HYPOMAGNESEMIA IN CRITICALLY ILL PATIENTS ON ADMISSION TO THE CRITICAL CARE UNITS AT THE KENYATTA NATIONAL HOSPITAL: A Prospective observational cohort study

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MMED INTERNAL MEDICINE

A thesis proposal submitted in partial fulfillment of the requirements for the award of degree of Master of Medicine in Internal Medicine of the University of Nairobi
DECLARATION
This dissertation is my original work. It has not been submitted either wholly or in part to any other university for the award of a Degree in Masters of Internal Medicine

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LIST OF ABBREVIATIONS

ACC: AMERICAN COLLEGE OF CARDIOLOGY
AFIB: ATRIAL FIBRILLATION
AHA: AMERICAN HEART ASSOCIATION
AMI: ACUTE MYOCARDIAL INFARCTION
APACHE: ACUTE PHYSIOLOGY AND CHRONIC HEALTH EVALUATION:
ATP: ADENOSINE TRIPHOSPHATE
CA: CALCIUM
CCU: CRITICAL CARE UNITS
ECG: ELECTROCARDIOGRAM
ICU: INTENSIVE CARE UNIT
IP 3: INOSITOL TRIPHOSPHATE
K: POTASSIUM
KNH: KENYATTA NATIONAL HOSPITAL
MAT: MULTIFOCAL ATRIAL TACHYCARDIA
MG: MAGNESIUM
N-K-ATPASE: SODIUM- POTASSIUM ADENOSINE TRIPHOSPHATE
PTH: PARATHYROID HORMONE
QTc: CORRECTED QT INTERVAL
SD: STANDARD DEVIATION
TAL: THICK ASCENDING LOOP OF HENLE
TPN: TOTAL PARENTERAL NUTRITION
VFIB: VENTRICULAR FIBRILLATION
VT: VENTRICULAR TACHYCARDIA
ABSTRACT

Background: The prevalence of hypomagnesaemia in critically ill adult patients varies between 14-66%. Magnesium depletion is described as the most under diagnosed electrolyte abnormality in current medical practice yet it plays a fundamental role in cell functions that include: energy transfer, protein, carbohydrate and fat metabolism, maintenance of normal cell membrane function and the regulation of parathyroid hormone secretion(PTH). Magnesium depletion has been directly associated with hypokalemia, hypocalcemia, and arrhythmias. It’s also been associated with worse clinical outcomes among the critically ill, hence hypomagnesaemia has prognostic importance on patient’s outcome. There’s lack of local data on the prevalence of hypomagnesaemia among the critically ill patients.

Objective: The aim of the study was to determine the prevalence of serum hypomagnesaemia in critically ill patients on admission to the Kenyatta National Hospital critical care units, to assess related electrolyte abnormalities and to explore the role of hypomagnesaemia in outcome prediction.

Study design: Prospective observational cohort study.

Study site: Kenyatta National Hospital’s critical care units.

Study Population: Critically ill patients on admission to the critical care units at Kenyatta National Hospital.

Methodology: Critically ill patients on admission to the critical care units (CCU) were screened for eligibility and recruited upon signing an informed consent either by patient or proxy. Patient’s demographics and clinical information were captured in a study proforma. Acute Physiology And Chronic Health Evaluation II( APACHE II) score was determined and a 12 lead ECG performed within 24 hrs of admission into the critical care units. Investigations done included; serum magnesium, potassium, sodium, calcium and albumin levels, full hemogram, serum creatinine and arterial blood gas analysis for which blood was drawn within 24 hours of admission. Patients were thereafter followed up for 2 weeks outcome. Data analysis was done using STATA version 11.
Results: Totally, 198 critically ill patients who were admitted to medical/surgical critical care units were enrolled in this study during a 4-month period. The mean age of patients was 42.8±18.9 yrs (range, 13-92 yrs). There were 138 males (69.7%) and 60 (30.3%) females. The mean APACHE II score was 24.1±6.5.

The mean serum magnesium level measured during the first 24 hours of admission was 0.9±0.4Mmol/L (range, 0.4-4.5 Mmol/L). On admission, 137 patients (69.2%) had normal serum magnesium level, while 33 patients (16.7%) had hypomagnesemia and 28 patients had hypermagnesemia (14.1%). The mean serum calcium levels were 2.3±0.2Mmol/L (range, 1.4-2.7 Mmol/L), 181 subjects (73.7%) had normal serum calcium levels, while 12 subjects (6.1%) had hypocalcemia and 5 patients (2.5%) had hypercalcemia. The mean serum potassium levels were 4.7±1.2Mmol/L (range, 2.5-9.0 Mmol/L), 121 subjects (61.1%) had normal potassium levels, while 58 subjects (29.3%) and hyperkalemia and 19 patients (9.6%) had hypokalemia.

The median length of CCU stay was 3 days (IQR; 1.75-10.75 days). Mechanical ventilation was applied for 36.8% (n=73) of patients. The length of mechanical ventilation for those attached to the ventilator was 48 hrs (IQR; 24-108 hrs). The mortality rate at 14 days was 55.1% (n=109).

A higher APACHE II score was observed more frequently in the patients who had low magnesium compared to the normal magnesemic patients (26.5±7.6 Vs 23.7±6.1 p= 0.03). A longer QTc interval was also observed more frequently in the hypomagnesemic patients compared to the normal magnesemic patients (434.8±39.9 Vs 408.8 ± 29.8 p< 0.001). There was no association between serum magnesium levels and clinical outcomes.

Conclusion: This study found that the prevalence of hypomagnesemia is common in the critical care setting and more so in the very severely ill patients. Therefore, routine monitoring of serum magnesium and clinical assessment of patients at risk for magnesium deficiency remains vital for making a timely diagnosis of magnesium depletion.
1.0 LITERATURE REVIEW

1.1 INTRODUCTION
Magnesium is the fourth most abundant cation in the body and the second most abundant intracellular cation after potassium. The total body magnesium level of an average adult is 24 g, or 1000 Mmol. Approximately 60% of the body’s magnesium is present in bone, 20% is in muscle, and another 20% is in soft tissue.

