortality, morbidity and length of hospital stay in patients presenting with a range of conditions.

Depending on the degree of loss or retention of water and solute specifically sodium, hyponatraemia can occur in three different dynamics. Euvolemic hyponatraemia occurs when the body's overall water content increases but its sodium content remains same. This typically is asymptomatic and requires no therapy. Correction of any reversible causes is beneficial. In hypervolemic hyponatraemia both sodium and water content in the body increase, but the water gain is to a greater extent. This is observed in reversible failure of the liver, heart and kidney. In such instances, treatment of underlying causes and administration of loop diuretics as well as water and sodium restriction are the mainstays of therapy.

Hypovolemic hyponatraemia occurs when the body loses both water and sodium, but the sodium loss is larger. This is a result of thiazide administration. Withdrawal of the thiazide diuretic and replacement of the fluid deficit are therapeutic. The rate of correction of serum sodium levels in hyponatraemia should be less than 8–12 mmol/L/day to prevent osmotic demyelination syndrome. Tauseef et al in a retrospective study which pooled data from 2016 to 2021 found hyponatraemia to be of negative consequence not only to the brain but to also be implicated in mortality and morbidity.[30] In a retrospective , multi-center study between the period of January 2000 to December 2006 where adults above the age of 18 years where admitted to medical and surgical ICUs, Stelfox et al found disturbances in sodium balance (both hypo and hypernatraemia) to be associated with longer ICU stays and higher APACHE II scores.[31] Chi et al also found hyponatraemia to be associated with increased risk of mortality.[32]

Hypernatraemia

Hypernatremia is defined as a serum sodium concentration greater than 145 mmol/L. It is prevalent in clinical practice, with a prevalence of 9 percent.[33] It is associated with significant mortality 40-60%.[34] It is typically caused by an imbalance in the body's water balance processes, resulting in a greater loss of free water relative to sodium excretion. It is seldom caused by high salt consumption. It is clinically manifested by a malfunction of the central nervous system (confusion, irritability, lethargy coma) and excessive thirst in awake or conscious individuals. [35] Osmolality is the solution concentration represented as the total number of solute particles per kilogram. Because sodium is the predominant extracellular cation and solute, dysnatraemia where serum levels surpass 145mmol/L is defined as a state of hyperosmolality.

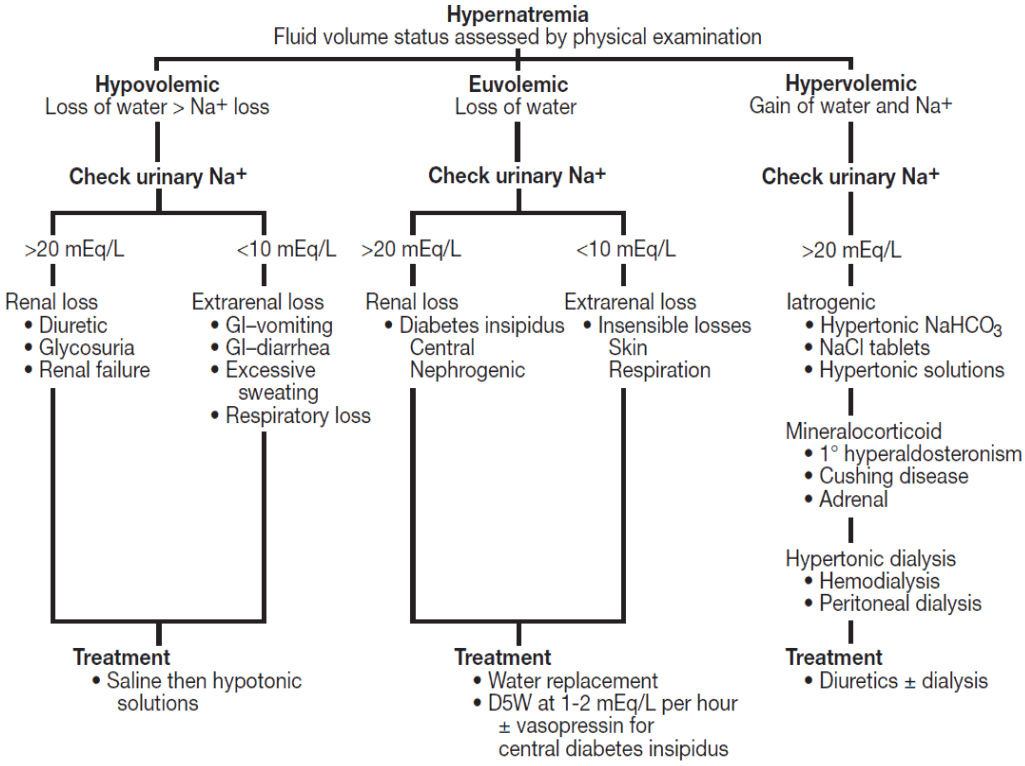
By means of Arginine Vasopressin (AVP), thirst, and the renal response to AVP, the human body maintains a normal osmolality between 280 and 295 mOsm/kg; a disturbance of all three of these processes can result in hypernatraemia. The most common cause of hypernatraemia and hypovolemia is the loss of total body water relative to the loss of solutes. Causes are categorised broadly as renal or extra-renal causes.

Some causes of extra-renal hypernatremia are fever, excessive sweating, vomiting, gastroenteritis, prolonged nasogastric drainage and burns. Renal losses occur when there is renal disease affecting sodium homeostasis or when diuresis persists due to ingestion of loop diuretics or on account of osmotic diuresis. Mannitol and hyperglycaemia are frequent osmotic diuresis triggers. Central or nephrogenic diabetes insipidus (DI) results in loss of free water. Inadequate generation of ADH, which is typically caused by head trauma, cranial neoplasm, infiltrating pituitary tumours, and sarcoidosis, can result in central DI. Nephrogenic DI is caused by the renal tubule's insensitivity to the action of ADH. This could be inherited as an X-linked disorder or acquired as a side effect of some drugs, including foscarnet and lithium

In chronic hypernatraemia (being elevated serum sodium levels for more than 48hrs), a slow correction rate (<10 mmol/L/24 h) is indicated to avoid neurological complications. In acute dysnatraemias (occurring <48 h) a rapid correction rate may be indicated.

As the neurological condition is closely monitored, it is generally recommended that half of the water deficit be supplied within 12 to 24 hours. The deficit can be managed during the next 48 hours. The maximum rate of drop in serum sodium levels should not exceed 2 mmol/L/hr. Hypernatraemia like hyponatraemia can be categorised as euvolemic, hypervolemic or

hypovolemic. Their treatments vary and treatment modalities are found in the figure below. Fluctuations in sodium levels are indicators of severity of disease and is also an independent indicator of morbidity and mortality.[36] Their treatments vary and treatment modalities are found in the figure below. A study by Lindner et al showed hypernatraemia to be associated with increased mortality rates and increased length of stay in critically ill patients admitted to a medical ICU in a University hospital in Vienna.[37]



Diagnosis and Management of Hypernatremia. D5W indicates 5% dextrose in water; GI, gastrointestinal tract; NA, sodium; NaCl, sodium chloride; $NaHCO_3$, sodium bicarbonate.
Source : Mayo Clinic Internal Medicine 8th

Figure 2. 3. Treatment of Hypernatremia

Source:[38] https://twitter.com/manualomedicine/status/955516033523122176

Potassium

Potassium is the most abundant intracellular cation and is present in all tissues in the body. It is so essential an electrolyte that its presence is needed for the normal functioning of the cell. It has a strong relationship with sodium as both electrolytes are integral in the maintenance of electrochemical gradients across membranes of cells. It is also vital for the maintenance of intracellular fluid volume.[39] The average potassium level of an adult person is approximately 40–50 mmol/kg body weight, therefore a 70-kg adult contains approximately 2800–3500 mmol

of potassium (110–137 g). [40]One (1) mmol is equivalent to 39.1mg of potassium. The serum potassium levels are maintained within narrow limits; 3.5 -5.0 mmol/L.

This is ensured by many mechanisms involved in potassium homeostasis. Most of potassium is found in the cells (150mmol/L) with only a small quantity found in the extracellular fluid. The sodium-potassium (Na+/K+) ATPase transporter maintains the electrochemical gradient across the intracellular and extracellular membranes. This active transport mechanism is needed because the intracellular concentration of potassium is roughly 30 times higher than the concentration found in the extracellular compartment.

A broad spectrum of crucial physiological processes is dependent on the strict regulation of potassium homeostasis. Resting membrane potential of cells, propagation of action potentials in nerves, cardiac, and muscular tissue, as well as hormone secretion and action, vascular tone, blood pressure control, acid–base balance, glucose and insulin metabolism, mineralocorticoid action, renal concentrating ability, fluid and electrolyte balance, and gut motility are all regulated by potassium[41]

Organs involved in the normal regulation of potassium are the kidneys, the intestines, liver and muscle. The kidneys are involved in chronic potassium homeostasis whilst the extrarenal organs manage acute potassium imbalances. Several hormones, including insulin, epinephrine, aldosterone, and glucocorticoids, maintain adequate extrarenal potassium metabolism.[42]

Potassium is excreted in sweat and faeces.

Bouadma et al in a large, observational multicentre cohort study where all critically ill patients were recruited from 22 French ICUs over a 5 year period found that both hypokalemia and hyperkalaemia were independently linked to an increased risk of 28-day death..[43]

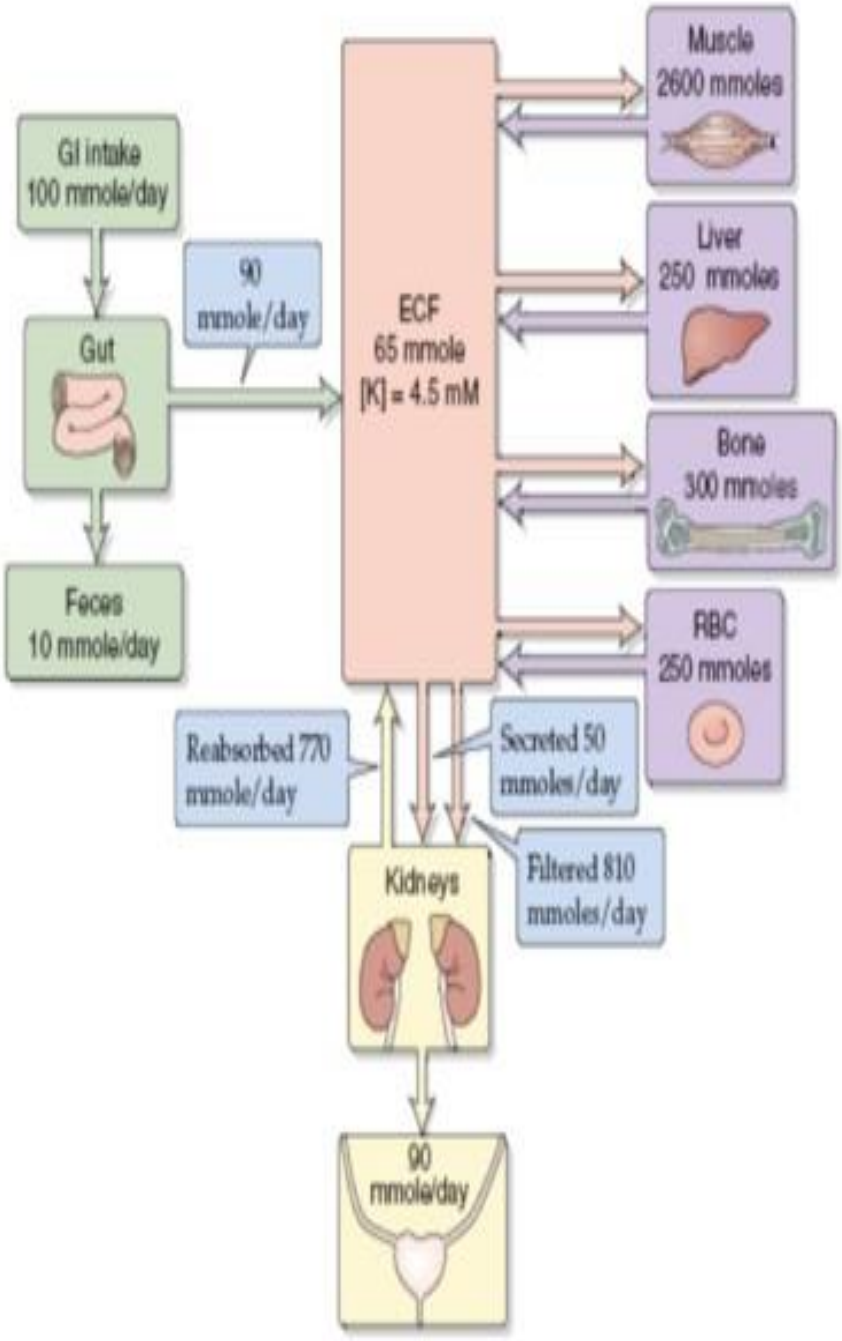


Figure 2. 4. Potassium Homeostasis

Source: [44] https://quizlet.com/188888955/506-potassium-homeostasis-flash-cards/

Hypokalaemia

This is defined as a serum potassium level below 3.5mmol/L. It is one of the most often observed electrolyte abnormalities in clinical practice. It is categorized as mild, moderate or severe when serum values are 3-3.4mmol/L, 2.5-2.9mmol/L and less than 2.5mmol/L respectively. Excessive potassium losses (renal or extrarenal), decreased potassium intake, and intracellular electrolyte shifts are the three main processes that lead to hypokalaemia.

Vomiting, excessive sweating, diarrhoea exhibit how excessive losses may result in hypokalaemia. Bartter's and Gitelman's syndrome lead to excessive loss of potassium by the kidneys also known as renal losses. Some medications such as thiazide diuretics, excessive mineralocorticoids (e.g., Cushing's syndrome, Conn's syndrome) and psychiatric conditions like anorexia nervosa may also be implicated in hypokalaemia. Alkalaemia, hypothermia and administration of albuterol(or commonly used and available in our setting, Salbutamol) which is a short acting bronchodilator all cause an intracellular shift of potassium leading to a drop in serum potassium levels.[45]

Clinical features usually occur when serum potassium<2.5 mmol/L. Some of these symptoms are cramps and muscle pain, muscle weakness, constipation, syncope, fatigue and palpitations.

Significant associations exist between abnormal serum potassium levels at admission and higher 28-day mortality however their correction by day 2 of admission improves prognosis.[46]

Chu et al found that there was a high incidence of hypokalaemia in hospitalized patients and is closely related to perioperative complications and prognosis. This was especially evident in the face of pre-operative hypokalaemia.[47]This study was a retrospective study amongst the elderly (aged 60-100 years) scheduled for elective surgery(excluding neuro- and cardiac surgeries).

Hyperkalaemia

Hyperkalaemia is when serum potassium levels are ≥ 5.5mmol/L and this is commonly found in patients who are diabetic or have chronic kidney disease or cardiovascular disease. It is a potentially life-threatening electrolyte abnormality and in the critically ill patient may lead to cardiac electrophysiological disturbances. Hyperkalaemia seldom results from high potassium intake. Like hypokalaemia, it can also be classified into three main subgroups; mild, moderate and severe when serum levels are 5.5 – 6mmol/L, 6-6.5mmol/L, ≥ 6.5mmol/L respectively.

Hyperkalaemia is associated with poor outcomes under different clinical settings and the main cause for increased mortality associated with cardiac rhythm or conduction abnormalities.[48]

A prospective, single centre study by Peng et al was conducted with over 3700 recruits. The data was pooled from the West China Hospital database and all patients who had been diagnosed with Acute Coronary syndromes were recruited. They found that patients with admission serum electrolyte levels greater than 4.5 mmol/L had a higher death rate.[49] Of interest to note from the same study was that the mortality risk was lowest in the group of patients with potassium levels of 3.5 to <4.0 mmol/L representing recruits that had normal serum potassium levels.

Mcmahon et al in a retrospective, observational study where almost 40,000 critically ill patients 18 years and above were recruited found that admission potassium concentration above the normal range was a strong predictor of all-cause mortality at 30 days after admission to the ICU.[50]

Hyperkalaemia is associated with higher mortality in individuals with chronic renal disease and ESRD receiving dialysis..[51]

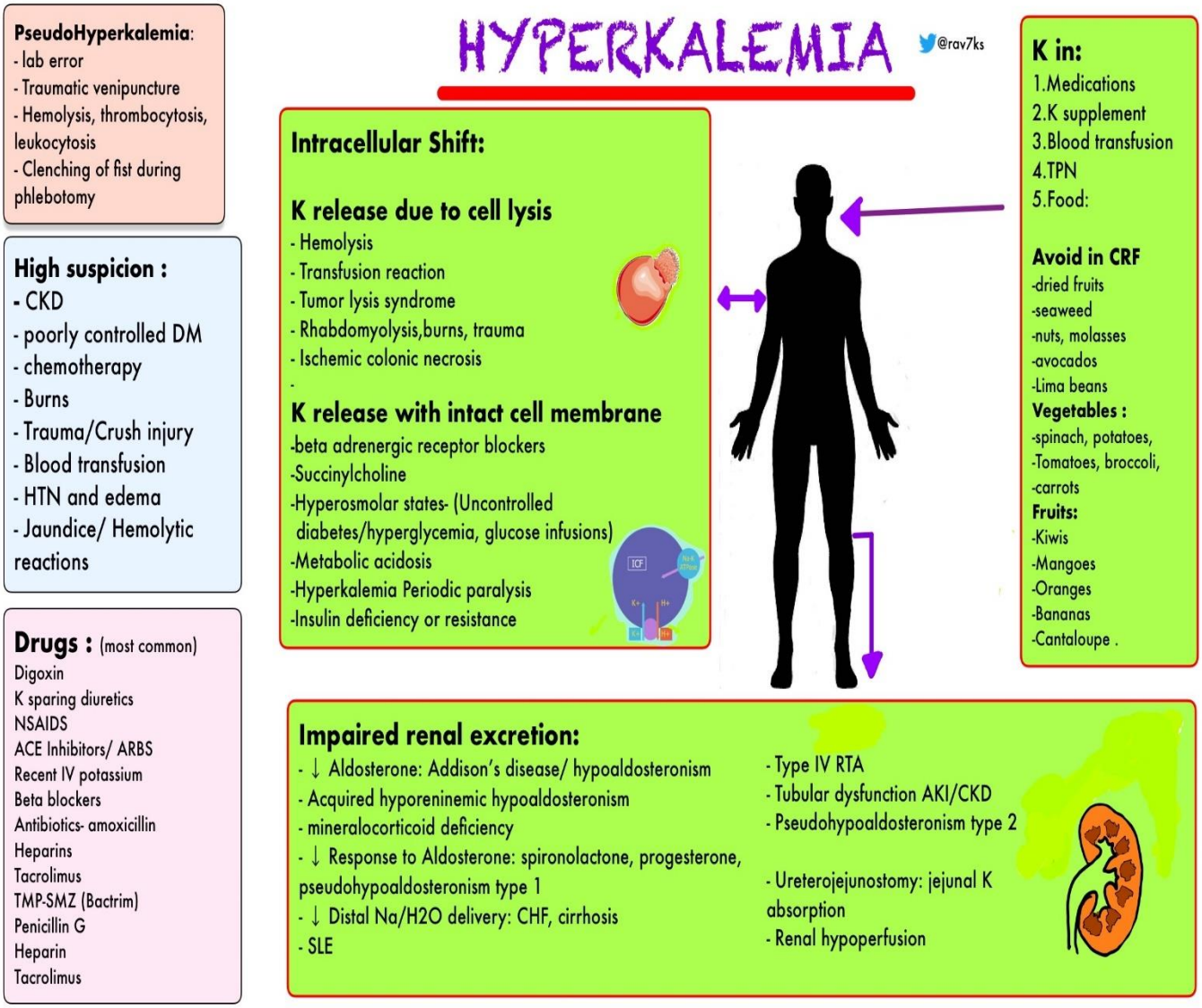


Figure 2. 5. Major Aetiologies of Hyperkalemia

Source:[52] https://www.grepmed.com/images/11651/causes-hyperkalemia-diagnosis-17

Chloride

The most abundant electrolyte in serum after sodium is chloride. It is the most predominant anion found in the extracellular space and its distribution is limited exclusively to the extracellular space. Its role is seen in many physiological roles in the body such as fluid and electrolyte balance, acid-base homeostasis and maintaining the electrochemical state of membranes and cells in the body.

Normal ranges are from 95-110mmol/L.

It is needed for the production of hydrochloric acid secreted from the parietal cells of the gastric mucosa in the stomach. Chloride is secreted by the stomach and absorbed by the small and large intestines. It can also collect in the skin. About 90% of chloride is lost via urine, while the remaining 10% is eliminated via stool and perspiration.

Isolated derangements of serum chloride levels are usually indicative of a serious metabolic derangement such as metabolic alkalosis or acidosis.[53] In patients with metabolic acidosis measurement to serum electrolyte levels of chloride is of benefit and enables the assessment of both normal and increased anion gap metabolic acidoses.[54]

Both hypochloraemia[55] (in a randomized control trial in 2699 patients with heart failure) and hyperchloraemia (in a retrospective study which enrolled 266 trauma patients)[56] was found to be associated to higher mortality.

Hypochloraemia

This is defined as serum chloride levels <95mmol/L.

Some causes of low levels of serum chloride are insufficient intake of chloride, dehydration, gastric lavage, metabolic alkalosis, administration of some diuretics and vomiting. Management is by treating the underlying cause and also includes assessment and correction of dehydration status. An intravenous (IV) saline infusion may be administered to restore your electrolyte levels as well as correct fluid deficits that may be present.

Tani et al conducted a retrospective study which recruited about 500 ICU patients in Okayama University Hospital, Japan. Using multiple regression analysis they found hypochloraemia not to be an independent prognostic factor but was associated with poorer outcomes.[57]

Hyperchloraemia

This occurs when serum electrolyte levels are above 110 mmol/L.

The kidney is essential to the regulation of serum chloride through transporters along the nephron. However, when the loss of water exceeds loss of chloride then the nephrons are overwhelmed with excess chloride.

Hyperchloraemia may occur due to dehydration or excess administration of sodium or other chlorides. It can present as a component of a normal anion gap metabolic acidosis.

Thongprayoon et al did a retrospective study of Hospital-Acquired Serum Chloride derangements and associated In-Hospital Mortality. This was in patients who were admitted with normal serum chloride levels but developed chloride abnormalities whilst on admission. It was found that hyperchloraemia was associated with increased in-hospital mortality[58] an outcome not associated with hypochloraemia. A retrospective study was conducted by Yeh et al to assess hyperchloraemia in critically ill patients and its associated outcomes. They found that hyperchloraemia was independently associated with a higher risk of ICU mortality, the onset of acute renal injury, and the development of MODS while the patient was in the ICU.[59]

Increased chloride in the body has been implicated in impaired renal perfusion, increased interstitial oedema including in the gut and kidneys and increased morbidity and mortality in critically ill patients.[60]

Magnesium

Magnesium is the fourth most abundant cation in the human body and the second most predominant intracellular electrolyte yet its levels in the critically ill are often overlooked.[61] The human body stores about 25g of Magnesium, with 53% of that amount being found in bone, 27% in muscles, 19% in non-muscular soft tissue and 1% in extracellular fluid. The range of serum values is 0.7-1.1 mmol/L (1.6-2.6 mg/dL). Magnesium is essential for about 300 enzymatic processes in the body, including energy synthesis, neuronal function, and neuromuscular transmission [62]

The main organ involved in regulating magnesium is the kidney. When magnesium is scarce, the kidneys store it, and vice versa. Renal magnesium waste is related to phosphate deficiency. Normal potassium and calcium metabolism requires magnesium. Low serum levels are usually attributed to decreased intake (Starvation, Alcoholism, patients receiving Total Parenteral

Nutrition), Endocrine Disorders (Hyperparathyroidism, Hyperthyroidism, and Diabetes Mellitus), Drugs (Loop and thiazide diuretics, Proton Pump Inhibitors, Aminoglycosides and Chemotherapeutic agents), Renal/Gastro-intestinal losses (acute/chronic diarrhoea, acute pancreatitis and familial hypomagnesaemia) and hypophosphataemia.

Its deficiency has been demonstrated in 10-20% of hospitalized patients and up to 60% in critically ill patients in a study by Zafar et al. [61] A prospective study was conducted by Djagbletey et al looking at the Prevalence and predictive factors of preoperative hypomagnesaemia among adult surgical patients. The prevalence of preoperative hypomagnesaemia was found to be as high as 68% in adults requiring emergency laparotomy. [63]Magnesium deficiency was also detected to be as high as 65 % in patients admitted to a medical ICU in the Korle-Bu Teaching Hospital in the same study. Significant and potentially fatal conditions have been attributed to hypomagnesaemia and it has also been associated with poor prognosis and increased mortality in the critically ill[63].

Hypomagnesaemia can cause anything from little tremors to generalized weakness, cardiac ischaemia, fatal arrhythmias, and even death. [64]The most significant neuro-muscular symptom in critically ill patients may be respiratory muscle weakness. Refractory potassium may be a sign of hypomagnesaemia because low plasma magnesium levels limit intracellular potassium replacement.

Hypermagnesaemia is often iatrogenic caused by excessive administration of magnesium salts in the presence of renal impairment. Acidosis may increase the extracellular concentration and haemolysis may spuriously elevate plasma levels of magnesium. Hypermagnesaemia may occur in obstetrics patients. [65]There is extensive experience regarding the use of Magnesium Sulphate in eclampsia patients for treatment of seizures and seizure prophylaxis in Ghana.[66] This may possibly account for the most common use of magnesium possibly in Ghana.

To ascertain if admission serum magnesium had an effect on 28-day mortality, Yue et al. conducted a study. They discovered that the risk of mortality was raised by both low and high serum magnesium levels. Despite the fact that this study involved children who had been admitted to the paediatric intensive care unit (PICU), it was discovered that the optimal range of serum magnesium levels at which the risk of death was the lowest was 0.74 to 0.93 mmol/L.[67] Wang et al also found similar effects of hypomagnesaemia and hypermagnesaemia on mortality in patients with traumatic brain injury.[68]

Hypomagnesaemia

Hypomagnesaemia is defined as a plasma Mg concentration of <0.7mmol/L and is a common finding in critically ill patients.[69] Due to the fact that this is usually coexistent with low levels of calcium and potassium its manifestations are relatively non-specific . Low levels of magnesium however can have a noticeable effect on the neuromuscular, cardiovascular and metabolic functions in the body.[69]

According to their pathophysiology, the following categories can be used to categorize the causes of hypomagnesemia: Reduced intake, redistribution due to an increase in the passage of magnesium from the extracellular to the intracellular space (present in pathologies such as hyperparathyroidism, hyperthyroidism, etc.), gastrointestinal losses (diarrhoea, vomiting, or surgical resection of portions of the intestine), and renal losses.[64]

Fairley et al in a retrospective study obtained data from 1975 to 2014 about magnesium status at admission. This study however excluded the obstetric and critically ill populations. Hypomagnesaemia was found to be associated with a greater risk of mortality.[70] According to a study by Jiang et al, low serum magnesium levels at ICU admission were associated with an increased risk of sepsis, an increased risk of mortality, and an increased need for ventilatory support.[70] In a related study, it was discovered that the hypomagnesaemic group had higher Sequential Organ Failure Assessment (SOFA) scores, a longer stay in the intensive care unit, and a higher probability of death.[71]

Hypermagnesaemia

A serum magnesium level greater than 1.2 mmol/L is referred to as hypermagnesemia. Clinically, hypermagnesemia is uncommon[72]; however, it can happen as a result of iatrogenic use of intravenous magnesium sulphate in patients with chronic renal failure, in people who regularly consume laxatives that contain magnesium, to prevent seizures in high risk obstetric patients against eclampsia[73], or as a treatment for eclampsia.[74] Though its occurrence is infrequent, it is a serious electrolyte disorder, which can be fatal if not detected and treated promptly.[75]

The clinical manifestations of higher serum levels will depend on the extent of derangement of elevated levels of Magnesium in the serum. In the case of mild hypermagnesaemia, it is largely asymptomatic.[76] Therefore, only levels exceeding 2.5 mmol/L may lead to its clinical signs to become visible The clinical manifestations of hypermagnesaemia include oliguria found in

about 3% of patients, loss of patellar reflex may be elicited in about 2% , cardiac conduction disturbance(complete heart block), respiratory depression, and cardiorespiratory arrest. [77]

Hypermagnesaemia is associated with an increased requirement for vasopressor medications, a higher risk of respiratory failure, and a higher mortality rate. [77] A study by Wang et al in elderly critically ill patients being managed for pneumonia found hypermagnesaemia to be associated with heightened risk of death and longer stays in the ICU.[78] Most hypermagnesaemic patients in one study had their clinical conditions complicated by renal dysfunction in different degrees.[71] Renal function plays an important role in the metabolism of magnesium. Up until the creatinine clearance drops below 20 ml/min, the kidneys can keep the level of magnesium in balance.[72] Also in patients undergoing haemodialysis there is the risk of damaging red blood cells and releasing significant levels of magnesium into the plasma causing serum elevations of magnesium.

Sharma et al conducted a study on Corona Virus Disease 19 (COVID-19) positive patients who were hypermagnesaemic at admission. These patients had confirmed pneumonia secondary to COVID -19. They determined from this study that study recruits with high serum magnesium levels at admission were more likely to require ICU admission , ventilatory support and were at increased risk of mortality.[79]

Another study in a similar cohort i.e. COVID 19 positive patients with high serum levels of magnesium at admission had similar findings however they also established an increased need for inotropic support and increased risk of developing severe Acute Kidney Injury (AKI).[80]

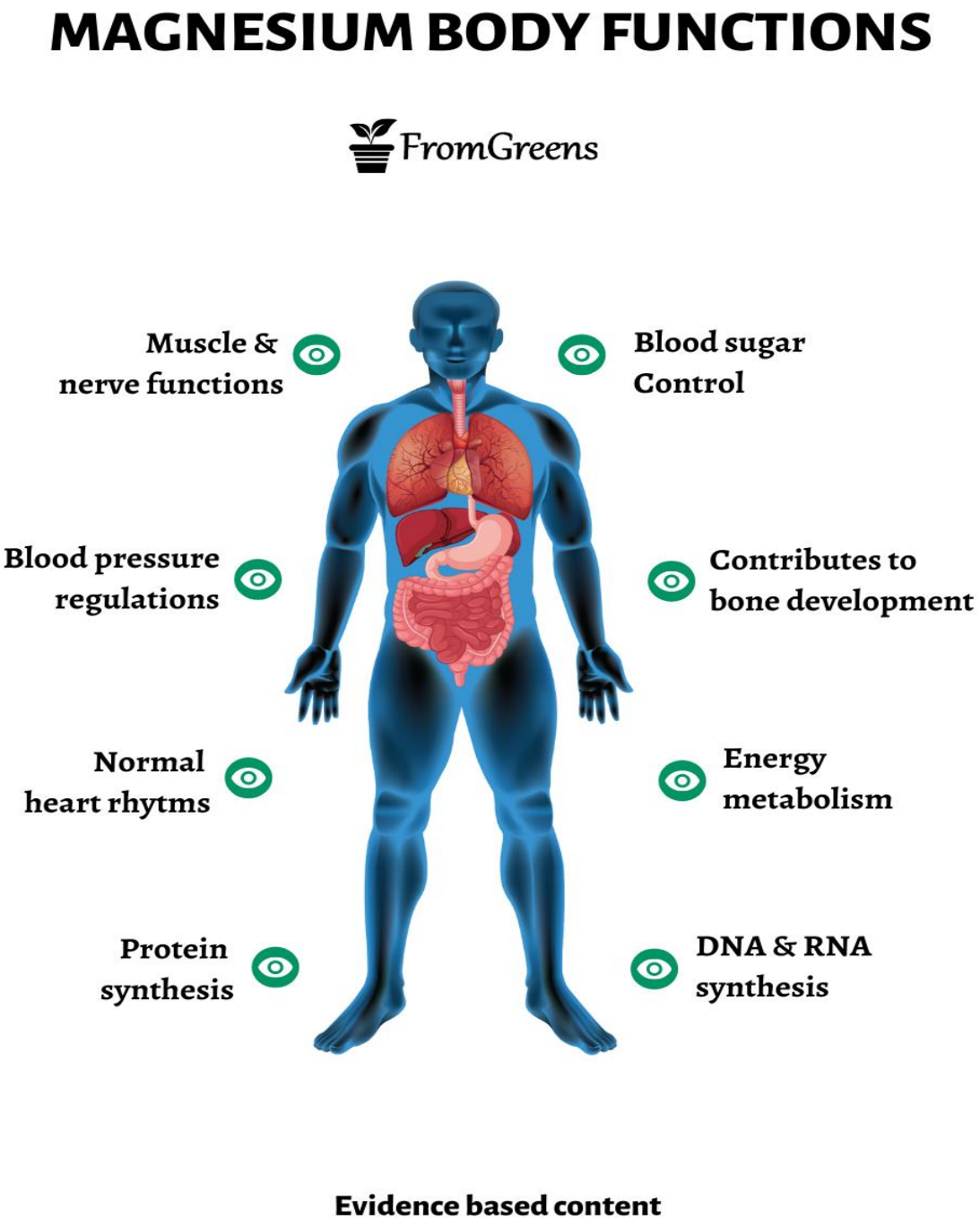


Figure 2. 6. Some functions of Magnesium

Phosphate

The most prevalent intracellular anion in the body, phosphate plays a key role in numerous physiological processes involving various organ systems. It is crucial for maintaining and developing the skeleton as well as for protein synthesis, pH buffering, cellular signalling, and energy metabolism. Of extreme importance is the fact that that it is involved in the generation of Adenosine Triphosphate (ATP) which is vital for normal nerve function and muscle contraction.

Almost all the Phosphorus is combined with oxygen to form Phosphate which is an electrolyte. Bone and teeth hold roughly 85% of the biological phosphorus, while soft tissue holds about 15%. The extracellular fluid is where the remaining phosphate, or less than 1%, is found. [81] Phosphate balance depends on a complicated interaction between the intestines, kidneys, bone, and parathyroid hormone, just like calcium homeostasis does (PTH). Aside the 85% of Phosphate that exists in bone, the remaining portions exist as free anions or become components of organophosphate compounds. These substances are found in the organism as energy (adenosine triphosphate, creatine phosphate), carbohydrates, lipids, transcriptional factors, nucleic acids, structural proteins and enzymes.

Although phosphate and calcium plasma concentrations are connected and minor in comparison to the total body content, their equilibrium is tightly regulated by hormones.[82]

Normal serum adult phosphate levels range from 0.75 to 1.45 mmol/L (2.5 to 4.5 mg/dL). A disturbance to normal serum levels can result in multiple organ dysfunction, which may involve the following organ systems: respiratory, cardiac, immunologic, haematologic or neuromuscular organ systems [7].

Hypophosphataemia

Hypophosphataemia is when serum phosphate levels are less than 0.7mmol/L.

Phosphate abnormalities are frequent in intensive care units, and low serum levels can cause tissue hypoxia, which can cause red blood cell failure, convulsions, unconsciousness, diaphragmatic weakness, rhabdomyolysis, and cardiac dysfunction (from decreased 2,3-Diphosphoglycerate)[5]. In critically ill patients, hypophosphataemia is linked to longer ICU stays, longer durations of mechanical ventilation, and higher 28-day death rates.[5,45] Wozniak et al established through their study that hypophosphataemia at admission to the ICU was associated with increased duration of stay in the ICU and prolonged duration of ventilatory support.[84]

Federspiel et al however had conflicting conclusions from their study where they found that hypophosphataemia at ICU admission was not associated with prolonged need for ventilatory support nor mortality.[85] It is possible that the fact that this was a retrospective observational study conducted at a Danish center explains the discrepancy between the results of other studies. Data was taken from 2013 and missing data was derived from multiple imputation.

One of the most common electrolyte abnormalities, hypophosphataemia has a wide range of potential causes in critically ill individuals[86]. Low serum levels maybe precipitated by a number of factors such as burns, drugs, hormonal influence, poor dietary intake, sepsis, malnutrition and alcohol withdrawal. Numerous clinical symptoms of hypophosphataemia include cardiac failure, diaphragmatic weakness, convulsions, coma, rhabdomyolysis, and dysfunction of the red blood cells as a result of tissue hypoxia (by reducing erythrocyte 2,3-DPG) [2] and compromised cellular energy storage.

Because hypophosphataemia is largely asymptomatic and frequently manifests as weariness and irritation, it is frequently misdiagnosed. Hypophosphataemia is reportedly linked to longer hospital and ICU stays[86], a higher risk of arrhythmia, and malfunction of the breathing muscles. Therefore, it is essential to identify phosphate imbalances in ICU populations and rectify them as soon as possible.

Table 2. 3. Causes of Hypophosphataemia

Hormonal triggers	Insulin, glucagon, epinephrine, dopamine
Drugs	steroids, xanthine compounds, -2 agonists, carbohydrate infusions, and phosphate-binding antacids
Respiratory alkalosis	Salicylate overdose, alcohol withdrawal, hepatic coma, sepsis, mechanical ventilation
Glucose shifts	Re-feeding after malnutrition, Treatment of DKA
Rapid cell uptake/proliferation	Acute leukaemia, post-parathyroidectomy hungry bone syndrome
Renal losses	
Drugs	Tenofovir, Imatinib, and the use of acetazolamide and metolazone as diuretics as part of glucocorticoid/mineralocorticoid therapy
Acute volume expansion	
Hyperparathyroidism—primary and secondary, Renal Transplantation, Fanconi Syndrome	
Primary renal phosphate wasting	Rickets due to X-linked hypophosphatemia Rickets caused by autosomal-dominant hypophosphatemia cancer-related osteomalacia
Decreased intestinal absorption: Poor dietary intake and/or malabsorption	
Steatorrhoea or chronic diarrhoea	
Vitamin D deficiency or resistance	

Hyperphosphataemia

This when serum phosphate levels are elevated usually above 1.45mmol/L.

Hyperphosphataemia is usually due to the kidneys inability to excrete phosphate from Acute and Chronic Kidney Disease. Other causes are from elevated exogenous phosphates in the form of enemas. Acidosis, rhabdomyolysis, and tumour lysis syndrome all exhibit a rapid release of phosphate from the intracellular space to the extracellular environment. Hypoparathyroidism causes low PTH leading to reduced renal excretion of Phosphate thus increasing serum levels.

Yang et al conducted a retrospective study on about 24,000 critically ill patients above the age of 60 years. They found that elevated serum phosphate levels were significantly associated with increased risk of ICU mortality in elderly patients. This study brought to light the potential association between abnormalities in serum phosphate, especially hyperphosphataemia, and unfavourable outcomes in hospitalized patients.[87]Al-Harbi et al also found high serum phosphate levels to be associated with higher scores to assess severity of disease in patients with sepsis who had been admitted to the ICU.[88] A study indicated that hyperphosphataemia was linked to all-cause mortality in critically ill patients. This was a finding from a retrospective study by Zheng et al.[89]

In critically sick patients who were septic, hyperphosphataemia rather than hypophosphataemia on the first day of admission to the ICU was linked to an increase in ICU and hospital mortality. These patients were admitted to medical/surgical ICUs in this study by Al Harbi et al.[90]

A study by Miller et al found hyperphosphataemia to be associated with an increased risk of mortality and reduction in the duration of ventilatory support.[91] This was a retrospective study conducted in critically ill adults with the diagnosis of sepsis/septic shock.

Table 2. 4. Causes of Hyperphosphatemia

Acute phosphate load	Rhabdomyolysis, exogenous phosphate, fosphenytoin, and tumour lysis syndrome
Cellular shifts	Metabolic acidosis
Decreased Renal Clearance	Kidney disease, whether acute or chronic, and increased tubular absorption
Hypoparathyroidism or Pseudohypoparathyroidism	
Bisphosphates	
Vitamin D toxicity	
Acromegaly	
Familial tumoral calcinosis	
Pseudohyperphosphatemia	EXOGENOUS Amphotericin B Heparin Tissue plasminogen activator ENDOGENOUS Hyperglobulinaemia Hyperlipidaemia Haemolysis Hyperbilirubinemia

Calcium

The average adult body contains 1-1.3 kg of calcium. In serum, total Calcium measures about 2.1-2.6mmol/L (8.4- 10.2mg/dL) and exists in three forms. It is bound to proteins, mostly albumin, forms organic complexes with anions such as citrate, lactate, or phosphate, or exists as a free ionized form called ionized calcium.[92]

Calcium plays a significant role in cell structural components and biochemical signalling in and out of the cell and is crucial for myocardial function[93] and vascular tone. It is fundamental for neuromuscular function and coagulation. It is the most prevalent cation in the body and is found in the bony skeleton, soft tissue and extracellular fluid. Approximately 99% of the body's calcium is stored in the bones, whereas just 1% is found in soft tissue and extracellular fluid. Approximately 8.7 mmol (350 mg) of calcium is found in blood plasma at a concentration of around 2.5 mmol/L (10 mg/dL).

Approximately 40% of 350 mg are bound to protein (mostly albumin, but also globulins) and 10% are complexed with a variety of anions (bicarbonate, lactate, phosphate, etc). The remaining 50% circulates as "free" ionized calcium (Ca2+ at concentrations between 1.1 and 1.3 mmol/L (4.4 and 5.2 mg/dL). Essentially, only the ionized calcium portion is physiologically active. To assess the Calcium status of a patient, direct measurements of the Ionized Calcium concentration should be taken.[94]

It is crucial to maintain blood calcium levels within a tight range. If serum calcium levels are excessively high or too low, muscle and nerve function is compromised. The body only gets the calcium it needs through the diet or from supplements this is because Calcium cannot be obtained endogenously. A diet that is low in Calcium or the impaired ability of the body to absorb enough calcium from diet or other exogenous sources causes Osteoporosis. This occurs when bones to become weak because Calcium is extracted from them to compensate for the low Serum levels.

Calcium levels are regulated by Gastro-Intestinal absorption and renal losses. Serum Ionized Calcium is primarily governed by the action of Parathyroid hormone (PTH) and Vitamin D. It acts on bone and kidney tissue by causing bone turnover and reabsorption of calcium from the renal tubules respectively.[95] Hypocalcaemia occurs due to Hypoparathyroidism, Vitamin D deficiency, Malabsorption, Magnesium deficiency and Acute Pancreatitis.

Serum calcium levels are tightly regulated and closely related to serum phosphate and magnesium levels; hence, any disruption in serum calcium homeostasis is accompanied by changed serum phosphate and magnesium levels.[96].

Zang et al found Calcium supplementation to be of benefit for critically ill patients and improving their clinical outcome with regards to 28-day mortality[97]. However, the study could not establish a direct causal relationship between calcium supplementation and mortality in critically ill patients. Contrary to the previous findings, Collage et al. (in an animal investigation) demonstrated that calcium supplementation mediated increased inflammation and vascular leakage, leading to increased organ dysfunction and mortality. In addition, they discovered that this adverse effect of calcium supplementation was related to calcium/calmodulin-dependent protein kinase signaling[98]. Thus, contradicting the findings of Zang et al regarding routine supplementation and impact on mortality.