Magnesium depletion is described as the most under diagnosed electrolyte abnormality in current medical practice. It commonly occurs in critical illness and correlates with a higher mortality and worse clinical outcomes. Low serum magnesium levels have been directly implicated in hypokalemia, hypocalcemia, and dysrhythmia. The principle causes of Mg loss among the critically ill are gastrointestinal and renal losses.

Magnesium serves as a cofactor in more than 300 enzymatic reactions mainly involving transfer of phosphate group for example formation of ATP. It also maintains neuromuscular excitability and it’s important for maintenance of cardiac function. By regulating enzymes controlling intracellular calcium, Mg affects smooth muscle vasoconstriction, important to the underlying pathophysiology of several critical illnesses.

The use of Mg therapy is supported by clinical trials in the treatment of symptomatic hypomagnesaemia and preeclampsia and is recommended for torsade de pointes. Magnesium therapy is not supported in the treatment of acute myocardial infarction and is presently undergoing evaluation for the treatment of severe asthma exacerbation, for the prevention of post coronary bypass grafting dysrhythmias, and as a neuroprotective agent in acute cerebral ischemia.

Clinical evaluation of magnesium status is associated with numerous difficulties. First, serum ionized Mg2+, the biologically significant fraction of magnesium, is not routinely measured. Second, no single laboratory test tracks total body magnesium stores. Finally, changes in extracellular (serum) magnesium levels may not necessarily reflect intracellular level.

Despite the fact that serum levels of magnesium represent only 0.3% of total body magnesium content and that serum magnesium concentrations do not correlate with other tissue pools, the total serum magnesium concentration is still used as the standard for evaluating magnesium status in patients.
1.2 EPIDEMIOLOGY

Hypomagnesaemia occurs in up to 12% of hospitalized patients\textsuperscript{13}. The incidence rises to as high as 60 to 65% in patients in intensive care settings in which nutrition, diuretics, hypoalbuminemia and amino glycosides may play important roles\textsuperscript{14,15,16}

Table 1 gives the prevalence of hypomagnesaemia and hypomagnesaemia in various international studies carried out previously in critically ill patients. Most of the studies carried out previously have measured total serum magnesium. The prevalence of hypomagnesaemia was in the range of 14% to 70%.

More important, patients who develop Mg deficiency in the ICU have mortality rates 2 to 3 times higher and prolonged hospitalization compared with those who are not Mg deficient. A retrospective study was done on 100 patients in Isfahan by Safavi and colleagues\textsuperscript{17}. At the time of admission, 51% of patients had hypomagnesaemia. They reported significant differences in mortality rates (55% vs. 35%) and the length of hospital or ICU stay between hypomagnesaemic and normomagnesemic patients.

1.3 MAGNESIUM METABOLISM

The normal adult human body contains approximately 1,000 Mmols of magnesium (22-26 g).\textsuperscript{18} The distribution of magnesium within the body is shown in Table 2. About 60% of the magnesium is present in bone, of which 30% is exchangeable and functions as a reservoir to stabilize the serum concentration. About 20% is in skeletal muscle, 19% in other soft tissues and less than 1% in the extracellular fluid. Skeletal muscle and liver contain between 7-9 Mmol/Kg, between 20-30% of this is readily exchangeable.

In normal adults, total serum magnesium ranges between 0.70 and 1.10 Mmol/L. Approximately 20% of this is protein bound, 65% is ionized and the rest is complexed with various anions such as phosphate and citrate\textsuperscript{18}. Of the protein bound fraction, 60-70% is associated with albumin and the rest is bound to globulins.\textsuperscript{19} The reference range for serum ionized magnesium concentration (0.54-0.67 Mmol/L) is narrower than that for calcium\textsuperscript{18}.
Magnesium homeostasis involves the kidney, small bowel, and bone. Absorption occurs along the entire intestinal tract but primarily occurs along the jejunum and ileum. There exist both a passive paracellular mechanism and an active transport process for Mg absorption. The paracellular mechanism is dependent on a transcellular potential difference generated by sodium transport and accounts for about 90% of intestinal Mg absorption. Paracellular movement of Mg occurs in the leaky epithelia of the small intestine, whereas in the large intestine, as yet unidentified membrane proteins on the luminal and basal surfaces transport Mg into the body. From 30% to 50% of dietary Mg is absorbed under normal dietary conditions. Unlike factors that regulate calcium metabolism, factors that control Mg absorption are unclear. Neither vitamin D nor parathyroid hormone (PTH) has been shown to directly affect Mg homeostasis.

<table>
<thead>
<tr>
<th>STUDY</th>
<th>YEAR</th>
<th>NO. OF PATIENTS</th>
<th>MAGNESIUM MEASURED</th>
<th>LOW MAGNESIUM</th>
<th>HIGH MAGNESIUM</th>
<th>NORMAL MAGNESIUM</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTERNATIONAL STUDIES</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ryzen et al</td>
<td>1985</td>
<td>94</td>
<td>Total</td>
<td>51%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Chernow et al</td>
<td>1989</td>
<td>193</td>
<td>Total</td>
<td>61%</td>
<td>5%</td>
<td>34%</td>
</tr>
<tr>
<td>Reinhart et al</td>
<td>1989</td>
<td>102</td>
<td>Total</td>
<td>20%</td>
<td>9%</td>
<td>71%</td>
</tr>
<tr>
<td>Rein et al</td>
<td>1993</td>
<td>197</td>
<td>Total</td>
<td>20%</td>
<td>7%</td>
<td>73%</td>
</tr>
<tr>
<td>Guerin et al</td>
<td>1996</td>
<td>179</td>
<td>Total and erythrocyte</td>
<td>44% 66%</td>
<td>6% 4%</td>
<td>50% 30%</td>
</tr>
<tr>
<td>Huijigen et al</td>
<td>2000</td>
<td>115</td>
<td>Ionized</td>
<td>14%</td>
<td>12%</td>
<td>74%</td>
</tr>
<tr>
<td>Deheinzelin et al</td>
<td>2000</td>
<td>226</td>
<td>Total</td>
<td>45.6%</td>
<td>-</td>
<td>54.4%</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Sample Size</td>
<td>Reabsorption</td>
<td>Ionized</td>
<td>Total</td>
<td>18%</td>
</tr>
<tr>
<td>-------------------</td>
<td>------</td>
<td>-------------</td>
<td>---------------</td>
<td>---------</td>
<td>-------</td>
<td>------</td>
</tr>
<tr>
<td>Soliman et al</td>
<td>2003</td>
<td>422</td>
<td>Ionized</td>
<td>18%</td>
<td></td>
<td>14%</td>
</tr>
<tr>
<td>C.S Limaye</td>
<td>2004/5</td>
<td>100</td>
<td>Total</td>
<td>52%</td>
<td>7%</td>
<td>41%</td>
</tr>
<tr>
<td>Safavi et al</td>
<td>2007</td>
<td>100</td>
<td>Total</td>
<td>51%</td>
<td>-</td>
<td>49%</td>
</tr>
</tbody>
</table>

The kidney is the primary site of Mg homeostasis. About 2.4 g of Mg is filtered each day, and 120mg (5%) is normally excreted in the urine. The sites of Mg reabsorption in the kidney involve the proximal tubule, the thick ascending loop (TAL) of Henle, and the distal tubule. The proximal tubule reabsorbs 15% to 20% of filtered Mg, whereas the TAL reabsorbs 65% to 75% and is the primary site of Mg reabsorption. Magnesium absorption in the TAL is modulated by the extracellular calcium sensing receptor (CASR) through changes in transepithelial voltage and alterations in the permeability of the paracellular pathway. Finally, the distal tubule is responsible for 5% to 10% of Mg reabsorption. The thick ascending limb of the loop of Henle and the distal convoluted tubule are the sites where hormones, such as parathyroid hormone, insulin, aldosterone and prostaglandins and drugs such as diuretics, affect magnesium excretion.
Extracellular (serum) magnesium concentrations are regulated through gastrointestinal absorption, renal excretion and exchange from bony compartments.

**1.3.1 PHYSIOLOGICAL ROLE OF MAGNESIUM**

Mg $^{2+}$ is a required cofactor in hundreds of enzyme systems. Magnesium may be required for substrate formation, as an allosteric activator of enzyme activity, and for membrane stabilization. Adenylate cyclase and the sodium-potassium-adenosine triphosphatase (Na,K,ATPase) are enzymes that are critically dependent on Mg.

Basic studies suggest that Mg ions modulate immunological functions such as granulocyte oxidative burst, lymphocyte proliferation, and endotoxin binding to monocytes. Mg deficiency is correlated with increases in interleukin-1, tumor necrosis factor-$\alpha$, interferon-$\gamma$, and substance P. Magnesium deficiency in rats has been associated with greater inflammatory response to an endotoxin challenge.
The effects of Mg on these enzymes, as well as on other important biological processes such as glycolysis, oxidative phosphorylation, nucleotide metabolism, protein biosynthesis, and phosphoinositol turnover, underscore the importance of Mg in cellular metabolism. Mg regulates the intracellular calcium levels and thereby influences smooth muscle tone. Smooth muscle tone is determined by calcium-dependent phosphorylation of myosin light chain. Higher levels of intracellular calcium are associated with more smooth muscle constriction. Activation of inositol triphosphate (IP3) releases intracellular calcium stored in the sarcoplasmic reticulum (SR). Calcium also enters from the extracellular space through ligand gated and voltage gated calcium channels. Intracellular Mg2+ decreases IP3 activation of SR calcium release. Moreover, Mg increases calcium ATPase, which moves calcium back into the SR and into the extracellular space. Extracellular Mg disrupts the electrochemical gradient that brings extracellular calcium into the cell via calcium channels. Therefore, a deficiency in Mg will lead to an increased release of SR calcium, decreased calcium returning to the SR and extracellular space, and an increased passage of extracellular calcium through gated channels. The net effect will be an increase in intracellular calcium and increased smooth muscle vasoconstriction. By regulating smooth muscle tone, Mg deficiency has been proposed to cause hypertension, neuromuscular hyperexcitability, bronchial airway constriction, coronary vasospasm, and seizures.

1.4 ASSESSMENT OF MAGNESIUM STATUS

Normal total serum Mg levels are reported as 0.7 to 1.0 Mmol/L (1.7-2.4 mg/dL). Similar to calcium, extracellular Mg2+ has significant protein bound fractions, creating the potential for large differences between total serum and ionized levels. As previously mentioned, only 0.3% of total body Mg is contained in serum. Thus, total serum Mg concentration may not adequately reflect body Mg stores, and patients may have a normal serum Mg and total-body Mg depletion. At present, there is no simple, rapid and accurate laboratory test to indicate the total body magnesium status. The most commonly used method for assessing magnesium status is the serum magnesium concentration. The total serum magnesium concentration is not the best method to evaluate magnesium status as changes in serum protein concentrations may affect the
total concentration without necessarily affecting the ionised fraction or total body magnesium status. Measurement of ultrafiltrable magnesium may be more meaningful than the total magnesium as it is likely to reflect ionised magnesium concentration, but methods are not available for routine use.