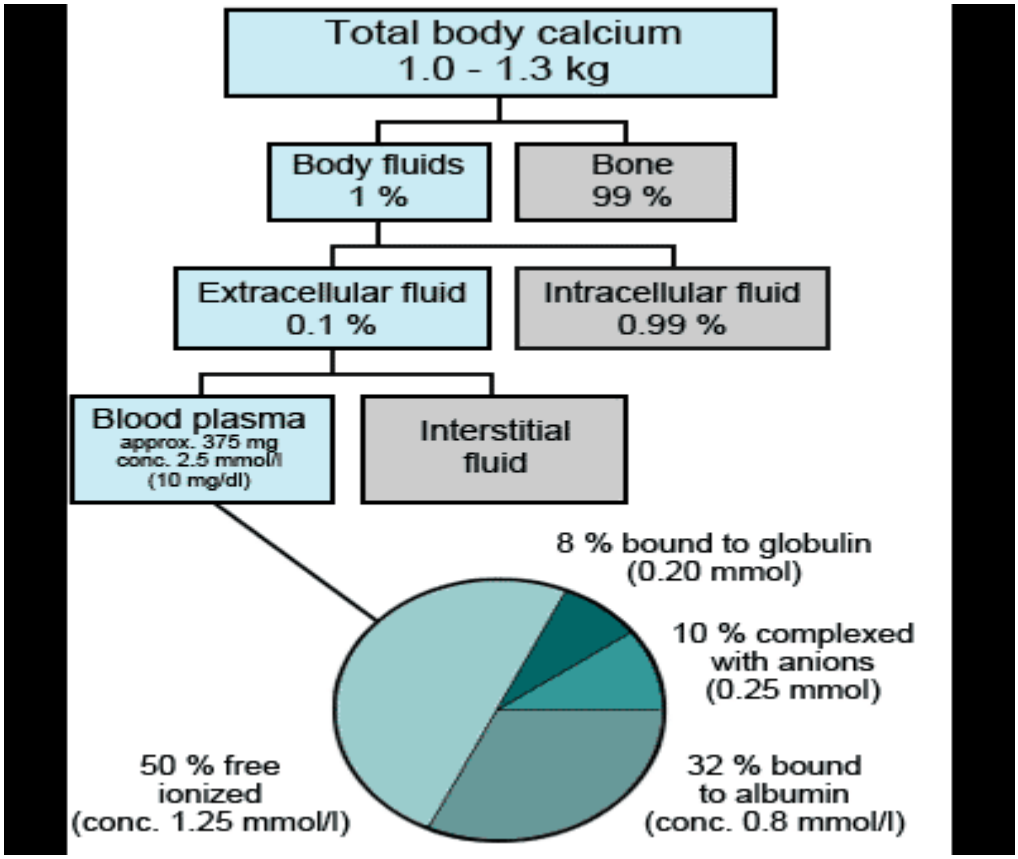


Figure 2. 7. Distribution of Calcium in the body

Source: [99] https://acutecaretesting.org/en/articles/ionized-calcium

Hypocalcaemia

In Hypocalcaemia Ionized serum levels are less than 1.1mmol/L.

Hypocalcaemia at admission is a common electrolyte disorder in critically ill patients with a prevalence 50-88%.[100] Hypocalcaemia occurs in around fifty percent of critically ill patients in intensive care. Its diagnosis is however made complex as a consequence of hypoalbuminemia and the effect of acid-base derangements on total calcium.[101] To determine a patient who is critically ill's actual serum Calcium level it is imperative to determine the Ionized Calcium levels. [95]

Mild and moderate hypocalcaemia are better tolerated however, severe hypocalcaemia may cause significant cardiovascular instability and impair drug action.[102]

A retrospective study by Naafs et al linked hypocalcaemia with adverse clinical outcome in critically ill patients.[97] Sanaie et al found that hypocalcaemia is a predictor of disease severity and mortality[96](however this study utilized the APACHE II scoring system as opposed to the SOFA score that will be implemented in this study to assess disease severity). A study by Yue

Yu et al in critically ill patients being managed for cardiogenic shock found hypocalcaemia to be associated to a heightened risk of 30-day ICU mortality.[103]

Hypocalcaemia was found to be the most prevalent electrolyte anomaly among individuals who required mechanical breathing, according to one study.[4] Another study in COVID 19 patients found hypocalcaemia as a frequently occurring electrolyte derangement with a significant negative impact on disease severity and mortality.[104] Mild and moderate hypocalcaemia were also related with an elevated mortality risk.[105]

Hypercalcaemia

This occurs when Ionized serum levels of calcium is more 1.3mmol/L and essentially due to carcinomatosis or hyperparathyroidism. It is generally less common.[102] This derangement in calcium concentration manifests asymptomatically or as nephrolithiasis or overt bone disease in hypercalcemia. The levels of parathyroid hormone are abnormally increased, while serum phosphate levels may be low. Hyperparathyroidism can arise as a standalone ailment or as part of the triad of diseases in Multiple Endocrine Neoplasia (MEN) Syndrome in the MEN1 or MEN2 variants. Hypercalcemia may also occur due to malignancy. This occurs as a result of the creation of a PTH-related peptide by the tumour or malignant lytic effects, such as in Multiple Myeloma or some haematological neoplasms. Other notable causes are Sarcoidosis. Kimura et al in a study in children under the age of 6 who had cardiac surgery for congenital abnormalities found hypercalcaemia to be associated with longer lengths of stay in the ICU.[106]

Scoring Systems in the ICU

These are systems that assign scores to selected variables and are predictive markers of outcomes typically morbidity and mortality in critically ill patients. Scoring systems also aid in prediction of prognosis and monitoring of the quality of clinical care delivery.[107] Scoring systems guide the clinician to determine the best therapy for patients and help measure the risk of death.

The majority of scoring systems are referred to by their acronyms and typically consist of two components. One part is a score derived from the sum of the various elements of the scoring system. The second aspect correlates the sum total to a probability model signifying severity of disease or probability of in- hospital mortality.[108]

Common scoring systems include Acute Physiology and Chronic Health Evaluation (APACHE), Simplified Acute Physiology Score (SAPS), Mortality Prediction Model (MPM),

Glasgow Coma Score (GCS), Logistic Organ Dysfunction Scoring (LODS), Multiple Organ Dysfunction Scoring (MODS), and Sequential Organ Failure Assessment (SOFA)[109].

It is imperative to understand that every scoring system has limitations and must be used appropriately under the right clinical setting. No scoring system is absolutely ideal. Some scoring systems have scores generated from data collected on the first day of admission to the ICU. These are the APACHE and SAPS scoring systems. Others are not restricted to only the first day of ICU admission such as SOFA, MODS, GCS and LODS and can be done repeatedly.[110]

The Sequential Organ Failure Assessment (SOFA) Score

The SOFA (Sequential Organ Failure Assessment) score system was devised in 1994 during a European Society of Intensive Care and Emergency Medicine consensus conference. The purpose of this conference was to provide a quantifiable and objective method for describing the degree of organ failure over time in critically ill patients with Sepsis. Consequently, its original name was "Sepsis-Related Organ Failure Assessment Score." The score was renamed the Sequential Organ Failure Assessment Score after it was realized that it could be applied to non-septic patients as well.[110]

At a given point/time, a score is assigned depending on the clinical condition of six organ systems (Respiratory, Cardiovascular, Hepatic, Coagulation, Renal, and Neurological Systems).

Scores range from 0-24. The Respiratory component gives a score based on the Partial Pressure of Oxygen expressed as a ratio to the Fraction of inspired oxygen. The Cardiovascular score is given based on the Mean Arterial Pressure and whether the patient requires Inotropic support or not. The Haematological System is scored based on the patient's Platelet Count. Bilirubin levels derived from the Liver Function Tests is used to determine the score assigned for the Hepatic system. The Glasgow core score is assessed and used to allocate scores for the Neurological compartment of the SOFA score. The Renal element of the Score is derived from either the serum Creatinine levels or hourly/daily urine output measurements. In cases where the physiological parameters do not match any row, zero points are given. In instances where the physiological parameters do not correspond to any row, zero points are awarded. When physiological parameters match multiple rows, the row with the most points is selected. Scoring Systems have two components: a severity score - a number (the higher the score, the greater the severity) – and a calculated chance of fatality. The SOFA grading system is a validated

instrument for predicting the clinical outcomes of critically ill patients and measuring the severity of disease. [100] It can be used to assess the severity of organ dysfunction and the risk of mortality in ICU patients. [111] The SOFA score incorporates nearly all disease severity indicators in critically unwell patients [112] Mortality rate increased by at least 50% regardless of the initial score if the score increased within the first 48 hours of admission.[113] It is a scoring system which is related to organ failure and used in the prediction of outcomes of patients being managed in Critical Care Units.[114]

[114] Some studies have indicated a high association between the change in score, or delta SOFA (total maximum SOFA score minus admission total SOFA score), and ICU mortality.[115] Hosseini et al undertook a prospective study where they consecutively recruited 300 critically ill patients. These patients were admitted to the Medical and Surgical ICU of a hospital in Iran. They found SOFA and APACHE II to be of equivalent sensitivities for predicting mortality however the SOFA score is an easier tool to apply and use in the ICU.[111]

Both the SOFA and APACHE II scores are sensitive for predicting mortality, however the SOFA score is easier to implement and utilise in the ICU.[111] Wang et al. discovered that the SOFA score is a more accurate and useful predictor of prognosis in patients undergoing Continuous Renal Replacement Therapy with Acute Kidney Injury than the APACHE II score. [116]. Saumy et al conducted a prospective study in adults admitted to the Medical and Surgical ICUs in which they recruited 157 participants in a hospital in India. They concluded that the SOFA score is a very useful validated tool for predicting mortality in Intensive Care Unit and was more sensitive and specific compared to MODS and LODS.[109] In the ICU, SOFA rating may be frequently utilized to predict mortality. [109] Both SOFA and APACHE II were found to be accurate mortality predictors and prognostic instruments. [117]

Table 2. 5. The Sequential Organ Failure Assessment Score

	Score				
	0	1	2	3	4
Respiratory system					
PaO_2/FiO_2 (mmHg)	≥400	<400	<300	<200 with respiratory support	<100 with respiratory support
Hepatic system					
Bilirubin (mg/dL)	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
Cardiovascular system					
	MAP ≥70 mmHg	MAP <70 mmHg	Dopamine <5 or dobutamine (any dose)[a]	Dopamine 5.1–15 or epinephrine ≤0.1 or norepinephrine ≤0.1[a]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[a]
Coagulation					
Platelets $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Central nervous system					
Glasgow coma scale	15	13–14	10–12	6–9	<6
Renal system					
Creatinine (mg/dL)	<1.2	1.2–1.9	2.0–3.4	3.5–4.9	>5.0
Urine output (mL/d)				<500	<200

Notes: [a]All catecholamine doses represent μg/kg/min. Organ dysfunction is identified as an increase in the SOFA score of ≥2 points. In patients with not known preexisting organ dysfunction, the baseline SOFA score is assumed to be zero. *Intensive Care Med.* The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. 22(7), 1996, 707–710, Vincent JL, Moreno R, Takala J, et al. With permission of Springer.[17]

Abbreviations: PaO_2, partial pressure of oxygen; FiO_2, fraction of inspired oxygen; MAP, mean arterial pressure.

Source: [118] https://www.researchgate.net/figure/Sequential-sepsis-related-organ-failure-assessment-SOFA-score-8-9_tbl1_331933474

Acute Physiology and Chronic Health Evaluation (APACHE) Score

APACHE is a popular tool used to classify severity of disease in critical care. It is applied within the first 24 hours ICU admission. Several measurements are taken and scores assigned to these scores. Scores are assigned ranging from 0- 71, a higher score denoting worsening prognostication. The first model was applied by Knaus et al in the early 1980s.

The APACHE II is also another popular ICU scoring tool however unlike the SOFA score it is limited to use only in the first 24 hours of stay. Many studies have tried to establish the superiority of one scoring system over the other. APACHE II has the advantage of incorporating history of chronic background disease and the age of the patient into the scoring.

APACHE II and SAPS II were found to be better calibrated than SOFA at predicting death risk in the critically ill.[107] Akavipat et al in a retrospective study in 250 patients that were admitted into a neurosurgical ICU in Thailand however found the APACHE II scoring system to be less accurate in its ability to predict mortality.[119]

It has a three-part component. The first component allocates points based on 12 physiological measurements including rectal temperature, serum sodium and potassium, serum creatinine, heart rate, respiratory rate, and blood pressure. The second component involves scores derived from the age of the patient. The last component takes into consideration any history of significant organ dysfunction and whether if any surgical intervention (if required) is an emergency or an elective.

The latest version is APACHE IV and was developed in 2006.

Table 2. 6. The Acute Physiology and Chronic Health Evaluation II (APACHE-11) Score

	+4	+3	+2	+1	0	+1	+2	+3	+4
Rectal temperature (°C)	≥41	39–40.9		38–38.9	36–38.4	34–35.9	32–33.9	30–31.9	≤29.9
MAP (mmHg)	≥160	130–159	110–129		70–109		50–69		≤49
Heart rate (/min)	≥180	140–179	110–139		70–109		55–69	40–54	≤40
Respiratory rate (/min)	≥50	35–49		25–34	12–24	10–11	6–9		≤5
If FiO_2 ≥50%, check A-a gradient; if FiO_2 <50%, PaO_2									
A-a gradient	≥500	350–499	200–349		<200				
PaO_2 (mmHg)					>70	61–70		55–60	<55
Arterial pH	≥7.7	7.6–7.69		7.5–7.59	7.3–7.49		7.25–7.3	7.15–7.2	<7.15
Na (mM)	≥180	160–179	155–159	150–154	130–149		120–129	111–19	≤110
K (mM)	≥7	6–6.9		5–5.9	3.5–4.9	3–3.4	2.5–2.9		<2.5
Creatinine(mg/L)	≥35	20–34	15–19		6.0–14		<6.0		
Hematocrit (%)	≥60		50–59.9	46–49.9	30–45.9		20–29.9		<20
WBC count(10^9/L)	≥40		20–39.9	15–19.9	3–14.9		1–2.9		<1

Glasgow coma score (GCS): 0–12 points = 15–GCS			
Age (y)	Points		
<44	0	Chronic health (history of chronic conditions)[a]	Points
45–54	2	None	0
55–64	3	If patient is admitted after elective surgery	2
65–74	5	If patient is admitted after emergency surgery or for reason other than after elective surgery	5
>75	6		

Source: [120] https://www.researchgate.net/figure/NRITLD-version-of-APACHE-II-Score-Modified_tbl3_236978939

The Simplified Acute Physiology Score

The Simplified Acute Physiology score is one of the ICU scoring systems used to determine severity of disease. It is applied within the first 24hours of ICU stay.

This is a scoring system in the critically ill population that has 17 variable components. 12 of which look at physiological parameters also, there are considerations of age, type of admission and three variables for any concomitant disease such as malignancy or an immunocompromised state. SAPS gives a good estimate of risk of mortality.[121]

The Simplified Acute Physiology Score has been found to be useful in the predicting of mortality.[122]

Table 2. 7. The Simplified Acute Physiology Score

Variables	Score																			
	26	13	12	11	9	7	6	5	4	3	2	0	1	2	3	4	6	7	9	10
HR (beats/min)				<40							40-69	70-119				120-159		≥160		
SBP (mmHg)		<70						70-99				100-199		≥200						
Temperature (°C)												<39			≥39					
PaO_2/FiO_2 only if VENT or CPAP				<100	100-199	≥200														
Urine output (L/day)				<0.5					0.5-0.999			≥1								
Urea (g/L)												<0.6					0.6-1.7			>1.8
TLC			<1									1-19.9		≥20						
Potassium										<3		3-4.9		≥5						
Sodium								<125				125-144	≥145							
Bicarbonate							<15			15-19		>20								
Bilirubin (mg/dl)												<40				40-59.9			≥60	
GCS	<6	6-8				9-10		11-13				14-15								

Age	Score	Chronic disease	Score	Type of admission	Score
<40	0	Metastatic cancer	9	Scheduled surgical	0
40-59	7	Hematological malignancy	10	Medical	6
60-69	12	AIDS	17	Emergency surgical	8
70-74	15				
75-79	16				
>80	18				
SAPS II score	29	40	52	64	77
Mortality risk %	10	25	50	75	90

GCS: Glasgow coma score; HR: Heart rate; SBP: Systolic blood pressure; PaO_2 (mm Hg) arterial oxygen tension; FiO_2: Fractional concentration of inspired oxygen; VENT: Ventilator; CPAP: Continuous positive airway pressure; TLC: Total leukocyte count; AIDS: Acquired immunodeficiency syndrome. Probability of death, *P* may be calculated using the following equation: $P=(e^{Logit})/(1+e^{Logit})$; Logit=−7.7631+0.0737 (score)+0.9971 (log [score+1])

Source: [123] https://www.researchgate.net/figure/Simplified-acute-physiology-score-II15_tbl3_262693049

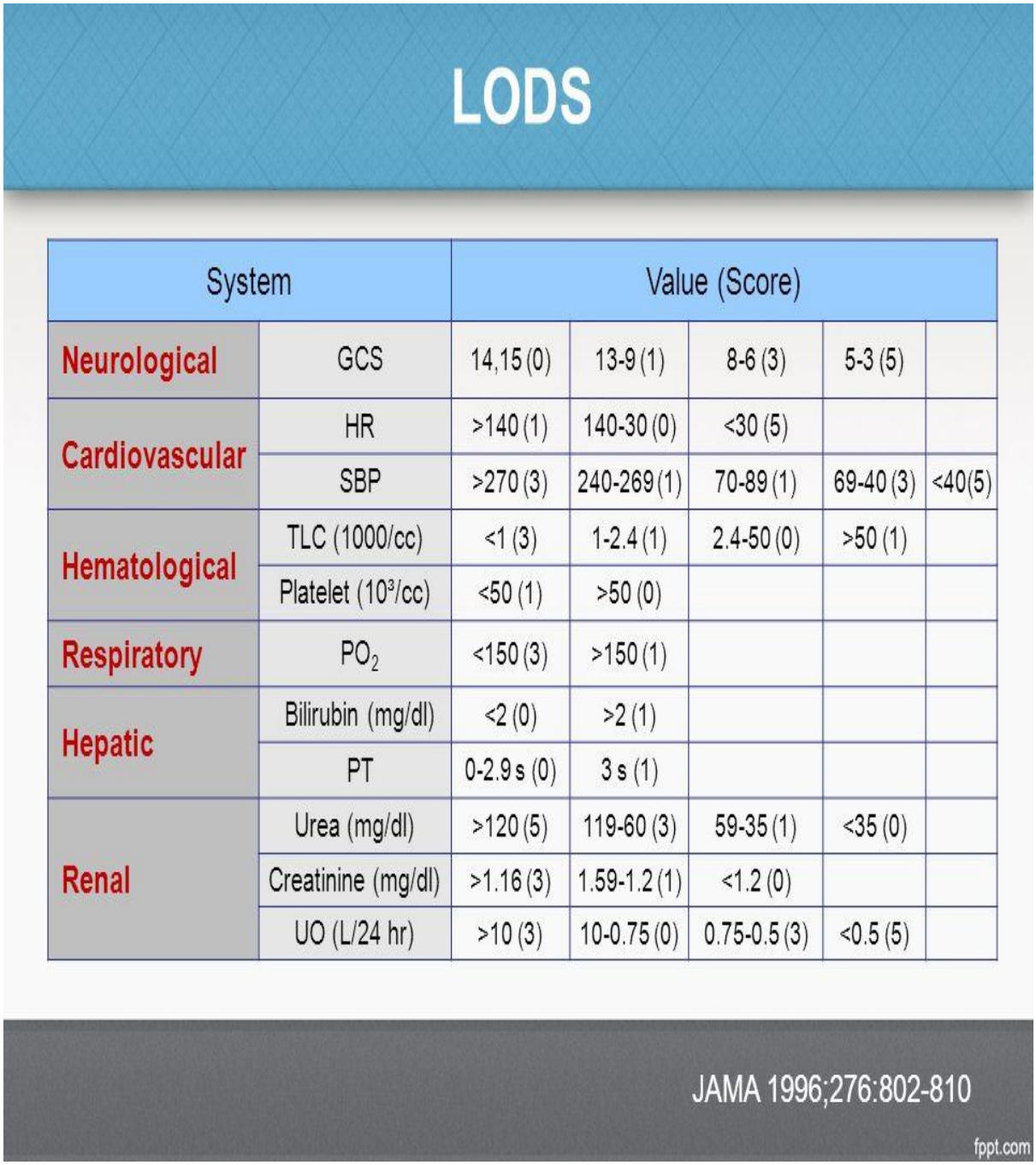
The Logistic Organ Dysfunction System Score

This is a scoring system implemented in the critically ill. It is identified as the acronym LODS score. It was developed by Gall et al in 1996 in their bid to develop a scoring system aimed at assessing organ dysfunction and as a tool to predict morbidity and mortality for patients admitted to the ICU[124]. This score involved scores assigned to a 6- physiological parameters and this assessment was done within the first 24 hours of admission. It is an established objective tool for measuring the degree of organ dysfunction in ICU patients who are severely unwell.[125].

The organs systems evaluated are the cardiovascular, hepatic, pulmonary, renal, haematological and the neurological systems. 11 variables are assessed as subsets of the organ systems evaluated using the scoring system. The score obtained can also be used as a predictor of mortality[126].

Heldwein et al validated it as a useful tool in the prediction of mortality in critically ill patients post cardiac surgery [127].

Table 2. 8. The Logistic Organ Dysfunction System Score



Source: [128] https://slideplayer.com/slide/3898477/

The Multiple Organ Dysfunction Scoring

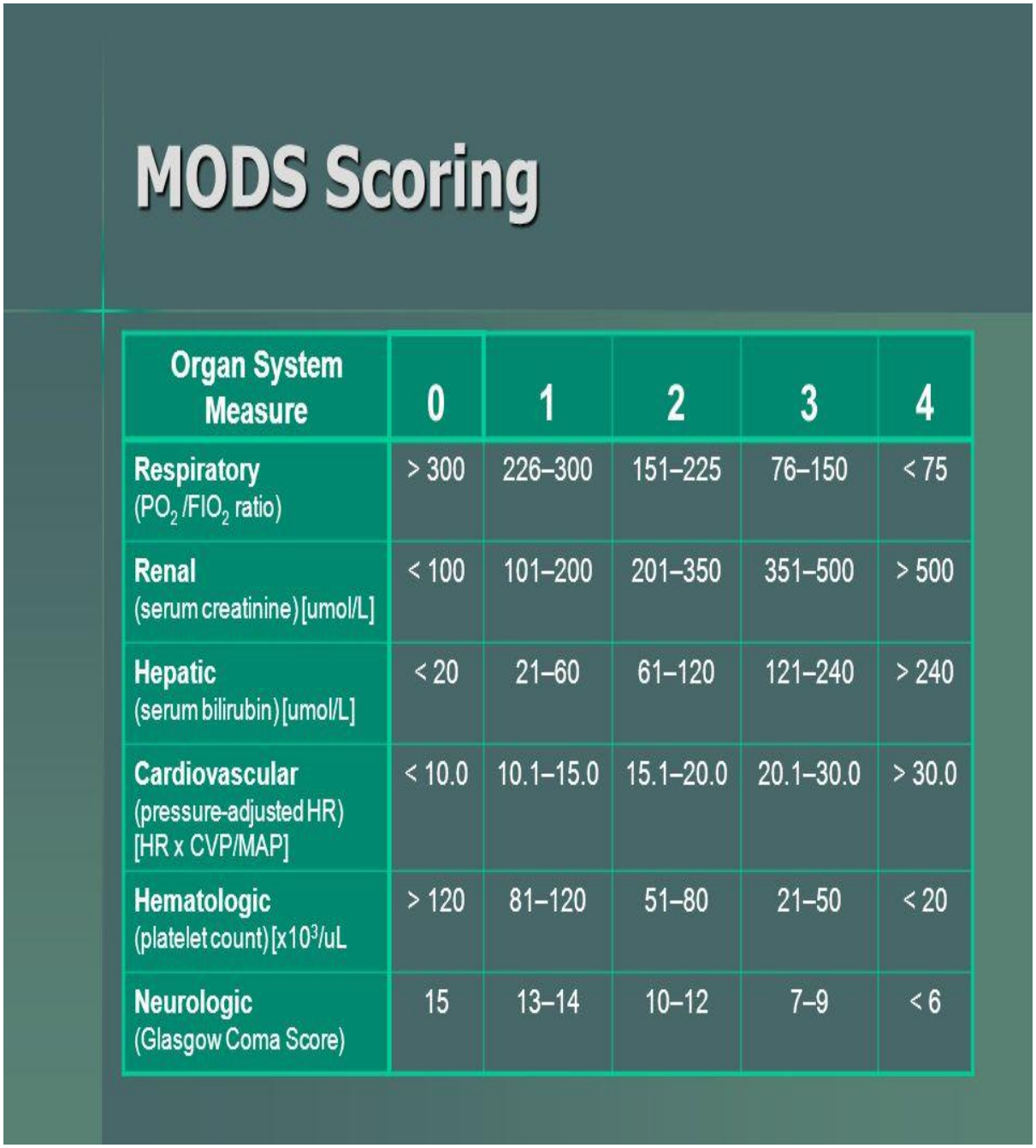
The Multiple organ dysfunction scoring system (MODS) was developed in 1993 and has been found to be a reliable predictor of the risk of ICU mortality[129]. A score of 0-4 is assigned to six organ systems after their individual function is assessed. The maximum score attainable is 24.