The utility of the total serum Mg and ionized serum Mg2+ to reflect body Mg status or to predict clinical outcome has not been established. The studies done are conflicting in terms of deciding whether serum ionized Mg2+ is better than total serum Mg and whether ionized Mg2+ will predict clinical outcome in the critical care setting. The problem may exist with the ion selective electrodes (ISE). Several different manufacturers produce ISE. Significant differences exist in terms of normal reference ranges as well as precision of the measurement\(^43\)\(^44\). Standardization of the ISE and further prospective studies assessing both total and ionized serum Mg are needed in the critically ill population.

Intracellular Mg2+ can also be estimated using circulating red blood cells, mononuclear cells, and skeletal muscle cells. Intracellular Mg2+ has been assessed as an index of Mg status\(^45\)\(^46\) and is generally a more accurate indicator of Mg status than the total serum Mg concentration\(^47\)\(^48\). However, a great deal of overlap with the normal range is seen, and intracellular Mg2+ is not a sufficiently discriminatory test to diagnose Mg deficiency in any given patient\(^49\).

The Mg tolerance test has been used for many years and may be the most accurate means of assessing Mg status\(^50\). The test is performed by measuring Mg in a 24-hour urine collection, followed by the administration of 2.4 mEq/kg of parenteral Mg, followed by a second 24-hour urine collection for Mg. Under circumstances of normal Mg balance and renal function, most of the Mg load will be excreted in 24 hours. Retention of more than 20% of the administered Mg is suggestive of Mg deficiency. Although the Mg tolerance test is accurate, it is too cumbersome and impractical in the ICU setting. Moreover, medications such as diuretics or conditions that produce renal Mg wasting will interfere with the test.

In summary, no single method is satisfactory to assess magnesium status. The simplest, most useful and readily available tests are the measurement of serum total magnesium and the magnesium tolerance test\(^51\). Ionized magnesium measurement may become more readily available with the development of reliable analyzers. Therefore, the clinical assessment of patients at risk for Mg deficiency remains vital for making a timely diagnosis.
1.5 ETIOLOGY OF HYPOMAGNESAEMIA IN CRITICALLY ILL PATIENTS

Critically ill patients who develop hypomagnesaemia fall into three broad categories: those with decreased intake, those with altered intracellular-extracellular distribution, and those with increased losses. Increased losses may occur from either the kidney or gastrointestinal tract. Approximate one-third of dietary magnesium is absorbed (120 mg) principally in the small bowel\(^\text{20}\). In addition, there is secretion of approximately 40 mg in intestinal secretions and absorption of another 20 mg in the large bowel\(^\text{21}\). Balance is achieved by the urinary excretion of the approximately 100 mg that is absorbed\(^\text{26}\). There is no physiologic hormonal control of plasma magnesium and urinary magnesium excretion\(^\text{22}\). Changes in intake are balanced by changes in urinary magnesium reabsorption, principally in the loop of Henle and the distal tubule in response to changes in plasma magnesium concentration\(^\text{26, 27}\).

1.5.1 DECREASED INTAKE

Malnutrition is common in patients at initial presentation to the ICU and those who have been under the care of intensivists for some time. Several studies have demonstrated marked decreases in muscle stores of magnesium in these patients\(^\text{20}\). A number of factors influence the serum magnesium levels. Dietary intake of magnesium is a critical determinant of magnesium levels\(^\text{20, 21}\). The factors that regulate magnesium absorption in the gastrointestinal tract are poorly understood; to date there has not been a regulatory factor discovered that is akin to vitamin D for calcium absorption, although in fact, vitamin D and its metabolites enhance magnesium absorption by the distal small bowel to a small extent\(^\text{22, 23}\). Patients with alcoholism have extremely poor magnesium intake and are prone to total body magnesium depletion\(^\text{52}\). The use of total parenteral nutrition (TPN) is often associated with hypomagnesaemia. The traditional practice of adding 0.20 Mmol/kg/day of magnesium to TPN solutions is simply not adequate for most critically ill patients. The highly concentrated glucose and amino acid infusions drive magnesium into cells at the same time that concentrated intralipid solutions are chelating free magnesium in serum.
1.5.2 INCREASED LOSSES

GASTROINTESTINAL

Substantial amounts of magnesium can be lost from the gastrointestinal tract. Diarrhea, regardless of the cause, is one of the most common reasons for gastrointestinal magnesium losses in ICU patients. Nasogastric suctioning also removes significant amounts of magnesium from the body over several days' time. Various malabsorption syndromes and short bowel syndromes that occur after surgery can produce high losses of magnesium. Pancreatitis can lead to hypomagnesemia because of sequestration of magnesium-rich fluid within the pancreas combined with losses through nasogastric suctioning and diarrhea.

RENAL

Renal magnesium wasting occurs when urinary magnesium losses exceed 12 mg (0.5 mmol) per day in the presence of ionized hypomagnesaemia. Patients at risk for renal magnesium wasting include those with diabetes, alcoholism, hyperthyroidism, hypercalcemia, and hypophosphatemia. In diabetics there is a strong relationship between insulin resistance and hypomagnesemia. Glucosuria probably contributes significantly to renal magnesium wasting in these patients. Any acute renal injury, particularly renal tubular injury or disorders, may promote wasting of magnesium. Many medications promote the excretion of magnesium in the urine. Most drugs induce magnesium wasting by inhibiting tubular reabsorption of magnesium. Chief among these are the diuretics, especially loop diuretics. Although drugs such as amphotericin-B and platinum-based chemotherapy agents have well deserved reputations for inducing severe hypokalemia and hypomagnesaemia, others like aminoglycosides are often underappreciated. Although alcoholics are at great risk for magnesium depletion primarily because of malnutrition, alcohol itself does promote renal magnesium wasting by an effect on renal tubular magnesium reabsorption.
1.5.3 ALTERED INTRACELLULAR-EXTRACELLULAR DISTRIBUTION

Acute intracellular shift of magnesium will occur in patients with metabolic acidosis; those with elevated levels of circulating catecholamines; those given exogenous glucose, insulin, or amino acid solutions; and those with refeeding syndromes \(^3\). There also is evidence that the hypomagnesaemia that occurs after cardiac bypass in a large majority of patients is caused by an acute intracellular shift of magnesium \(^10\). Large-volume resuscitations with hypotonic fluids not containing electrolytes will promote hypomagnesaemia as will citrate present in blood products (by chelation of magnesium) \(^10\).