The systems assessed are the cardiovascular, hepatic, renal, hematological, respiratory and the neurological systems.

Even in the paediatric age group the MODS was found to be an objective method used to assess the degree of organ dysfunction and also reliably predict mortality in patients admitted to the paediatric intensive care units[130].

In patients who had confirmed Malaria from the Falciparum species, the MODS as a tool was able to predict morbidity such as prolonged duration of disease and hospital admission[131].

Table 2. 9. The Multiple Organ Dysfunction System Scoring



Source: [132] https://slideplayer.com/slide/5685505/

The Glasgow Coma Score

The Glasgow coma score is a scoring tool which facilitates the assessment of the neurological status of a patient[133]. This instrument analyses the patient's responsiveness by measuring three parameters: the patient's best verbal response, best motor response, and eye opening The lowest score that can be awarded per assessment is one (1). The least total score a patient can thus be assigned is 3 and in the absence of reversible factors such as sedatives and electrolyte derangements, a low GCS is usually indicative of a poor prognosis[134].

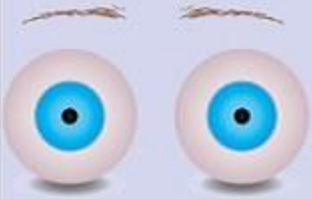
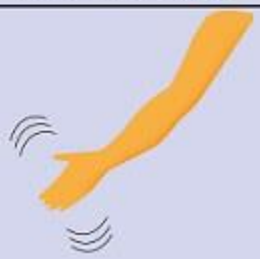
Behaviour	Response
 Eye Opening Response	4. Spontaneously 3. To speech 2. To pain 1. No response
 Verbal Response	5. Oriented to time, person and place 4. Confused 3. Inappropriate words 2. Incomprehensible sounds 1. No response
 Motor Response	6. Obeys command 5. Moves to localised pain 4. Flex to withdraw from pain 3. Abnormal flexion 2. Abnormal extension 1. No response

Figure 2. 8. The Glasgow Coma Score

Source: [135] https://biologydictionary.net/glasgow-coma-scale/

CHAPTER THREE

MATERIALS AND METHODS

3.1 Study Design

This was a longitudinal study involving critically ill patients in the Korle- Bu Teaching hospital (KBTH).

3.2 Study Area

(KBTH) is the premier health-care facility in Ghana. Located in Accra, it is the only public tertiary hospital in the southern part of the country. KBTH affiliated with the University of Ghana Medical School was the study area. It has a capacity of 2,000 beds and 17 clinical and diagnostic facilities. It was founded on October 9, 1923. The hospital has six (6) ICUs made up of the: Medical, Trauma, Burns, Paediatric, Cardio-Thoracic and Surgical ICU. The latter is the main ICU of the facility.

Data was collected from the following Departments in the hospital: The Ground Floor Surgical ICU, The First Floor Surgical Recovery Ward and the First Floor Labour Ward Recovery (the latter two are High Dependency Units-HDUs, which also function as ICUs when the need arises). The Ground Floor ICU has 4 ICU beds and 6 HDU beds with an average annual admission of 84 patients. The First Floor Surgical and Labour Ward Recovery Wards are essentially Recovery Wards for post-operative patients but sometimes double as HDUs /ICUs for critically ill patients. The First floor Surgical Recovery Ward has monthly ICU admissions ranging from 5-10 patients per month as well as doubling as a post Anaesthesia care unit. This duality of function also pertains to the Labour Ward Recovery ward which in December 2021 had a total of 7 ICU patients and 9 ICU patients in January, 2022.

3.3 Study Population

The study population consisted of Critically Ill patients hospitalized to the aforementioned KBTH departments between the ages of 18 and 65 years. Subject recruitment was done after Ethical clearance was obtained and participant and/ or Participant's next of kin consented. In the event that the consciousness of the patient was impaired rendering the patient unable to make critical decisions , the Next of Kin was required to consent. In this setting the recognised next of kin was counselled and a written consent sought for their relation to be recruited into the study. A Critically Ill patient was defined as one who had a life-threatening multi-system

process that had resulted in significant morbidity and mortality requiring support for one or more organ systems.

3.4 Inclusion Criteria

• Critically ill patients admitted to any of the above stated wards.

• Age between 18-65 years old.

3.5 Exclusion Criteria

- Pre-morbid intake of Magnesium supplements
- Pre-morbid intake of Phosphate supplements
- Pre-morbid intake of Calcium supplements
- Patients with established Chronic Renal Failure

3.6 Sample Size Determination

The primary outcome of this study that would yield the maximum sample size was a study reporting hypophosphataemia in ICU patients shown to be 24%[4]. This study used this prevalence at 0.05 margin of error and 95% confidence level.

The sample size was determined by the formula:

$$N=\frac{Z^2 * p(1-P)}{d^2}$$

Where,

N = minimum sample size.

Z = value on standard normal distribution at 95% confidence level =1.96

p = prevalence = 0.24

d = degree of accuracy at 5% = 0.05

Therefore,

$$N = 1.96^2 \frac{(0.24)(1-0.24)}{0.0025}$$

$$N = 280.3 \approx 281$$

Since there was a finite study population for the given duration of study, a corrected sample size (N_f) will be calculated by this formula.

$$N_f = \frac{N_0 \, x \, N}{N_0 + (N-1)}$$

Where

N_0 = maximum number of ICU cases per month, estimated as an average of 21 per month.

$$N_f = \frac{21x281}{21+(281-1)}$$

$$= 19.6.$$ Hence minimum sample size is 20.

Accounting for 10% increase in the minimum sample size, the total samples size was 22.

3.7 Study Period

The study was conducted over a period of 5 months (July 2022 – November 2022) and the total number of participants enrolled was 26.

3.8 Study Procedure

At the time of admission, patients who met the inclusion criteria and consented to participate in the study were selected consecutively. Patients were recruited when they were considered as critically ill. This was when they required organ support for one or more organ systems that had shut down and were admitted into the listed study sites. Venepuncture site was cleaned with methylated spirit. Sample of blood was taken using a 19G hypodermic needle or via a Central Venous line.

Central Venous access: Under strict asepsis, the Internal jugular or subclavian vein was cannulated under ultrasound guidance or using anatomical landmarks . A 7.5Fr central venous catheter was inserted using Seldinger technique. The catheter was secured using nylon 2-0 non-absorbable sutures, the site cleaned with spirit and waterproof film dressing applied.

Phosphate:4.5 millimetres(ml) of blood was then drawn into a Serum Separator tube (yellow top sample bottle). Agitation of the sample bottle was avoided to prevent haemolysis. Serum Phosphate was determined by VITROS Chemistry System.

Magnesium and total serum calcium: The serum magnesium and calcium levels were determined using a Flame Atomic Absorption Spectrometer, (Variant 240FS manufactured by VARIAN Australia Pty Ltd). Without using a tourniquet, a six (6) milliliter blood sample was collected into gel separator tubes. Avoiding agitation or shaking of the complete blood sample to prevent its haemolysis.

Formula for derivation of Serum Ionised Calcium from Total Calcium: 0.815 x Total Calcium$^{0.5}$

The total amount of blood taken for investigations was 15mls and this was taken once. The blood was then separated into the appropriate sample bottles for analysis of serum Magnesium, Calcium, Phosphate, blood urea and electrolytes and for the full blood count.

Blood sampling was done on the day of admission within the first 12 hours and samples centrifuged after collection for analysis. To compute the Partial Pressure of Oxygen to Fraction of Inspired Oxygen (PaO2/FiO2) or P/F Ratio, an arterial blood gas analysis was performed. This was done simultaneously during sampling for the study electrolytes. These parameters were to assist in the calculation of the patient's SOFA score at admission. The SOFA Score is a six-parameter scoring system. It allocates scores to a patient based on: P/F ratio, platelet count, bilirubin levels, Mean arterial pressure and requirement of inotropes, urine output measurements or serum creatinine and Glasgow coma score. Sampling of blood for measurement of serum electrolyte levels was done concurrently.

Primary outcome measure of the study was duration of stay in the ICU. This was determined by the calculating the time from the day of admission to the day of discharge from the ICU/day of death. Secondary outcome measures of the study were duration of ventilatory support and duration of inotropic support required during stay in the ICU. This was tallied and documented on the data collection tool when patient was discharged from the ICU or died.

Variables such as Gender, Age, Admission Diagnosis, Ethnicity and Comorbid Conditions were obtained at admission and documented on the data collection sheet/s.

Full Blood Count: Four (4) millilitres of blood was drawn into a Purple covered sample bottle. Haematological analyser used is the Beckman Coulter®.

Liver function Test: Five (5) millilitre of blood was drawn into the Serum separator- SST gel tube. It was imperative to avoid agitation of the tube to prevent haemolysis of the sample. The sample was gently inverted 8- 10 times and allowed to clot for thirty (30) minutes. Specimen was centrifuged within two (2) hours of collection.

Blood Urea and electrolytes: Five (5) millilitre of blood was drawn into the Serum separator- SST gel tube. It was imperative to avoid agitation of the tube to prevent haemolysis of the sample. The sample was gently inverted 8- 10 times and allowed to clot for thirty (30) minutes. Specimen was centrifuged within two (2) hours of collection.

Arterial Blood Gas: Under strict asepsis arterial cannulation was performed using a 20 G length appropriate catheter and secured. 0.5ml of arterial blood was drawn using a heparinized two (2) millilitre syringe. Specimen was analysed within 15-30 minutes of sampling and transported in an ice chest containing ice whilst awaiting analysis.

All Laboratory investigations were done at Central Laboratory of the KBTH and the Arterial blood gases were run at the Ground Floor Surgical ICU (Edan i15 Blood Gas Analyzer, Edan Instruments Inc, China) or the Cardio-Thoracic Centre ICU (Gem Premier 3000 Blood Gas Analyzer, Synergy Medical Systems LLP, India).

3.9 Data Storage and Management

A data collection sheet was used to collect the relevant data for the study. All members of the research team treated all data with strict confidentiality. Data was entered into Microsoft® Excel version 2016 (Microsoft Corporation, One Microsoft Way, Redmond Washington, 98052-6399, United States of America) for cleaning and storage. The data was then exported to Statistical Package for the Social Sciences (SPSS) software version 25 (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corporation) for analysis. To ensure data security, the following strategies were employed:

1. Distinct serial numbers were assigned to each participant to maintained confidentiality.
2. Patient identifiers (name, date of birth, and contact information) were separated from the remaining data. This data was secured by a password. Only the lead investigator and supervisors had database and password access.
3. Hard copies of personally identifying data and codebook were kept securely locked away at all times when not in use.

4. The remaining (anonymized) data was recorded in a separate Microsoft® Excel file (and exported into SPSS for analysis). MS Excel and SPSS data files were password-protected. The only individuals with access to anonymized data were the PI, supervisors, and statistician.
5. Hard copies of patient's data (questionnaires and physical examination forms) were kept physically restricted in a locked cabinet in the research supervisor's office. The keys to the cabinet remained on the persons of the research supervisor and research candidate at all times.
6. While operating on the internet, logical security measures were implemented. On our research machines, we utilised antispyware and virus-detection software.
7. Data were backed up daily to external drives during the period of data entry.

3.10 Statistical Data Analysis

Data was analysed in SPSS version 20. Categorical variables such as Gender, Admission Diagnosis, Ethnicity and Comorbid Conditions were summarized as tables and graphs. Continuous variables such as Age, Admission Serum Electrolyte (Magnesium, Calcium and Phosphate, Sodium. Potassium and Chloride) levels and Admission SOFA scores were summarized as means and standard deviations. Pearson correlation coefficient was used to determine the effect of:

- Admission Serum levels of Phosphate, Magnesium and Calcium on duration of I.C.U stay.
- Admission serum levels of Phosphate, Magnesium and Calcium on severity of disease at admission.
- Admission serum levels of Phosphate, Magnesium and Calcium on SOFA scores at admission of critically ill patients.
- Admission Serum Phosphate levels on duration of mechanical ventilation.
- Admission Sodium, Chloride and Potassium levels on SOFA scores.

Fisher's Exact test was used to determine the effect of electrolyte levels and mortality rate. All p-values less than 0.05 were judged to be statistically significant.

3.11 Ethical and Legal Considerations

Approval for the study was sought from the KBTH Ethics and Protocol Review Committee as well as the dissertation review committee of the Ghana College of Physicians and Surgeons.

Participation in the study was absolutely voluntary. Participants were sufficiently informed of the study's objective, nature, procedures, and potential dangers. Emphasis was placed on anonymity, secrecy, and the ability to decline participation or withdraw from the study without consequence at any time. Refusal to participate had no bearing on the patient's clinical therapy. Before enrolling patients in the trial, they provided a signed or thumb-printed informed permission form.

CHAPTER FOUR

RESULTS

4.1 Demographic characteristics

A total of twenty- six (26) participants were recruited into this study with 53.8% being females and mean age of 44.6 (± 15.9) years. Majority of the participants were aged between 30 and 39 years. Majority (61.5%) of the participants were Akans and 3.8% were foreigners from Liberia. (Table 4.1).

Table 4. 1. Demographic characteristics of participants

Variable	**n (%)**
Gender	
Male	12 (46.2)
Female	14 (53.8)
Age (years)	
20-29	4 (15.4)
30-39	9 (34.6)
40-49	5 (19.2)
50-59	3 (11.5)
≥60	5 (19.2)
Ethnicity	
Akan	16 (61.5)
Ga-Adangbe	2 (7.7)
Mole-Dagbani	6 (23.1)
Ewe	1(3.8)
Foreigner	1(3.8)

4.2 Co-morbid conditions

The commonest co-morbidity, hypertension was seen in 50% of the participants. Asthma and Cardiomyopathy/Valvular lesions were the least common co-morbidities. (Table 4.2).

Table 4. 2. Co-morbid conditions of participants

Variable	**n (%)**
Hypertension	7 (50.0)
Diabetes	3 (22.0)
Asthma	2 (14.0)
Cardiomyopathy/Valvular lesions	2 (14.0)

4.3 ICU admission diagnoses

The table shows the common diagnoses participants presented with in the ICU. There were often overlaps where a patient had multiple diagnoses upon admission into the ICU. The most common diagnosis was post-surgical complications which accounted for 30.5% of the admission diagnoses, with malignancies (1.7%) accounting for the least ICU diagnosis. (Table 4.3).

Table 4. 3. Admission Diagnoses

Variable	**n (%)**
Pregnancy related complications	**7(11.8)**
Sepsis/septic shock	**9 (15.3)**
Post-cardiac arrest	**7(11.8)**
Pneumonias	**4(6.8)**
CNS disorders/CNS surgery	**8(13.6)**
Poly-trauma	**2(3.4)**
Malignancies	**1(1.7)**
Vascular condition	**3(5.1)**
Post-surgical procedures	**18(30.5)**

4.4 Antimicrobials administered in the first 48 hours of ICU admission

The commonly prescribed antibiotics at admission in the ICU are displayed in the diagram. The most common antibiotics prescribed in the ICU were Amoxicillin Clavulanate and Metronidazole. The least prescribed antibiotic in the ICU was Levofloxacin. (Figure 4.1).

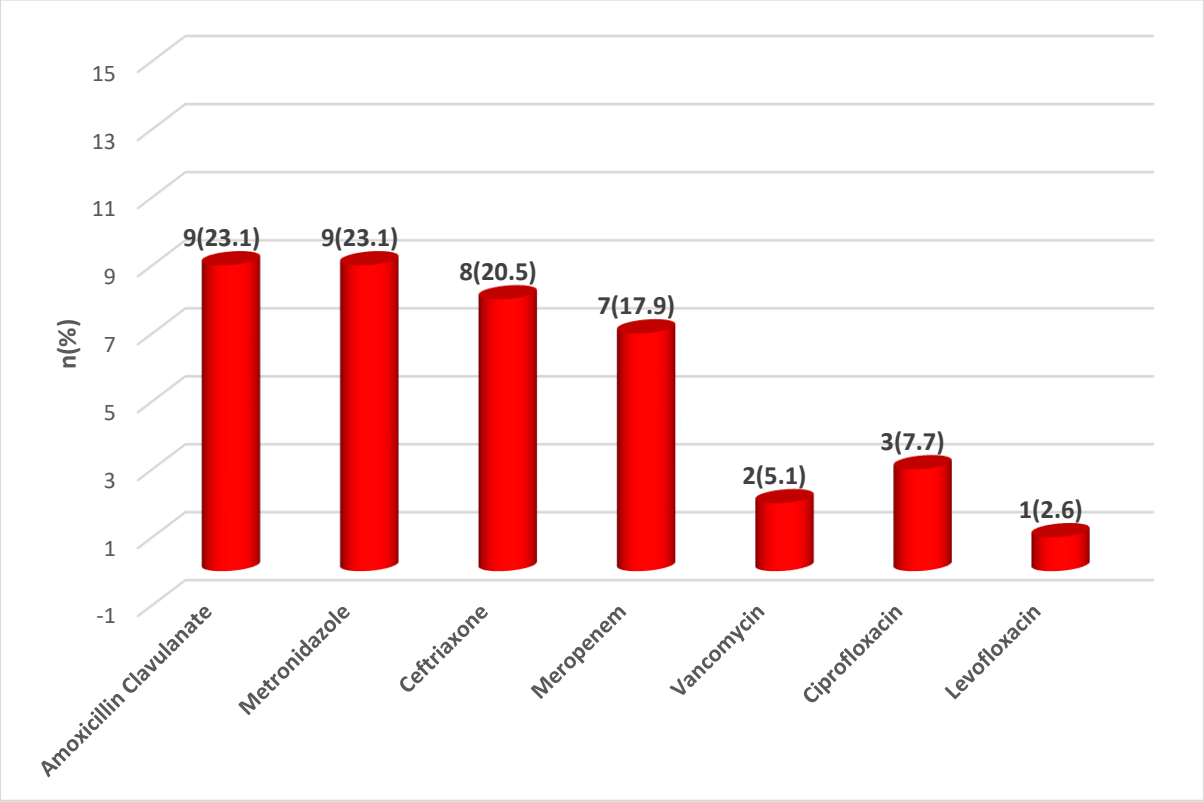


Figure 4. 1.Antimicrobials administered in the first 48 hours of ICU admission

4.5 Selected serum electrolyte levels at Admission

The mean serum phosphate level of the participants at admission was 1.35(± 0.84) mmol/L and ranged between 0.11mmol/L and 4.77mmol/L. More than half (54%) of the study participants had normal serum phosphate levels at admission (Table 4.4).

The mean serum ionised calcium level of the participants at admission was 1.12(±0.12) mmol/L and ranged between 0.73 mmol/L and 1.25 mmol/L. A high proportion (92.3%) of the participants had normal serum ionised calcium levels (Table 4.4).

Table 4. 4. Serum Phosphate and Ionised Calcium levels

Serum Electrolyte	Mean (±SD)	Serum Levels	n(%)
Serum Phosphate level (mmol/L)	1.35(±0.84)	Reduced	4(15.0)
		Normal	14(54.0)
		Increased	8(31.0)
Serum Ionised Calcium (mmol/L)	1.12 (±0.12)	Reduced	2(7.7)
		Normal	24(92.3)
		Increased	0(0.0)

Serum phosphate (**reference range:0.80-1.45mmol/L**): Serum ionised calcium (**reference range:1.20-1.40mmol/L**)

The mean serum magnesium level of the participants at admission was 0.83 (± 0.25) mmol/L and ranged between 0.50mmol/L and 1.43mmol/L. Twelve (46%) of the study participants had normal serum magnesium levels at admission (Table 4.5).

The mean serum sodium level of the participants at admission was 139 (± 5.3) mmol/L with a minimum value being 131 mmol/L and maximum value being 154 mmol/L. A high proportion (81%) of the participants had normal sodium levels at admission (Table 4.5).

Table 4. 5. Serum Magnesium and Sodium Levels

Serum Electrolytes	Mean (±SD)	Serum Levels	n(%)
Serum Magnesium (mmol/L)	0.83 (± 0.25)	Reduced	8(31.0)
		Normal	12(46.0)
		Increased	6(23.0)
Serum Sodium (mmol/L)	139 (± 5.3)	Reduced	4(15.0)
		Normal	21(81.0)
		Increased	1(4.0)

Serum magnesium (**reference range: 0.70-1.00mmol/L**): serum sodium (**reference range**:**135-150mmol/L**)

The mean serum potassium level of the participants at admission was 4.32 (±1.06) with minimum value being 2.50mmol/L and maximum being 7.00 mmol/L. Seventeen (65%) of the study participants had normal serum potassium levels at admission (Table 4.6).

The mean serum chloride level of the participants at admission was 104 (±6) mmol/L. The minimum chloride level at admission was 90mmol/L and the maximum was 115mmol/L. Participants with normal chloride levels at admission accounted for 84% (Table 4.6).

Table 4. 6. Serum Potassium and Chloride Levels

Serum Electrolyte	Mean (±SD)	Serum Levels	n(%)
Serum Potassium (mmol/L)	4.32 (±1.06)	Reduced	6(23.0)
		Normal	17(65.0)
		Increased	3(12.0)
Serum Chloride (mmol/L)	104 (± 6)	Reduced	2(8)
		Normal	22(84)
		Increased	2(8)

Serum potassium (**reference range: 3.5- 5.5mmol/L**): serum chloride (**reference range**:**95-110mmol/L**)

4.6 Relationship between admission serum Phosphate and Magnesium levels

There was a positive, significant relationship between serum phosphate and serum magnesium levels. As serum magnesium levels increased, serum phosphate levels increased (Figure 4.2).

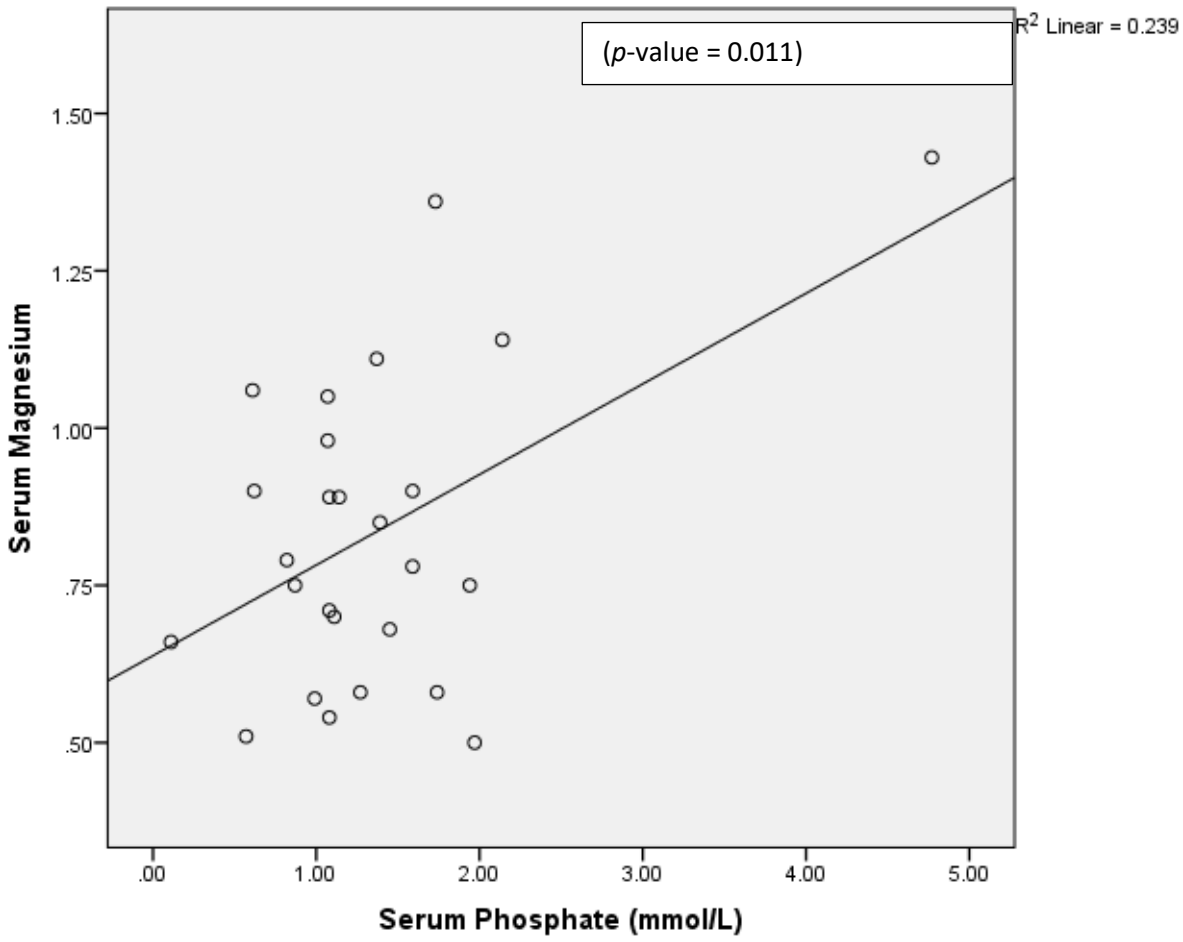


Figure 4. 2. Relationship between admission serum Phosphate and Magnesium levels

4.7 Relationship between admission serum Ionised Calcium and Phosphate levels

The study found that serum ionised calcium levels showed a non-significant positive relationship with serum phosphate levels. As serum ionised calcium increased, serum phosphate levels increased (Figure 4.3).

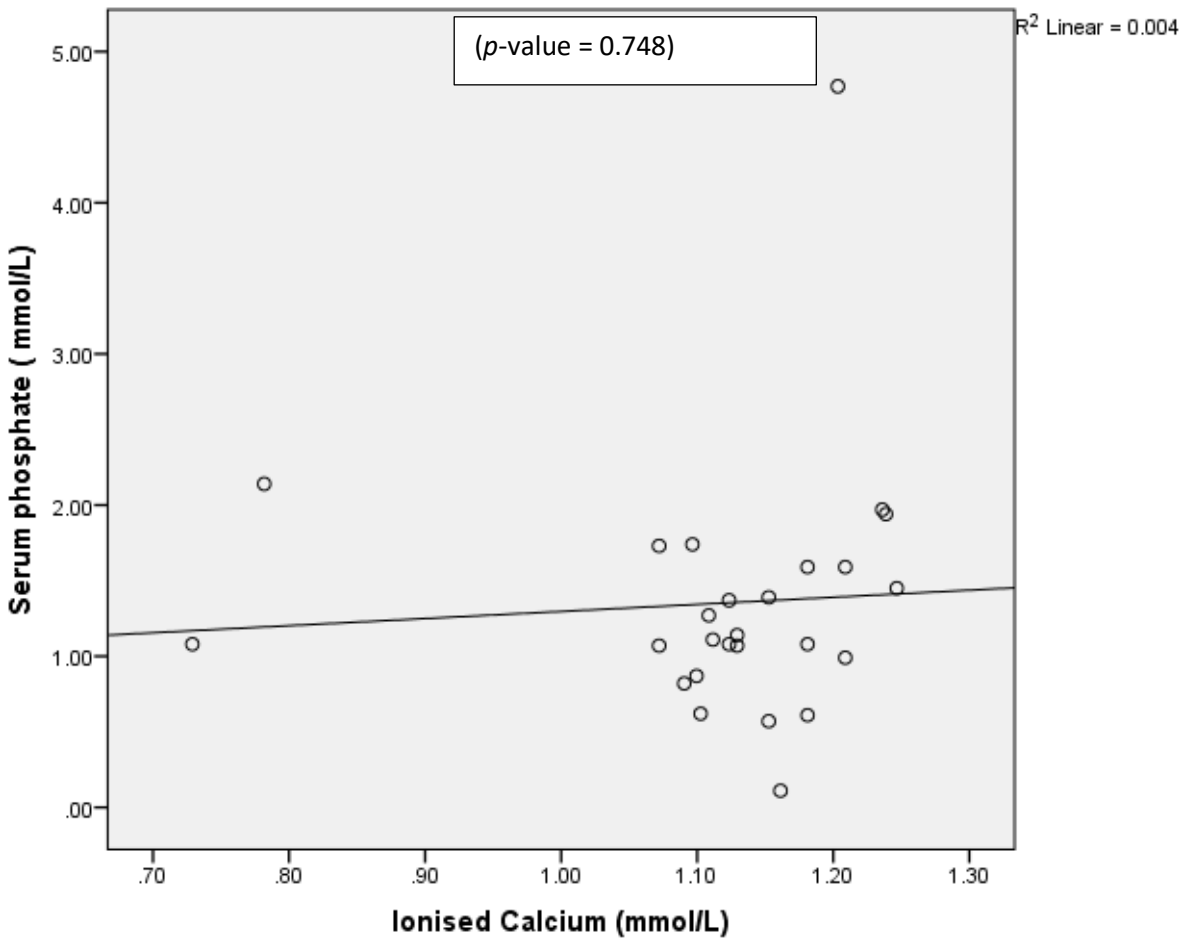


Figure 4. 3. Relationship between admission serum Ionised Calcium and Phosphate levels

4.8 Relationship between admission serum Ionised Calcium and Magnesium levels

There was a non-significant negative relationship between serum ionised calcium and serum magnesium levels. When calcium was high, magnesium was low and vice versa (Figure 4.4).

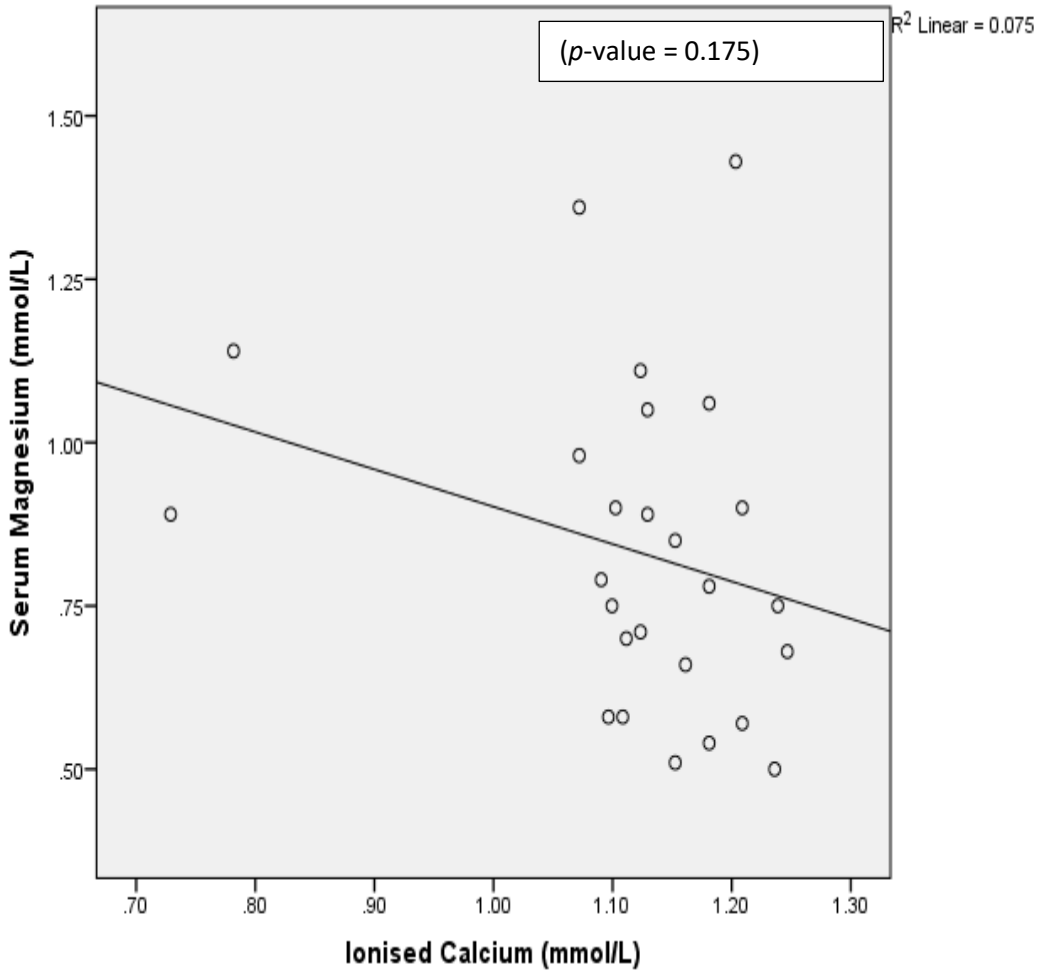


Figure 4. 4. Relationship between admission serum Ionised Calcium and Magnesium levels

4.9. Admission SOFA Scores, Length of ICU stay (LOS), Duration of inotropic support and Duration of ventilatory support among participants

The lowest SOFA score was 2 and the highest score calculated was 15 with a mean of 8. Majority (38.5%) of the participants had SOFA score ranging between 11 and 15 (Table 4.7).

The median duration of ICU stay was 7.5 days. The shortest duration of stay of the study participants was less than 24 hours (18 hours post admission into the ICU). The longest duration of time spent by a study participant in the ICU was 58 days. Half of the participants stayed in the ICU for a period of 7 days or less, whilst 11.5% stayed for 30days or more. (Table 4.7)

Majority of the participants (85%) were on inotropic support for 7 days or less. Only 3.8% were on inotropic support for between 15-21 days (Table 4.7). Majority of the participants (68.2%) had ventilatory support of 7 days or less

Table 4. 7. Admission SOFA score, ICU length of stay, Duration of inotropic support and Duration of ventilatory support among participants

	n(%)
SOFA score	
≤ 5	9(34.6)
6-10	7(26.9)
10-15	10(38.5)
Length of stay (days)	
≤ 7	13(50.0)
8-14	8(30.8)
15-21	1(3.8)
22-29	1(3.8)
≥30	3(11.5)
Duration of inotropic support	
≤ 7	17(85.0)
8-14	2(10.0)
15-21	1(3.8)
Duration of ventilatory support	
≤ 7	15(68.2)
8-14	4(18.2)
15-21	2(9.1)
22-29	0(0.0)
≥30	1(4.5)

4.10 Effect of admission levels of some selected serum electrolytes (Phosphate, Calcium and Magnesium) on SOFA scores at admission, duration of ICU stay and duration of inotropic support

A statistically significant positive association was found between serum phosphate levels at admission and SOFA scores (Figure 4.5).

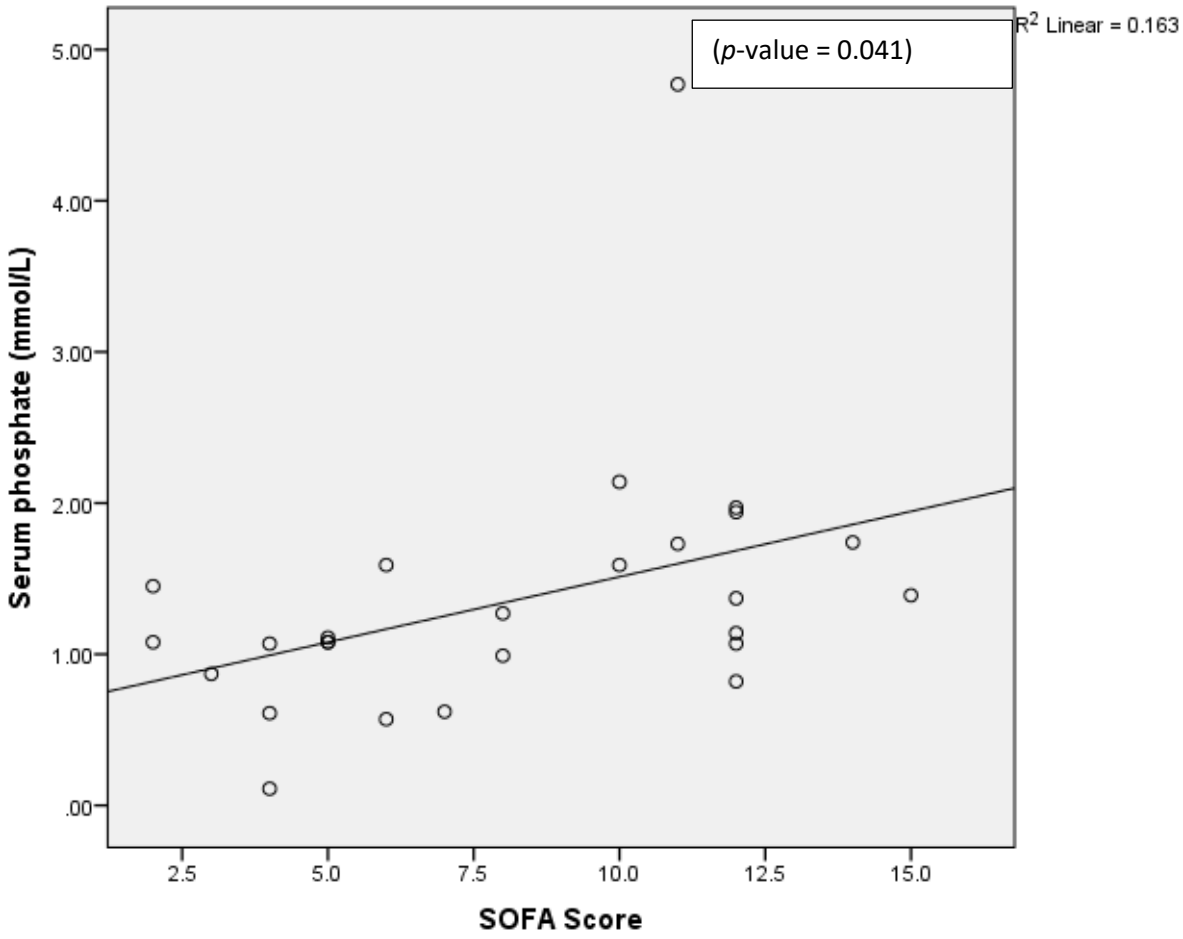


Figure 4. 5. Correlation between admission SOFA score and serum phosphate levels

Effect of admission Serum ionised calcium levels on SOFA scores

A non-significant positive correlation was found between serum ionised calcium and SOFA scores at admission (Figure 4.6).

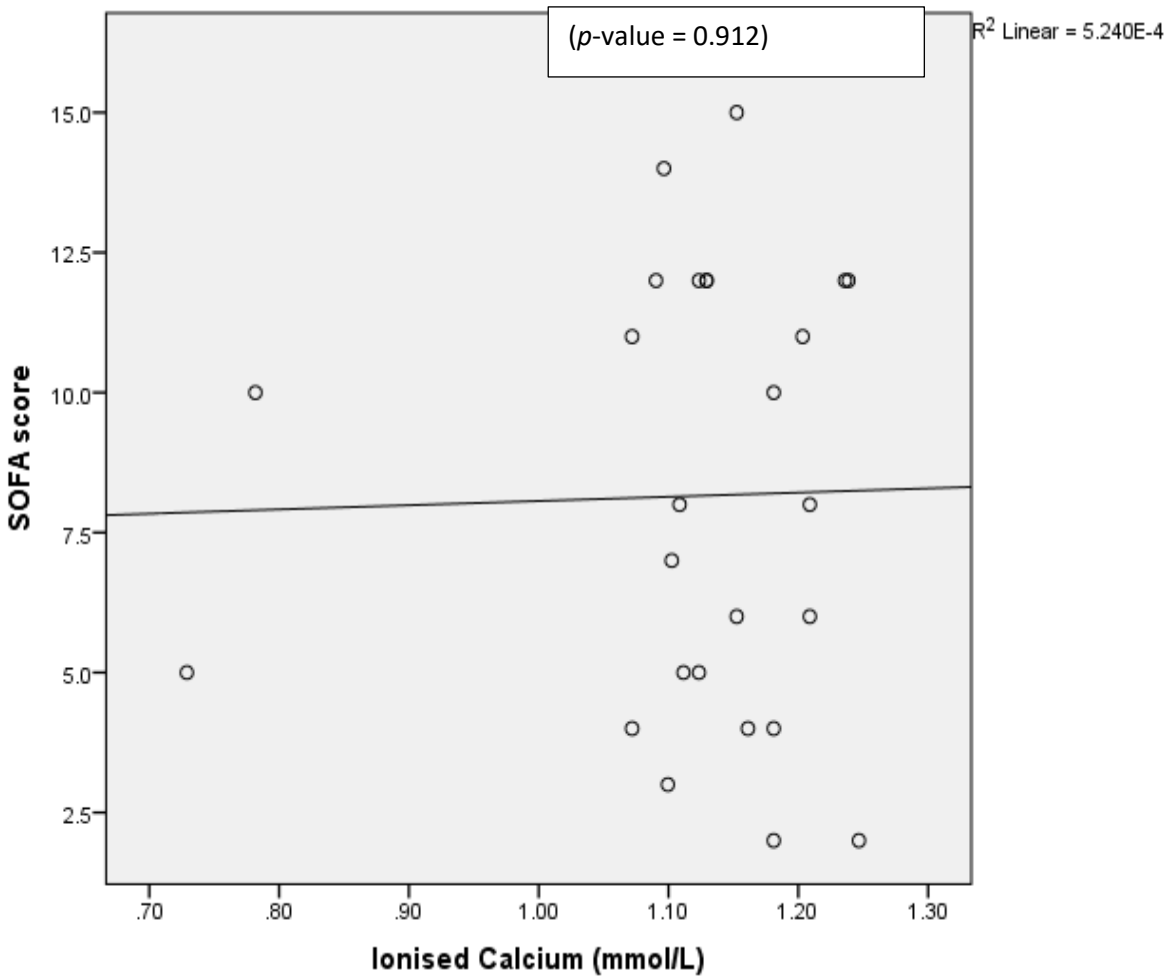


Figure 4. 6. Correlation between admission SOFA score and serum ionised calcium levels.

Effect of admission Serum Magnesium levels on SOFA scores

A non-significant positive correlation was found between serum magnesium levels and SOFA scores at admission (Figure 4.7).