1.6 IMPACT OF HYPOMAGNESEMIA ON ELECTROLYTES

Symptomatic magnesium depletion is often associated with multiple biochemical abnormalities in the critically ill, such as hypokalemia, hypocalcaemia, and metabolic alkalosis. Whang et al \(^60\,^61\) had found hypomagnesemia in 42% patients with hypokalemia, 29% patients with hypophosphatemia, 27% patients with hyponatremia and 22% patients with hypocalcaemia. Hypokalemia, hypocalcaemia, hypophosphatemia are said to be the predictors of hypomagnesaemia.

1.6.1 HYPOCALCEMIA

Hypocalcaemia is a common manifestation in hypomagnesaemia. Up to one third of patients with hypomagnesaemia in intensive care units may have hypocalcaemia. Symptomatic hypocalcaemia is usually seen in moderate to severe magnesium deficiency and there is a positive correlation between serum magnesium and calcium concentrations. Even mild degrees of magnesium depletion can cause a significant decrease in serum calcium concentration \(^62\). Hypocalcaemia of magnesium deficiency cannot be corrected by treatment with calcium, vitamin D or both. Magnesium therapy alone will restore serum calcium concentration to normal. Several factors contribute to the hypocalcaemia of magnesium deficiency \(^63\). One of the important factors is impaired secretion of PTH. Although the acute effect of extracellular magnesium on PTH secretion is similar to that of calcium, in magnesium deficiency there is impaired PTH
release. In addition to impaired PTH secretion there is evidence for an increase in metabolism of PTH and end-organ resistance for PTH. End-organ resistance is suggested by the presence of normal or elevated serum concentration of PTH in the face of hypocalcaemia, and decreased osteocalcin concentration.

Administration of exogenous PTH to patients with hypocalcaemic hypomagnesaemia has little effect on serum calcium concentrations or on urinary excretion of cyclic AMP and phosphate. In magnesium deficiency, vitamin D metabolism is altered with a decrease in serum 1,25 dihydroxyvitamin D due to impairment in conversion of 25 hydroxyvitamin D to 1,25 dihydroxyvitamin D. There is also evidence for increased clearance of 1,25 dihydroxyvitamin D and end-organ resistance.

CS Limaye et al found that of the 52 patients with hypomagnesemia 36 (70%) also had hypocalcemia. The incidence of hypocalcemia was significantly higher in patients with hypomagnesemia (p<0.05).

1.6.2 HYPOKALEMIA

Hypokalemia is a frequently encountered laboratory feature of Mg deficiency. Hypokalemia occurs in 40% to 60% of hypomagnesemic patients. This relationship is in part due to underlying disorders that cause both magnesium and potassium loss, such as diarrhea and diuretic therapy. It has been shown experimentally that during Mg deficiency, there is loss of potassium from the cell with the subsequent development of intracellular potassium depletion. In addition, the kidney is unable to conserve potassium. Attempts to replete the potassium deficits with potassium therapy alone are not successful without simultaneous Mg therapy. The reason for this disrupted potassium metabolism may be related to Mg2+ dependence of the Na, K, ATPase. This enzyme uses the energy derived from ATP hydrolysis to actively pump sodium and potassium across the plasma membrane against their respective concentration gradients to maintain the physiologically normal intracellular concentrations of these cations. Cyclic binding and release of Mg2+ occur between the enzyme complex and the intracellular space during the sodium and potassium exchange. During Mg depletion, intracellular sodium and calcium increase, and Mg2+ and potassium decrease. Mg2+ also appears to be important
in regulation of potassium channels in cardiac cells that are characterized by inward rectification\textsuperscript{72}.

1.7 IMPACT OF HYPOMAGNESEMIA ON THE CARDIOVASCULAR SYSTEM

Magnesium deficiency can affect cardiac electrical activity, myocardial contractility and vascular tone. Magnesium depletion can induce changes in the electrocardiogram. Widening of the QRS complex and peaking of T waves have been described with modest magnesium loss\textsuperscript{73}, while more severe magnesium depletion can lead to prolongation of the PR interval, progressive widening of the QRS complex, and diminution of the T wave\textsuperscript{74}. Walter van den Bergh\textsuperscript{75} studied ECG abnormality and serum magnesium levels in 62 patients admitted within 72 hrs after Subarachnoid hemorrhage, 23 (37\%) of the patients had hypomagnesaemia and 38 (61\%) of the patients had a long QTc duration.

The clinical disturbance of greatest potential importance, however, is the association of mild hypomagnesaemia with ventricular arrhythmias in patients with cardiac disease. Hypomagnesaemia is associated with cardiac arrhythmias such as multifocal Atrial tachycardia, premature ventricular contractions, torsades de pointes, Atrial fibrillation, ventricular tachycardia, and ventricular fibrillation. Torsade de pointes, a repetitive polymorphous ventricular tachycardia with prolongation of QT interval, has been reported in cases of hypomagnesaemia, and this arrhythmias have been successfully treated with magnesium\textsuperscript{76}.

Mg\textsuperscript{2+} is an obligatory cofactor for Na+-K+ATPase- that pumps K+ into the cell thus hyperpolarizing the cell membrane. If deficient, the pumps’ function is impaired and intracellular K+ falls. The relatively/partially depolarized cell membrane is more predisposed to ectopic excitation and tachyarrhythmias. Further, the repolarization is delayed leading to prolonged QT or QU intervals.
Magnesium deficiency increases angiotensin II induced plasma aldosterone concentration and production of thromboxane and vasoconstrictor prostaglandins. Insulin resistance caused by magnesium deficiency also increases vascular tone. Changes in cytosolic free calcium produced by magnesium deficiency may increase vascular reactivity even further. Magnesium deficiency has been implicated in progression of atherosclerosis, increased incidence of hypertension and acute myocardial infarction.

The 2004 American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the management of patients with ST-elevation myocardial infarction recommend that magnesium therapy is reasonable in two settings:

- For documented magnesium deficiency, particularly in patients who were treated with diuretics prior to the acute episode.
- For torsades de pointes associated with a prolonged QT interval. In this setting, magnesium should be given as an intravenous bolus of 1 to 2 grams over five minutes.

No changes to this approach were made in the 2007 ACC/AHA focused update.

Although tissue Mg deficiency is associated (perhaps causally) with the development of serious consequences such as arrhythmias, the total serum Mg concentration may not be as useful a marker of tissue levels. Chernow et al. findings supported the concept that total serum hypomagnesaemia may not reflect tissue Mg levels and may help to explain why so many patients with hypomagnesaemia are asymptomatic; however, those with severe hypomagnesaemia are more symptomatic.
1.9 IMPACT OF HYPMAGNESEmia ON CLINICAL OUTCOME IN THE CRITICALLY ILL; HOSPITAL MORTALITY, LENGTH OF STAY, VENTILATION USE

1.9.1 MORTALITY
The relationship between hypomagnesaemia and mortality rate varies from study to study. A higher mortality rate was detected in hypomagnesemic patients as compared to normomagnesemic patients by Chernow et al\textsuperscript{14} (41\% vs 13\%), Rubiez et al\textsuperscript{80} (46\% vs 25\%) and Safavi et al\textsuperscript{17} (55\% vs 35\%). Guerin et al\textsuperscript{81} had found no difference in ICU mortality between hypomagnesemic and normomagnesemic groups (18\% vs 17\%); but noted a higher mortality rate among hypermagnesemic patients. Soliman et al\textsuperscript{82} observed that patients who develop ionized hypomagnesemia during their ICU stay have higher mortality rates. In the CS Limaye et al\textsuperscript{66} study the mortality rate in hypomagnesemic group was 57\% which is significantly higher as compared to 31\% in the normomagnesemic group and 43\% in the hypermagnesemic group (p<0.05). The higher mortality rates in the hypomagnesemic patients can be explained by greater incidence of electrolyte abnormalities especially hypokalemia and cardiac arrhythmias and a strong association of hypomagnesemia with sepsis and septic shock which is a common cause of death in ICU patient.

1.9.2 LENGTH OF STAY IN THE CRITICAL CARE UNITS
In the study carried out by Soliman et al\textsuperscript{82} there was no difference in the length of ICU stay among the hypomagnesaemia, normomagnesaemic and hypermagnesaemic groups. However the patients who developed hypomagnesemia during their ICU stay had longer duration of stay in the ICU. They also found the length of ICU stay as an independent risk factor for development of hypomagnesemia. CS limaye et al\textsuperscript{66} found no difference in length of ICU stay among hypomagnesemic, normomagnesemic, hypermagnesemic groups.
1.9.3 VENTILATOR USE

Hypomagnesemia is known to cause muscle weakness and respiratory failure. It is one of the factors causing difficulty in weaning the patient from the ventilator. CS Limaye et al\textsuperscript{66} showed that patients with hypomagnesemia needed ventilatory support more frequently and for a longer duration. In a study performed by Fiaccordori et al\textsuperscript{83} it was found that patients with low muscle magnesium were on ventilatory support for more number of days. In a study carried out by Molloy et al\textsuperscript{84} magnesium was administered to the hypomagnesemic patients and normomagnesemic controls and improvement in respiratory muscle weakness was noted in hypomagnesemic patients while there was no effect on normomagnesemic controls. Safavi et al\textsuperscript{17} had found that in patients with hypomagnesemia the duration of mechanical ventilation was longer (7.2 vs 4.7 days, $p < 0.01$).
2.0 STUDY JUSTIFICATION

Magnesium deficiency is a common yet under diagnosed problem in the ICU.

Hypomagnesaemia is associated with other electrolyte imbalances specifically hypokalemia and hypocalcaemia, a higher morbidity and a higher mortality rate in the critically ill patients, and hence hypomagnesaemia has prognostic importance on patient’s outcomes.

Further to that, correction of hypomagnesaemia has shown a positive outcome on management of a critically ill patient and mortality benefit in several studies.

There’s lack of local data on the prevalence of hypomagnesaemia, however data generated by this study will provide physicians with the magnitude of hypomagnesaemia in the local population hence guide on intervention strategies.
3.0 RESEARCH QUESTION

What is the prevalence of hypomagnesaemia in critically ill patients on admission to the critical care units at Kenyatta National Hospital?

4.0 OBJECTIVES

4.1 BROAD OBJECTIVE

To study the serum magnesium levels and its correlates in critically ill patients upon admission to the critical care units

4.2 SPECIFIC OBJECTIVES

1) To determine the prevalence of hypomagnesemia in critically ill patients on admission to the critical care units

2) To determine serum calcium, serum albumin, serum potassium levels in the study population

3) To assess the severity of the critical illness by use of APACHE II score in the study population
4.3 SECONDARY OBJECTIVES

1) To determine the primary medical/surgical conditions associated with abnormalities of serum magnesium among critically ill patients at KNH.

2) To determine ECG features in the study population

3) To determine patients clinical outcome in 2 weeks considering the following parameters; Length of stay in CCU, duration of ventilator use and mortality.