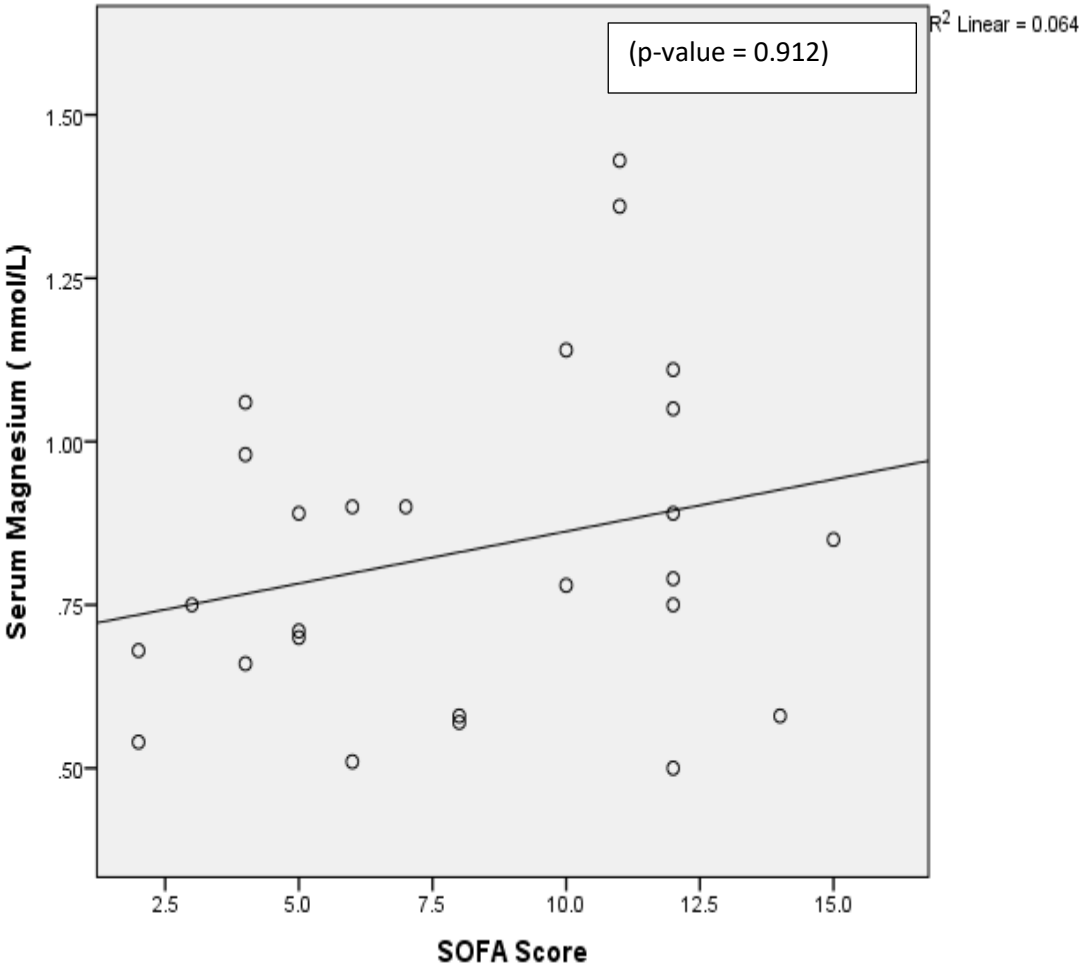


Figure 4. 7. Correlation between admission SOFA score and serum magnesium levels.

Effect of admission Serum Phosphate levels on length of stay

There was a negative non-significant relationship between duration of ICU stay and serum phosphate levels (*p*-value = 0.683).

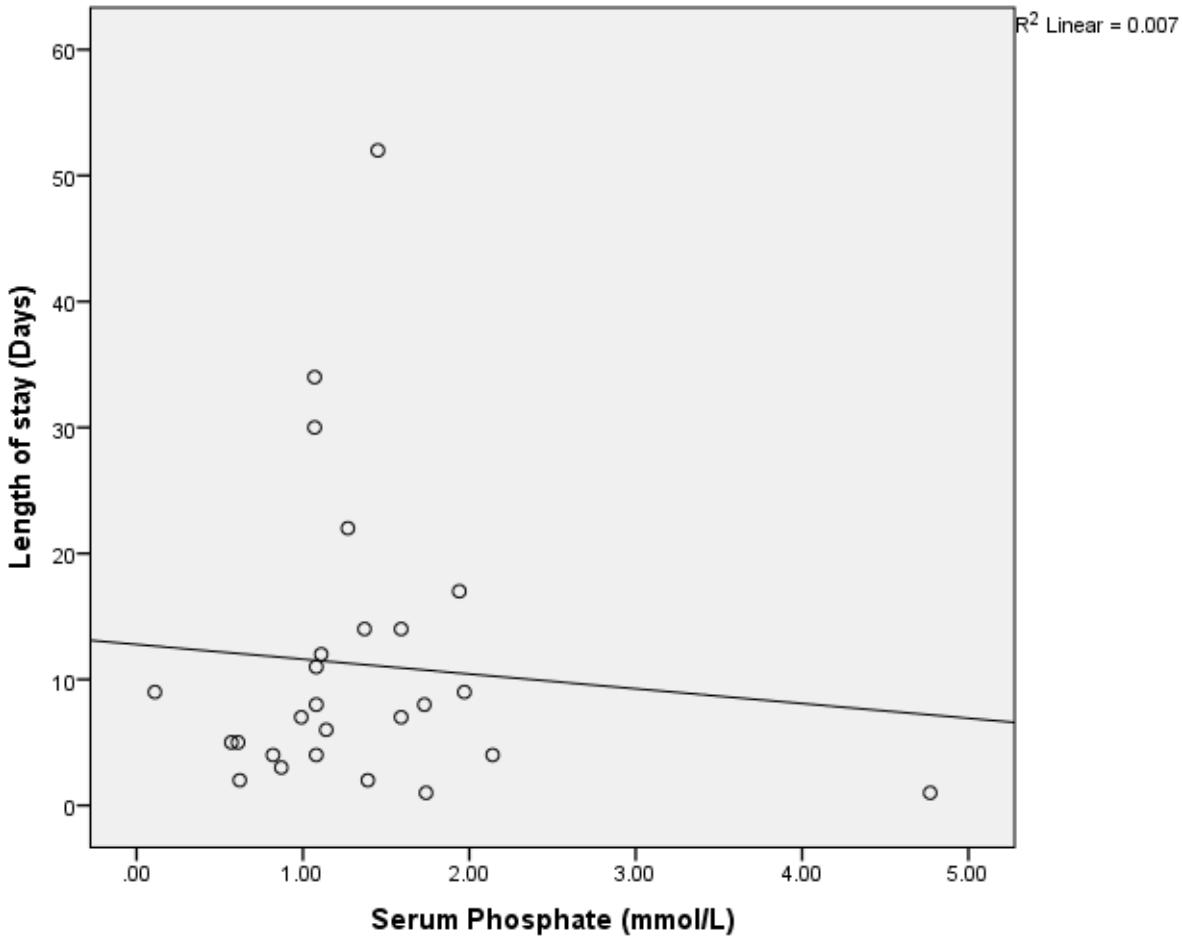


Figure 4. 8. Correlation between length of ICU stay and serum phosphate levels.

Effect of admission Serum Magnesium levels on length of stay

There was a negative non-significant relationship between duration of ICU stay and serum magnesium levels (*p*-value = 0.772).

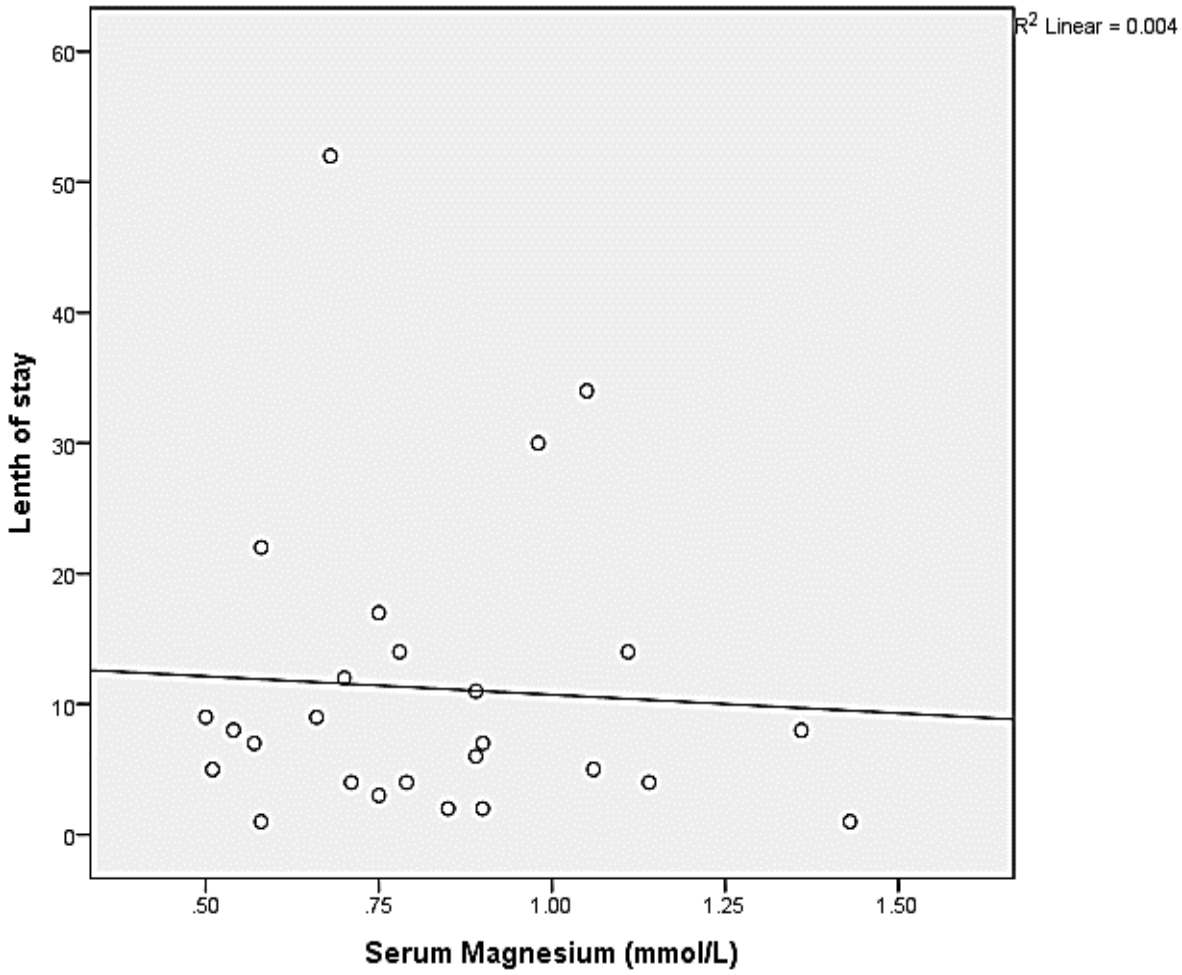


Figure 4. 9. Correlation between length of ICU stay and serum magnesium levels.

Effect of admission Serum ionised calcium levels on Length of stay

There was a positive non-significant relationship between duration of ICU stay and serum ionised calcium levels (*p*-value = 0.439).

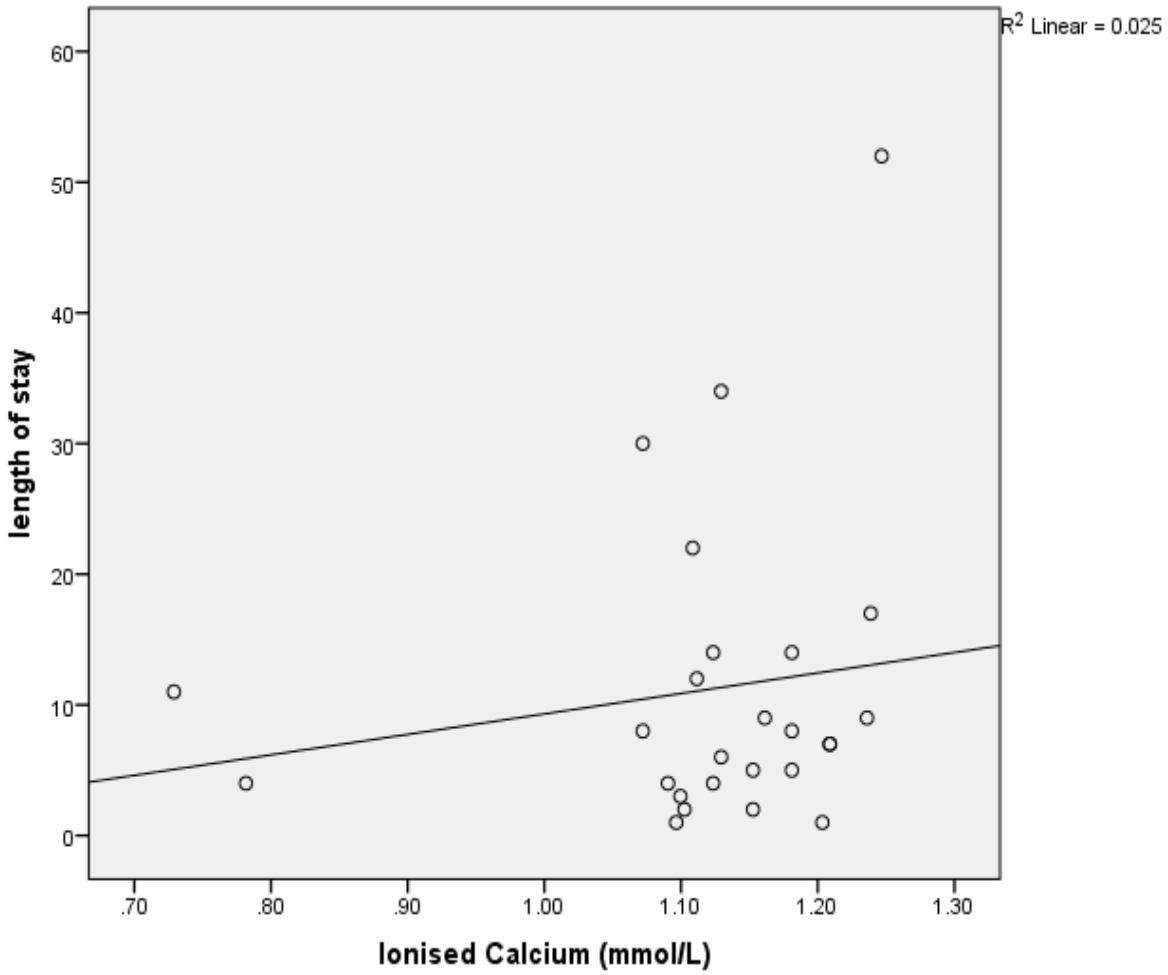


Figure 4. 10. Correlation between length of ICU stay and serum ionised calcium levels.

Effect of admission Serum Phosphate levels on duration of inotropic support

There was a non-significant negative correlation between serum phosphate levels and duration of inotropic support (Figure 4.11).

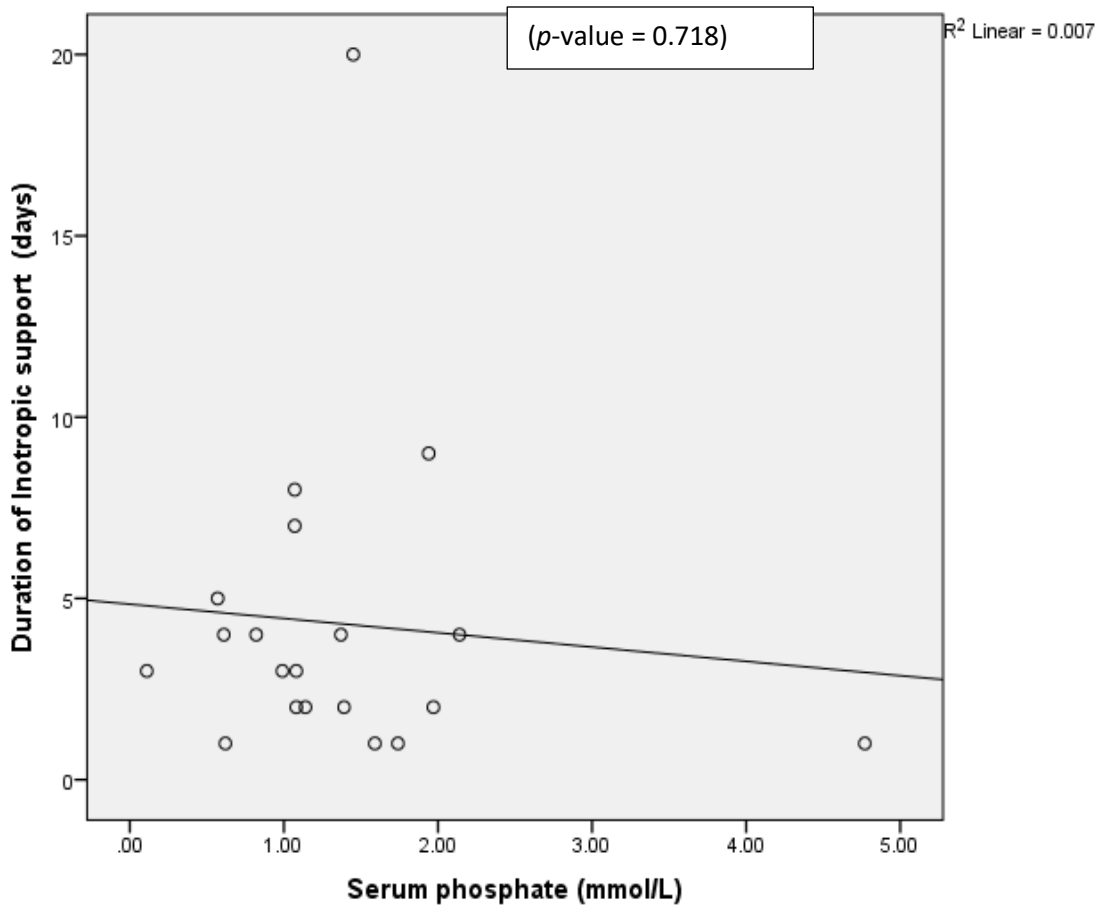


Figure 4. 11. Correlation between Duration of inotropic support and serum phosphate levels

Effect of admission Serum Magnesium levels on duration of inotropic support

There was a negative correlation which was not statistically significant between serum magnesium levels at admission and the duration of inotropic support (Figure 4.12).

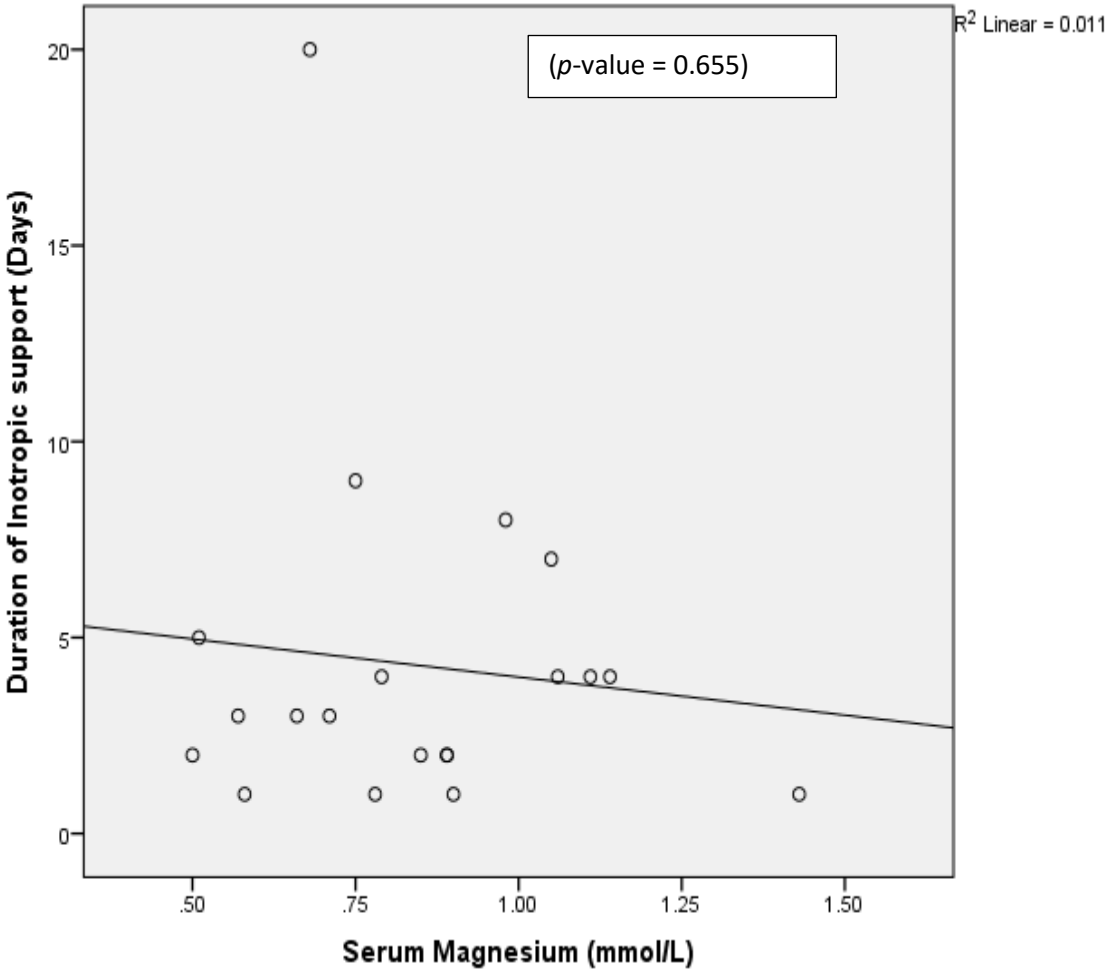


Figure 4. 12. Correlation between Duration of inotropic support and serum magnesium levels.

Effect of admission Serum ionised calcium levels on duration of inotropic support

A positive non-significant correlation was established between serum ionised calcium at admission and the duration of inotropic support (Figure 4.13).