4) To determine association between hypomagnesaemia and:
   a. Serum Calcium & potassium
   b. APACHE II Score
   c. ECG features
   d. Clinical outcome variables

5.0 METHODOLOGY

5.1 STUDY DESIGN

This is a prospective, observational cohort study involving the adult population of critically ill patients.

5.2 STUDY SITE

The study was conducted in Kenyatta National Hospital’s critical care units i.e. the Intensive care unit, the Emergency ward and Acute room. The Acute room and Emergency ward are
facilities at the KNH which are used for acutely ill critical patients at the accident and emergency unit. The Acute room is a holding area for patients stabilization pending admission to the intensive care unit. The emergency ward is an extension of the ICU with a fewer bed capacity compared to the intensive care unit. The patients are then transferred to the intensive care units once a bed is available.

5.3 STUDY POPULATION

The adult population admitted into the critical care units.

5.4 STUDY PARTICIPANTS

Any person meeting the selection criteria, admitted into the critical care units

5.4.1 INCLUSION CRITERIA

- Age above 13yrs
- Admission into the critical care units
- Informed consent from the patient (where feasible), surrogate or proxy

5.4.2 EXCLUSION CRITERIA

- Patients who declined to participate/consent to the study
- Patients admitted to the ICU post-operatively for monitoring
- Patients with burn injuries
- Patients with acute or chronic renal failure already on dialysis
5.5 SAMPLE SIZE CALCULATION

- The sample size was calculated using the following method

\[ N = \frac{Z^2 \times p (1-p)}{d^2} \]

- \( N \)=minimum sample size required
- \( Z \)=confidence interval at 95% (standard value of 1.96)
- \( P \)=estimated prevalence from the study of reference=52%  
- \( D \)=margin of error(0.07)

\[ N = \frac{1.96^2 \times 0.52 (1-0.52)}{0.07^2} \]

\[ N = 196 \text{ patients} \]

5.6 SAMPLING METHOD

Consecutive patients admitted into the critical care units of Kenyatta National Hospital were selected to participate in the study on a daily basis.

5.7 SCREENING AND RECRUITMENT

The patients or proxy were approached about participation in the study and details of the study were explained to them in hopes of obtaining informed consent from them. A study explanation
was given to them to read through, and any questions or concerns raised were addressed. (Appendix i)

Once the patient or proxy understood the study explanation and was willing to participate in the study, they were allowed to sign the consent form. (Appendix ii)

All patients recruited into the study had their biodata as well as the provisional diagnosis obtained at the time of admission. (Appendix iii)

5.8 PATIENTS FLOW CHART

- SCREEN PATIENTS FOR ELIGIBILITY
  - Age > 13yrs
- WRITTEN INFORMED CONSENT
- ADMINISTER STUDY PROFORMA
- BLOOD ASSAY, APACHE, ECG
5.9 DATA COLLECTION
The principal investigator and the two research assistants collected data daily. Once written consent obtained, 6mls of blood was drawn from the patients forearm. Laboratory evaluation of serum magnesium, potassium, albumin, calcium, full haemogram and arterial blood gas was done within 24 hrs of admission. APACHE II score was determined within 24 hrs of admission and a current ECG performed on all patients using Philips Pagewriter Trim II Interpretive ECG machine. The data was then recorded into the study proforma and entered into data entry sheets. The blood sample needed no special storage and analysis of the blood samples was done immediately after the blood was drawn.

5.10 LABORATORY METHODS
Serum Magnesium analysis was done in the Lancet laboratory by a dedicated technician using the COBAS Integra analyzer. The Cobas Integra analyzer uses a calorimetric method using chlorophosphanazo III (Cobas-Integra; Roche) which is validated for precision, accuracy, linearity, sensitivity and specificity in the measurements of electrolytes.
Serum Calcium, Potassium and Albumin analyses were also done at the Lancet laboratory using the same COBAS Integra analyzer. Calcium levels were adjusted according to the serum albumin levels.
Arterial blood gas analysis was done in CCU laboratory using an ion selective electrode machine by a dedicated technician.
Full hemogram analysis was done in KNH hematology laboratory by a dedicated technician using the Cell Dyn 3700 automated machine.

5.11 FOLLOW UP AND OUTCOMES
The patients were then followed up for 2 weeks, noting the following parameters: duration of ventilator support, length of stay in the critical care units and mortality.
5.12 STUDY VARIABLES

5.12.1 INDEPENDENT OUTCOME VARIABLES.
We utilized reference ranges provided by Lancet Kenya Laboratories. These levels are in accordance with the universally agreed upon reference ranges\(^1\).\(^4\).

- Serum magnesium
  - Hypomagnesemia was defined as serum magnesium <0.7 mmol/L
  - Normal magnesium levels defined as serum magnesium 0.7-1.1 mmol/L
  - Hypermagnesaemia was defined as serum magnesium >1.1 mmol/L

5.12.2 DEPENDENT OUTCOME VARIABLES

1) Serum calcium, serum potassium and serum albumin
Hypocalcaemia (Alb corrected calcium= measured Ca+[0.25(40-albumin )]/10) ; Ca < 2.15 mmol/L. Normal range defined as 2.15 mmol/L to 2.65 mmol/L

Hypokalemia; K<3.5 mmol/L. Normal range defined as 3.5 mmol/L to 5 mmol/L

Hypoalbuminemia ; Albumin <3.5 g/dL. Normal range defined as 3.5 g/dL to 5.0 g/dL

2) Severity of illness

Severity of illness was assessed using the acute physiology and chronic health evaluation (APACHE II) score\(^86\). This is a scoring system that provides a means for describing and predicting acute illness severity over a broad range of intensive care unit (ICU) patients. The Apache-II Score provides an estimate of ICU mortality based on a number of laboratory values and patient signs taking both acute and chronic disease into account. The data used should be from the initial 24 hours in the ICU, and the worst value (furthest from baseline/normal) should be used. The score ranges from 0-71 points, the maximum score is 71.