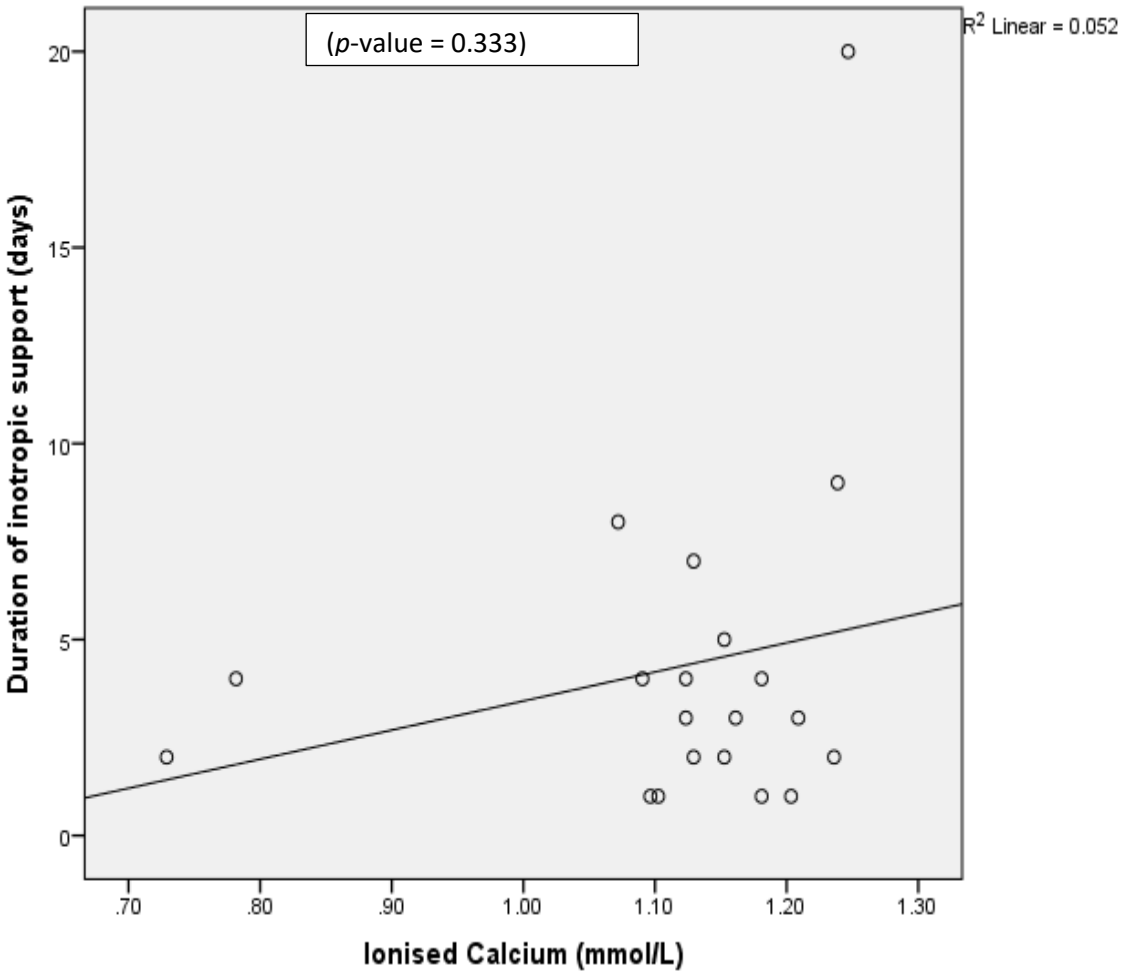


Figure 4. 13. Correlation between Duration of inotropic support and serum ionised calcium levels

4.11 Effect of admission Serum Phosphate levels on duration of mechanical ventilation.

There was a non-significant negative correlation between admission serum phosphate levels and duration of ventilatory support (*p*-value = 0.638).

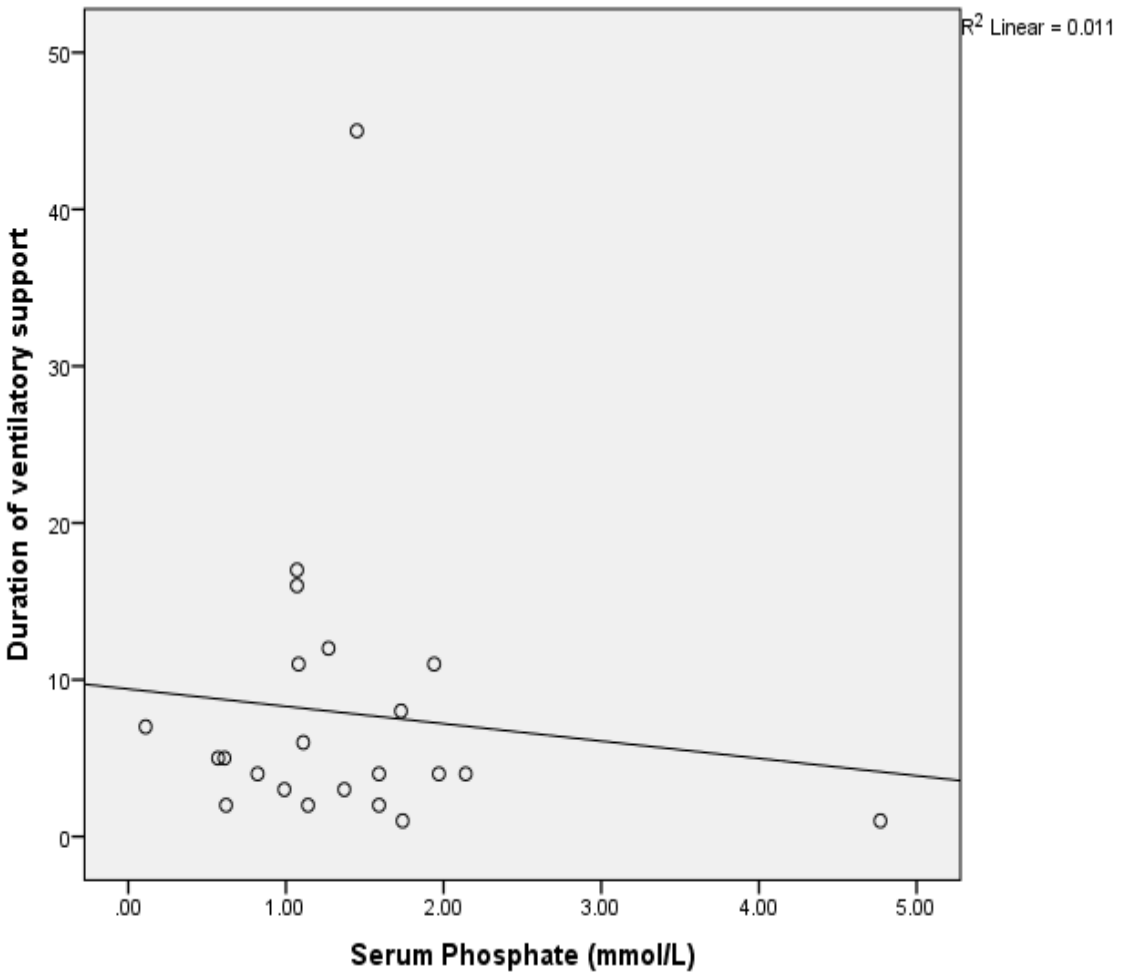


Figure 4. 14. Correlation between Duration of ventilatory support and serum phosphate levels

4.12 Effect of admission Sodium, Chloride and Potassium levels on the SOFA score

There was no relationship between SOFA scores and serum chloride levels at admission (Figure 4.15).

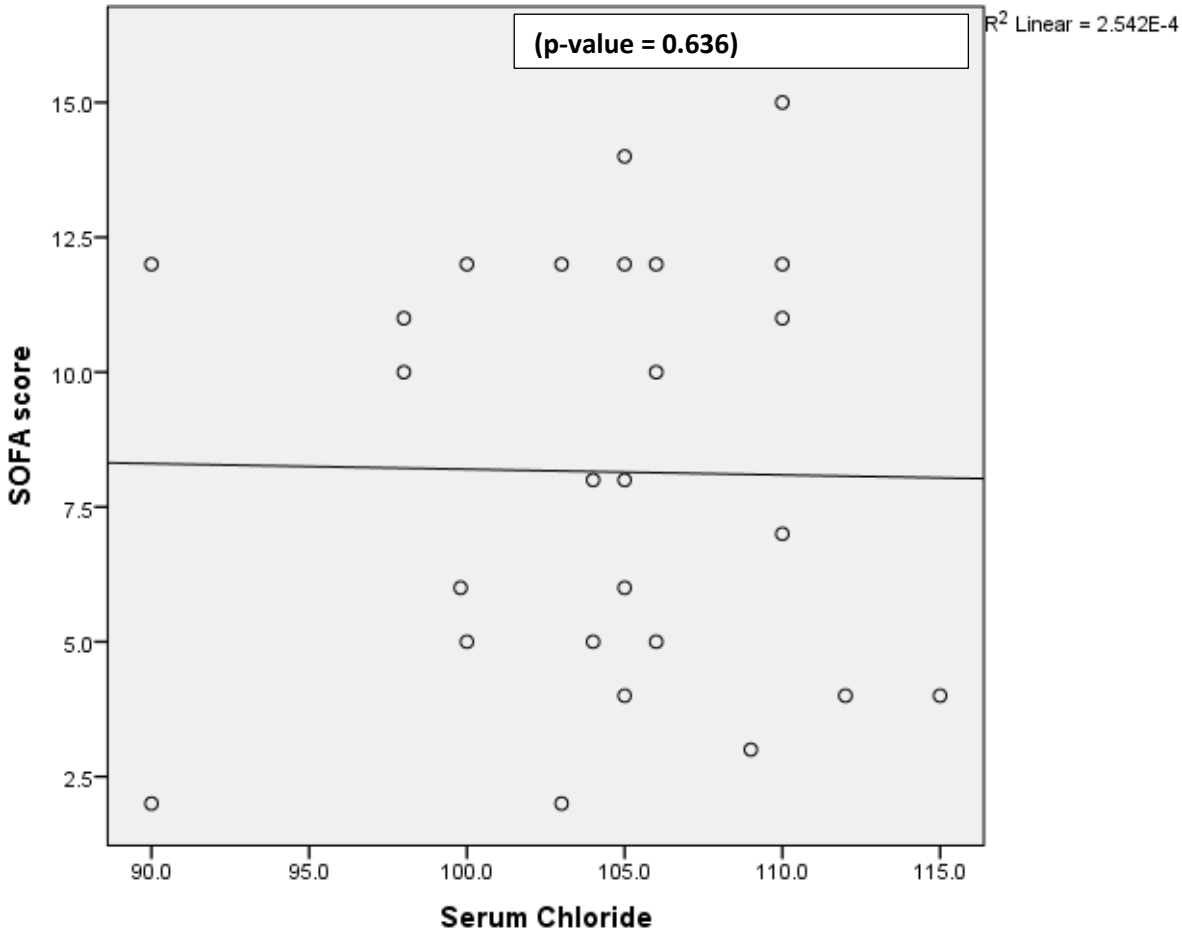


Figure 4. 15. Correlation between serum chloride levels at admission and SOFA scores

A positive non-significant correlation was found between SOFA scores and serum potassium levels at admission (Figure 4.16).

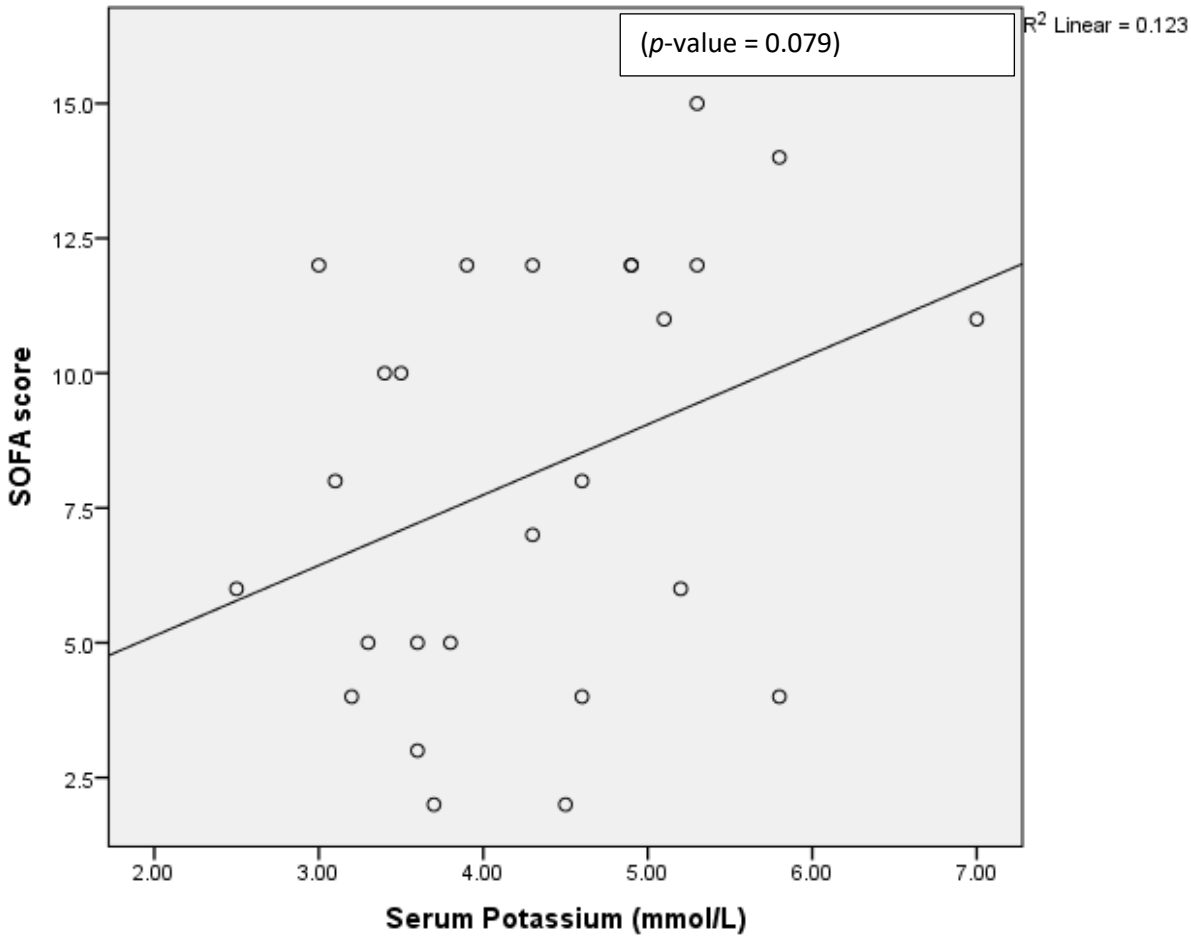


Figure 4. 16. Correlation between serum potassium level at admissions and SOFA score

The study found a non-significant negative correlation between serum sodium levels at admission and SOFA scores (Figure 4.17).

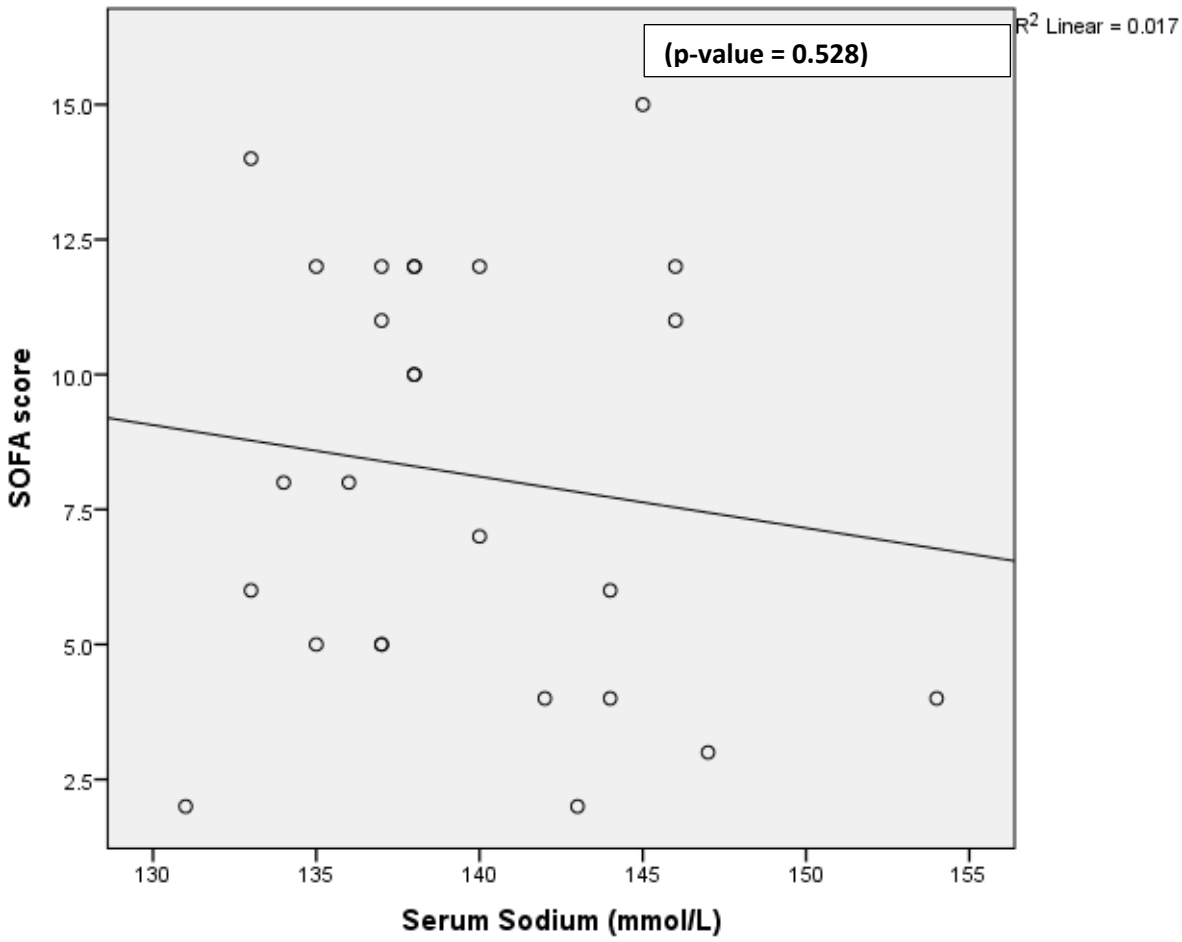


Figure 4. 17. Correlation between serum sodium level at admissions and SOFA score

4.13 Effect of admission Sodium, Chloride and Potassium levels on Mortality

Of the total number of study participants recruited 13 which accounted for 50% of them died and the other 50% also making up 13 of them were discharged. This translates into a mortality rate of 50% for the recruited number of patients in this study. At admission 25% of the hyponatraemic patients died and 100% of those with high serum sodium levels died. The risk of mortality was higher in the hypernatraemic group compared to those with normal serum levels (Table 4.8)

Equal number of the participants who were hypokalaemic and hyperkalaemic died. The hypo and hyperkalaemic participants had greater risk of mortality compared to those who had normal serum potassium levels. There was an equal risk of mortality for both hypo and hyperkalaemia at admission (Table 4.9).

The risk of mortality was higher in the group that had normal serum chloride levels at admission. This was followed by the recruits who were hyperchloremic and least in those who had low serum chloride levels. The patients who were normochloraemic had the highest proportion of the participants dying (54.5%) (Table 4.10).

Table 4. 8. Association between Serum Sodium levels at admission and mortality

	Mortality, n (%)		Fisher's Exact test	*p*-value
	Died	**Discharged**		
Hyponatraemia	1 (25.0)	3(75.0)	1.92	0.593
Normal	11(52.4)	10(47.6)		
Hypernatraemia	1(100)	0(0.0)		

Table 4. 9. Association between serum potassium level at admission and mortality

	Mortality, n (%)		Fishers' Exact test	*p*-value
	Died	**Discharged**		
Hypokalaemia	4(66.7)	2(33.3)	1.58	0.509
Normal	7(41.2)	10(58.8)		
Hyperkalaemia	2(66.7)	1(33.3)		

Table 4. 10. Association between Serum Chloride levels at admission and mortality

	Mortality, n (%)		**Fishers' Exact test**	***p*-value**
	Died	**Discharged**		
Hypochloraemia	0(0.0)	2(100)	2.05	0.729
Normal	12(54.5)	10(45.5)		
Hyperchloraemia	1(50.0)	1(50.0)		

4.14 Effect of admission Serum Phosphate, Magnesium and Ionised Calcium levels on Mortality

All participants who had low serum phosphate levels died whereas 50% of those with high serum phosphate levels died. Both low and high serum levels of phosphate at admission had a higher risk of mortality than those who had normal serum levels. (Table 4.11).

The highest risk of mortality was found in those who were hypermagnesaemic (83.3%). Those who had normal serum magnesium levels at admission had a higher risk of mortality than those who had low levels (Table 4.12).

A 100% mortality was seen in the patients who had their serum ionized calcium levels at admission below the lower limit of normal serum levels. Those with normal serum ionized had 45.8% of them dying (Table 4.13).

Table 4. 11. Association between Serum Phosphate levels at admission and mortality

	Mortality, n (%)		Fishers' Exact test	*p*-value
	Died	**Discharged**		
Hypophosphataemia	4(100)	0(0.0)	4.86	0.110
Normal	5(35.7)	9(64.3)		
Hyperphosphataemia	4(50.0)	4(50.0)		

Table 4. 12. Association between Magnesium levels at admission and mortality

	Mortality, n (%)		Fishers' Exact test	*p*-value
	Died	**Discharged**		
Hypomagnesemia	3(37.5)	5(62.5)	3.33	0.199
Normomagnesemia	5(41.7)	7(58.3)		
Hypermagnesemia	5(83.3)	1(16.7)		

Table 4. 13. Association between serum ionized Calcium levels at admission and mortality

	Mortality, n (%)		Fishers' Exact test	*p*-value
	Died	**Discharged**		
Hypocalcaemia	2(100)	0(0.0)	2.94	0.240
Normo-calcaemia	11(45.8)	13(54.2)		
Hypercalcaemia	0(0.0)	0(0.0)		

CHAPTER FIVE

DISCUSSION

Demographic and background clinical characteristics

Females formed the majority (53.8%) of the participants in this study. This might be attributable to the fact that amongst the top three admission diagnoses (up to 12%) were due to pregnancy related complications. The annual report (2021) for the ground floor surgical ICU, one of the study sites listed obstetric complications as one of the top three admission diagnosis. A study in a sub-Saharan country also showed similar finding of ICU admission diagnoses due to obstetric complications.[19] The mean age of study participants was 44.58 (± 15.94) which was comparable to a study by Suleiman et al(47.4 ± 18.3) in a Sudanese ICU[136] however this study listed neurological pathologies and sepsis as the two leading reasons for ICU admission. The ethnic groups that were most commonly recruited into the study were the Akan (61.5%) and the Mole-Dagbani (23.1%). The Ghana Statistical service states that these two ethnic groups are the most populous in the country accounting for 47.5% (Akan) followed by 16.6% (Mole-Dagbani). The presence of more recruits of the Mole-Dagbani ethnicity in the study centre which is in Accra may be attributable to rural- urban migration of Mole-Dagbani's from their northern enclaves to the south of the country. More than 80% of the migrants from the northern territories of Ghana settled in the two major cities in Ghana (Accra and Kumasi). [137]

Characteristics of ICU stay

The median length of ICU stay was 8 days which was comparable to a study by Sawe et al in a Tanzanian ICU which also found the median LOS in their ICU to be 8 days.[138]

Post-surgical complications (30%) was found to be the most common ICU diagnoses at admission in this study which was in keeping with a study by Dunser et al in a Ugandan ICU. They found the most frequent diagnosis at admission to the ICU to be a post-operative state(39%).[139]

More than 80% (84.6%) of the study recruits required mechanical ventilation which compared to another study in an ICU in a sub-Saharan country was high as this study had 49.7% of study participants requiring ventilatory support.[140] The discrepancy in the rate of ventilated patients

between this study and the current analysis may be attributable to the exclusion of severely ill patients from the MICU and PICU from the current study.

The rate of inotropic support was 76.9% at admission amongst recruited study participants.

The mortality rate was 50%, which was significantly higher than the 27.8 and 36% mortality rates seen in prior sub-Saharan African research.[19,141] This difference in mortality rate could be attributed to the fact that the authors used higher sample sizes than in this study and their studies were both retrospective.

Antibiotic administration within the first 48hours of ICU admission

Antibiotic administration in the ICU is a commonplace occurrence as most patients admitted into the ICU was due to sepsis or septic shock (about 15%) thus requiring antimicrobial agents as part of the therapeutic regimen. The patients that were in the ICU due to post-surgical complications were also on antibiotics prophylactically. Amoksiklav® (a trade name for Amoxicillin and Clavulanic acid) an antimicrobial agent with gram-positive cover and Flagyl® (a trade name for Metronidazole) an agent which covers anaerobic bacteria were the most commonly administered (23% each) in the ICU within the first 48 hours of ICU admission. This is due to the fact that these two agents are given routinely as prophylaxis for the clean surgeries as per protocol in the study centre.

Rocephin® (Ceftriaxone) is a third-generation Cephalosporin with the ability to pass the blood-brain barrier (BBB) and provide effective protection against meningitis. It is thus part of the protocol for antibiotic prophylaxis in neurosurgical surgeries in the centre where the study was conducted. In contrast to a study conducted on antibiotics in the ICU of a tertiary hospital in Malawi, Rocephin accounted for 20.5% of the antibiotics provided upon ICU admission. Rocephin represented a significant 73.4% followed by Metronidazole that was prescribed for 55.3% of ICU patients[142]. The variation in antibiotic prescription was due to the fact that as per the national treatment guidelines of Malawi, Ceftriaxone was the last line treatment antibiotic and was administered to the critically ill in the ICUs.

Admission serum electrolyte levels of critically ill patients

The main electrolytes that were measured at admission were Phosphate, Magnesium and Ionized Calcium. The mean serum electrolyte level for Ionised Calcium was 1.12 (± 0.12). None of the participants had high serum ionized calcium levels and about 7% were hypocalcaemic. Chepsy et al[4] however found a high prevalence (55%) of low serum ionised

calcium compared to this study. The reason could be the higher sample size used in their study and ionised calcium levels were obtained using ion specific electrodes; however, in this study ionised calcium was mathematically derived from total calcium.

Hother et al found the mean serum magnesium at admission to be 0.95 ± 0.23 mmol/L. This study found the mean serum electrolyte level of magnesium at admission to be 0.83 (± 0.25)[143]. The variation in means may be due to the fact that the study by Hother et al looked specifically at serum magnesium levels in children between 6-59 months who were undernourished in Ethiopia. However, this study sampled only adults older than 18 years.

Sepsis and septic shock accounted for 15% of the admission diagnoses of the study participants. Velisarris et al. found that hypomagnesemia is related with sepsis. [144] In this study, the prevalence of hypomagnesemia was 31% findings similar to Wang et al[68] who found 30.7% to be the prevalence of hypomagnesaemia. However, a study by Djagbletey et al found the prevalence of hypomagnesaemia in adults for emergency abdominal surgery to be 68%[63]. The higher prevalence may stem from the fact that there may be a longer duration of starvation in this patient group (for emergency abdominal surgery) with associated vomiting and diarrhoea lowering serum magnesium levels.

About 12% of the current study's recruits were due to pregnancy related complications where Magnesium Sulphate may have been administered as seizure prophylaxis for Eclampsia or as a part of the treatment regimen for Pre-eclampsia. This may result in high serum magnesium levels at admission. The prevalence of hypermagnesaemia in this study was 23%, a finding higher than found (2.3%) in a study by Wang et al. This variation may be attributed to the sample population being patients with traumatic brain injury.

The average serum phosphate level at admission was 1.35 (± 0.84) with 15% being hypophosphataemic and 31% being hyperphosphataemic. However, Cheuk Kin Sin et al revealed an average serum phosphate levels at admission to be 1.25 (±0.43) mmol/L with 10.8% of the study participants being hypophosphataemic and 19.3% being hyperphosphataemic.[145] The difference in values obtained may be due to the fact that the study by Cheuk Kin Sin was a multi-centre retrospective study.

Admission serum Phosphate levels and duration of Mechanical ventilation

The duration of ventilatory support was found to be negatively correlated with the serum phosphate levels in this study. Study participants with high serum phosphate levels required a

shorter duration of mechanical ventilation. This was due to the fact that they died within the first 72 hours of admission into the ICU.Al- Harbi found an association between hyperphosphataemia and increased mortality in adult patients being managed for sepsis .[90] Miller et al also found that hyperphosphataemia was associated with increased mortality (especially in patients on ventilatory support) and reduced duration of ventilatory support[91]. However, Wang et al revealed that patients who have a low serum phosphate levels required longer duration of mechanical support [5].This could be attributed to the physiological role phosphate plays in respiration through the contraction of the diaphragm and production of energy required for the active component of breathing..

Effects of admission serum electrolyte levels (Ionized Calcium, Magnesium and Phosphate) on LOS

There was a negative correlation between serum magnesium and phosphate upon admission and the length of ICU stay. It was noticed that the ICU stay was shorter the higher the serum entry levels of magnesium and phosphate. The reason for this brief stay was an elevated risk of mortality. Hyperphosphataemia was associated with longer ICU stays, according to Zheng et al., but this was a retrospective analysis.[146]

Another study indicated that a higher serum magnesium level at admission was related with a longer ICU stay and an increased risk of death.[78] This study was conducted on older patients with community-acquired pneumonia, whereas the current study recruited all critically sick patients between the ages of 18 and 75.

This study revealed a significant correlation between admission serum ionised calcium levels and length of ICU hospitalization. This data concurred with Kimura et al revealed that elevated ionised calcium at admission was associated with prolonged ICU stays.[106]

Effects of admission serum electrolyte levels (Ionised Calcium, Magnesium and Phosphate) on duration of inotropic support

A negative correlation was found between serum magnesium and phosphate at admission and the duration of inotropic support. It was observed that the higher the serum admission levels of magnesium and phosphate, the shorter the number of days inotropic support required. This relationship is deduced to be associated with the increased risk of mortality. This association is concluded to be linked with an increased mortality risk. Al- Harbi et al. also discovered that hyperphosphataemia is related with a considerably increased risk of mortality, which could potentially account for the shorter length of inotropic support required due to mortality.[88]

Another study showed that increase in serum phosphate levels contributed to increased requirements in inotrope doses but the study did not assess the duration of vasopressor use[147]. A previous study by Celi et al found high admission serum magnesium to be associated with increased need for vasopressor support due to hypotension but the study did not speak to the duration of inotropic support as it focused on need for vasopressors in the first 24 hours of ICU stay[146].

The association admission serum ionised calcium had with the duration of inotropic support was a positive association, high serum levels were related to an increased duration of inotropic support. This contradicts the findings of Desai et al who found that there was a strong significant association between hypocalcaemia and hypotension thus increasing need for vasopressor administration[148]. The study was undertaken in a Medical ICU and serum ionised calcium was directly measured as opposed to data being taken from the surgical ICU and critically ill Obstetric patients in the current study. Serum ionised calcium was as mathematically derived and not directly measured as was done by Desai et al.

Effects of admission serum electrolyte levels (Ionized Calcium, Magnesium and Phosphate) on SOFA scores

At admission, the SOFA score was determined concurrently with the collection of the main electrolytes being examined. High entrance serum levels of phosphate and magnesium were related to higher SOFA scores. The relationship between serum phosphate and SOFA scores in this study were statistically significant. Li et al had similar findings where hyperphosphataemia was associated with higher SOFA scores[147]. Al-Harbi et al also found an association between high serum phosphate levels at admission and higher scores of APACHE II[88]. Although the current study implemented the SOFA score as a severity of illness scoring system, Kumar et al found APACHE and SOFA scoring systems to have comparable sensitivities and specificities in the prediction of outcomes in the critically ill[140].

The SOFA scoring system is a valuable scoring system in forecasting mortality in the critically ill[140]. Increases in scores are associated with increased risk of mortality[140].SOFA scores were also found to be significantly higher in participants who fell into the hypermagnesaemia group in another study by Cirik et al[149] which was in keeping with the current study. High levels of serum magnesium[80] and high serum levels of phosphate [146] have been shown to be associated with increased risk of mortality it is therefore understandable that they would be associated

with higher SOFA scores. In this investigation, there was no correlation between admission serum ionised calcium and SOFA scores. Cekmen et al., however, found a negative connection between ionised calcium and SOFA scores. Hypocalcaemic patients exhibited a higher SOFA score and, thus, a higher mortality risk[150]. This retrospective investigation examined only septic patients, whereas the current analysis included all critically sick patients admitted to the surgical ICU

Effects of admission serum electrolyte levels (Sodium, Potassium and Chloride) on SOFA scores

In this study no significant corelation was found between serum chloride levels at admission and SOFA scores. Breen et al found a negative corelation between serum chloride levels and SOFA scores [151]. Low serum levels of chloride are associated with higher SOFA scores. The study by Breen et al was conducted amongst unselected patients admitted into a Cardiac ICU (CICU) whereas the current study was amongst critically ill patients admitted to an ICU that treated mainly surgical and obstetric patients.

The study revealed a correlation between admission serum potassium levels and SOFA scores. As demonstrated in the present study, high serum potassium levels were related with high SOFA scores, which is consistent with a study by Cai et al. [152]. High serum levels of potassium may cause abnormal cardiac rhythms such as ventricular fibrillation which is often lethal and may even lead to death.

A negative corelation was seen between SOFA scores and admission serum sodium levels. It was revealed that low serum levels were connected with high SOFA scores and vice versa. Despite being a retrospective research of ICU patients, Breen et al. had comparative findings. He found a significant association between low serum sodium levels at admission and an increased risk of mortality, resulting in higher SOFA scores[26]. Stelfox et al also found that hyponatraemia was also associated with higher APACHE scores.[31]

Relationship between serum levels of Ionized Calcium, Magnesium and Phosphate at admission

Consistent with a study by Moe et al., there was a positive and significant correlation between serum magnesium and serum phosphate upon admission.[153]. The study found a positive, non-significant relationship between serum ionised calcium and serum phosphate[153]. The correlation between serum ionised calcium and serum magnesium was found to be negative

and non-significant in the present investigation. Na et al. found a negative correlation between serum calcium and serum magnesium.[152]

Association between serum electrolyte levels at admission and Mortality

Twenty-five percent (25%) of patients who were hyponatraemic at admission died and 100% of those with high serum sodium levels at admission died. Those with hypernatraemia had a greater risk of mortality than those with normal serum levels. Chi et al. found that serum sodium abnormalities at admission were associated with an increased risk of mortality[32]. Breen et al. revealed that those with low serum sodium levels had a significantly higher risk of dying [26]. This study was however a retrospective study amongst CICU patients.

Equal number of the participants who were hypokalemic and hyperkalemic died. The hypo and hyper-kalaemic participants had greater risk of mortality compared to those who had normal serum potassium levels. There was an equal risk of mortality for both hypo and hyper-kalaemia at admission. A study by Collins et al had similar findings where risk of mortality was more in deranged serum levels of potassium compared with normal levels[154].

Mortality risk was greater in the group with normal serum chloride levels at admission. This group had a much higher mortality rate (54.5%). Another study indicated that low serum chloride levels were associated with an increased risk of mortality[155].

All participants who had low serum phosphate levels died whereas 50% of those with high serum phosphate levels died. Both low and high phosphate levels at admission were associated with a greater risk of mortality than normal phosphate levels. Hypophosphataemia carried a higher risk of mortality than hyperphosphataemia. Zheng et al rather ascribed high serum phosphate levels a higher mortality risk.[146] The disparity in findings may be attributed to the fact that this was a retrospective study.

Hypermagnesaemia was associated with an 83.3% increased risk of mortality. Those with normal serum magnesium levels upon admission had a greater mortality risk than those with low levels. Another study indicated that hypermagnesaemia is associated with an increased risk of mortality.[78]

There was a 100% mortality of the hypocalcaemic patients in the current study. Yue Yi et al. showed a correlation between low serum ionized calcium and higher 30-day death risk in critically ill patients.[103]. This finding corroborates with the findings in the current study.

Study Limitations

1. The laboratory used for analysis of electrolytes was the Central Laboratory of the Korle-Bu Teaching Hospital. In their analysis of serum Calcium levels, only total Calcium in mmol/L and mg/dL is reported. Calcium adjusted against albumin is also reported. Ionised calcium is not reported by the laboratory. Hence ionised calcium had to be mathematically calculated from the serum total calcium(mmol/L).
2. This was a single-center study therefore care needs to be taken to generalize findings to the entire population.
3. The study population excluded participants under the age of 18 years. Therefore, it may be challenging to apply the study's findings to younger ICU patients.
4. The sample size was quite small and a larger number of recruits may have increased the power of the study.

CHAPTER SIX

CONCLUSION AND RECCOMMENDATIONS

6.1 CONCLUSION

The mean selected admission serum electrolyte levels were within the normal ranges. There was a positive, significant relationship between serum phosphate and serum magnesium at admission. A positive, non-significant relationship was found between serum ionized calcium and serum phosphate at admission. There was a negative relationship between serum ionized calcium and serum magnesium at admission.

Hyperkalaemia, hyponatraemia, hyperphosphataemia, hypermagnesaemia and hypercalcaemia were associated with higher SOFA scores.

There was a positive correlation between admission ionized calcium and LOS. Hypermagnesaemia and hyperphosphataemia were associated with shorter LOS in the ICU.

There was a positive correlation between admission ionized calcium and duration of inotropic support. Hypermagnesaemia and hyperphosphataemia were associated with shorter duration of inotropic support.

Hyperphosphataemia was associated with shorter duration of mechanical ventilation.

Hypokalaemia and hyperkalaemia, hypernatraemia, hyperchloraemia, hypophosphataemia, hypermagnesaemia and hypocalcaemia were associated with increased mortality.

6.2 RECOMMENDATIONS

1. It should be made part of the study institution's ICU protocol to check at admission and as frequently as possible serum phosphate levels and correct levels whenever required. This is due to the correlation between derangements of serum phosphate levels and negative outcomes.
2. A larger, multi-center study is required to extrapolate the findings to all critically ill patients
3. A further study should be undertaken in which serial samples of the study electrolytes are taken and analyzed at different times during the stay in the ICU.
4. Involvement of the Dieticians to aid in correction of mild-moderate derangements of serum phosphate levels using Dietherapy. This would involve phosphate rich dietary formulations and diet plans.
5. Local Pharmaceutical companies can be engaged to ensure availability of agents needed to manage serum phosphate derangements. These include intravenous and oral formulations of phosphate and phosphate binders such calcium carbonate and calcium acetate.

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APPENDICES

Appendix 1: Informed Consent form

Dr Lorraine Baffour-Awuah

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P.O. Box 77

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I am Dr. Lorraine Baffour- Awuah, a Specialist with the Department of Anaesthesia, Korle-Bu Teaching Hospital. I am conducting a study to assess selected admission serum electrolyte levels and associated clinical outcomes of critically ill patients at the Korle-Bu Teaching Hospital. We are asking you/your relation to enrol in this study. This form is designed to provide you with information and answer any questions you may have pertaining to this study. If your decision is not to enrol in the study, this decision will not affect your management in any way whatsoever.

TITLE OF STUDY

Selected admission serum electrolyte levels and associated clinical outcomes in critically ill patients at the Korle- Bu Teaching Hospital.

PURPOSE OF STUDY

To determine the serum electrolyte levels of Phosphate, Magnesium, and Calcium at admission and associated clinical outcomes in critically ill patients at the Korle-Bu Teaching Hospital.

PROCEDURES

Once your consent is sought, you/your relation will have their blood sample taken to measure serum levels of the electrolytes being studied on the day of admission to the Intensive Care/ High Dependency Unit (ICU/HDU). Other laboratory investigations that are routinely done during management of the Critically Ill will be done and Scores will be derived from these results. These scores will be calculated on the day of admission.

BENEFITS

The findings of this study will inform the implementation of protocols concerning serum electrolytes that are not routinely checked and corrected as per standard practices in our ICU. This would improve outcomes; reduce duration of ICU stay, ventilatory support and inotropic support and be of benefit to patients as serum phosphate levels which are not routinely checked will be done and corrected when derangements occur.

RISKS

The risks of this study are from associated risks due to obtaining the peripheral/ central venous access and arterial cannulation. These are infection, pain, hematoma formation and embolization. To avoid these complications, the needed levels of sterility will be observed during performance of the procedures and they will be performed by Physicians of the requisite competencies.

CONFIDENTIALITY

All information obtained from this study will be kept confidential. In the event that this study is published, you/your relation shall be kept anonymous and identified as a number.

SUBJECT RIGHTS

Any enquiries or concerns pertaining to the research may be addressed to me. You/ your relation's participation in this study is voluntary and you are at liberty to withdraw without any penalty at any time within the course of the study.

SUPERVISORS

Prof Ernest Aniteye
Consultant Anaesthetist/Associate Professor
National Cardiothoracic Centre/University of Ghana Medical School

Dr Audrey Anno
Consultant Anaesthetist
Department of Anaesthesia
Korle-Bu Teaching Hospital

INFORMED CONSENT FORM TO PARTICIPATE IN THE STUDY

I have fully explained this research to the patient or relation and have given sufficient information about the study, including that on procedures, risks and benefits to enable the prospective participant to make an informed decision whether or not to participate

Investigator …….

Date …….

I have read the information of this study or have had it translated into a language I understand. I have also talked it over with the interviewer to my satisfaction. I understand that it is not compulsory to participate in this study. I have been made to understand the benefits, risks and methods of this study. I understand that I may withdraw from this study at any time without it impacting my/ my relation's care.

Signature/ Thumbprint of Patient or Relation……

Date…….

Witnessed by……

Designation ……

Date…….

Appendix II : Data Collection Sheet

SELECTED ADMISSION SERUM ELECTROLYTES AND ASSOCIATED CLINICAL OUTCOMES IN CRITICALLY ILL PATIENTS ADMITTED TO THE KORLE-BU TEACHING HOSPITAL

DATA COLLECTION FORM

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Appendix 3- Korle Bu Teaching Hospital Institutional Approval Letter

In case of reply the number
And the date of this
Letter should be quoted

My Ref. No. KBTH/IRB/03/22

Your Ref. No.....

KORLE BU TEACHING HOSPITAL
P. O. BOX KB 77,
KORLE BU, ACCRA

Tel: +233 302 667759/673634-6
Fax: +233 302 667759
Email: info@kbth.gov.gh
pro@kbth.gov.gh
Website: www.kbth.gov.gh

21st June, 2022

DR. LORRANINE BAFFOUR-AWUAH
DEPARTMENT OF ANAESTHESIA
KORLE BU

INSTITUTIONAL APPROVAL: KORLE BU TEACHING HOSPITAL-SCIENTIFIC AND TECHNICAL COMMITTEE/INSTITUTIONAL REVIEW BOARD (KBTH-STC/IRB/000189/2021

Following approval of your study entitled "Selected Admission Serum Electrolyte Levels and Associated Clinical outcomes in Critically Ill Patients Admitted at the Korle Bu Teaching Hospital" by the Korle Bu Teaching Hospital-Scientific and Technical Committee/Institutional Review Board.

I am pleased to inform you that institutional approval has been granted for the conduct of your study in Korle Bu Teaching Hospital.

Please contact the Head of Department to discuss the commencement date of the study.

Please note that, this institutional approval is rendered invalid if the terms of the Institutional Reviewed Board/Scientific and Technical Committee approval are violated.

Sincere regards,

Dr. Harry Akoto
Ag. Director of Medical Affairs
For: Chief Executive

Appendix IV : IRB Approval Letter

In case of reply the number
And the date of this
Letter should be quoted
My Ref. No. KBTHIRB/000189/22
Your Ref. No.....

KORLE BU TEACHING HOSPITAL
P. O. BOX KB 77,
KORLE BU, ACCRA.

Tel: +233 302 667759/673034-6
Fax: +233 302 667759
Email: Info@kbth.gov.gh
pr@kbth.gov.gh
Website: www.kbth.gov.gh

20th June, 2022

DR. LORRAINE BAFFOUR-AWUAH
DEPARTMENT OF ANAESTHESIA
KORLE-BU TEACHING HOSPITAL
P. O. BOX 77
ACCRA

SELECTED ADMISSION SERUM ELECTROLYTE LEVELS AND ASSOCIATED CLINICAL OUTCOMES IN CRITICALLY III PATIENTS ADMITTED AT THE KORLE BU TEACHING HOSPITAL

KBTH-IRB /000189/2021

Investigator: DR LORRAINE BAFFOUR-AWUAH

The Korle Bu Teaching Hospital Institutional Review Board (KBTH IRB) reviewed and granted approval to the study entitled: "Selected Admission Serum Electrolyte Levels and Associated clinical outcomes in Critically III Patients Admitted at the Korle Bu Teaching Hospital"

Please note that the Board requires you to submit a final review report on completion of this study to the KBTH-IRB.

Kindly, note that, any modification/amendment to the approved study protocol without approval from KBTH-IRB renders this certificate invalid.

Please report all serious adverse events related to this study to KBTH-IRB within seven days verbally and fourteen days in writing.

This IRB approval is valid till 30th May, 2023. You are to submit annual report for continuing review.

Sincere regards,

DR. DANIEL ANKRAH
VICE CHAIR (KBTH-IRB)
FOR: CHAIR (KBTH-IRB)

Cc: The Chief Executive Officer, KBTH
The Director of Medical Affairs, KBTH