A score of 25 represents a predicted mortality of 50%

A score of > 35 represents a predicted mortality of 80%
3) CCU morbidity and mortality

- Length of stay in ICU – in days/hrs
- Ventilator use – duration in days/hrs
- Discharge from CCU - alive or dead

4) ECG analysis

Manual interpretation of the ECG was employed in liaison with a cardiologist in the recommended manner and ECGs were analyzed for heart rate, PR and QTc - (heart rate–corrected QT) interval duration, width of the QRS complex, ST-segment depression or elevation, T-wave abnormalities and U-wave presence.

Definition of study variables:

- PR-interval prolongation, duration >200 ms
- QRS widening, QRS duration >120 ms;
- QTc prolongation, duration >440 ms;
- ST-segment depression, horizontal or down sloping ST segment (>0.05 mV) with or without ST-J depression;
- ST-segment elevation, ST segment (>0.1 mV) with or without ST-J elevation
- T-wave abnormalities, T waves that are of low voltage or are flat or inverted in leads in which they are normally upright or that are abnormally tall and peaked
- Prominent U wave, top >25% of the highest T wave in precordial leads

5.13 QUALITY CONTROL

The research assistants underwent training by the principle investigator on how to fill the transcription form to ensure standardization and minimize pre analytical errors.
Recommended procedure for specimen collection, proper labeling, preparation and storage was followed strictly to minimize pre analytical sources of error. To ensure quality was maintained, the serum magnesium, serum calcium, serum albumin and serum potassium laboratory tests were carried out in Lancet Kenya laboratories. Machines used were properly calibrated using standard calibration methods and materials and tests assayed against controls. Lancet Kenya laboratory carries out internal and external quality control.

The other laboratory tests which are routinely done in CCU patients were done at the KNH hematology lab, the KNH biochemistry lab and the CCU lab. These labs all adhere to strict internal quality control measures. This is done by ensuring that the personnel running the tests are well trained in the procedures to be carried out. Also, they concurrently run control samples to ensure that the results of the samples being analyzed are not erroneous. The labs also adhere to external quality control protocols and have random assessment by external teams to assess this. To minimize ECG errors a pre-programmed ECG machine was used. We also ensured competent operator, patient preparation with unrestricted access to the skin in the chest area, arms and lower legs and operators in adherence to the Trusts chaperone policy of limb and precordial electrode placement. Biomedical technologists in KNH routinely calibrated the ECG machine. Manual interpretation of the ECGs was employed in liaison with a cardiologist in the recommended manner.

5.14 DATA MANAGEMENT

Data was coded, entered and managed in a pre-designed Microsoft Access database. At the end of data entry, cleaning of data was performed and analysis done using SPSS version 17.0. Categorical and continuous variables were summarized and presented in form of proportions and means or medians respectively. Prevalence of hypomagnesaemia was reported as a proportion based on the minimum normal magnesium cut off levels in blood. Serum magnesium levels were correlated with serum calcium, serum potassium and APACHE II score using Pearson correlation coefficient. Prevalence of ECG abnormalities was calculated and presented as a proportion. Associations between hypomagnesaemia and continuous / categorical variables were analyzed using Student’s t test and Chi square test respectively. The data was presented using tables, pie
charts and graphs. All statistical tests were performed at 5% level of significance (95% confidence interval).

6.0 ETHICAL CONSIDERATIONS
Before commencing, permission to carry out this study was sought from the University of Nairobi’s Department of Clinical Medicine and Therapeutics, as well as the Ethics and Research Committee of Kenyatta National Hospital/University of Nairobi. Only patients who gave informed consent were recruited into the study. No patient was coerced into participating. There was no discrimination against any patient who declined to participate. All information collected was treated as confidential. Only blood samples intended for study were drawn. Any information that was deemed as important to the management of the patient was communicated to the primary health care provider. The cost of the study was met by the principal investigator.
7.0 RESULTS
Between April and July 2012, the files of two hundred and fifty patients on admission to CCU were consecutively screened at Kenyatta National Hospital. Fifty patients did not meet the inclusion criteria – 15 patients were excluded because of inability to obtain magnesium measurement at admission, 10 were aged below 13 yrs, another 10 had hemodialysis prior to admission, 6 declined consent, 5 had prior supplementation with magnesium, 4 had severe burn injuries. Two hundred patients were recruited and subsequently examined, APACHE II score determined, 12 lead ECG done and blood samples drawn for serum magnesium, calcium, potassium and albumin concentration. Out of those who met the inclusion criteria, two patients’ blood sample was severely hemolysed, leaving one hundred and ninety eight (198) patients whose data was submitted for analysis.
7.1 POPULATION CHARACTERISTICS

The study population was relatively young with a mean age of 42.8 (SD 18.9 yrs) with a range of 13-92 yrs. Two thirds of the patients were from the Emergency CCU ie Acute room /Emergency ward (n=148) with one third of the patients (n=50) being recruited from medical/surgical ICU. There were 138 males (69.7%) and 60 females (30.3%). Surgical patients were more than medical patients (54.5 % Vs 45.5%). (Table 2). As illustrated in figure 2 below, majority of the patients i.e.70% of the patients were aged below 50 yrs. Only 10.6 % of the population was aged above 70 yrs.

**TABLE 2 SOCIO-DEMOGRAPHIC CHARACTERISTICS OF THE PATIENTS**

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>FREQUENCY (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unit of admission</strong></td>
<td></td>
</tr>
<tr>
<td>ICU</td>
<td>50 (25.3)</td>
</tr>
<tr>
<td>Acute room/emergency ward</td>
<td>148 (74.7)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>42.8 (18.9)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>40.0 (28.0-55.0)</td>
</tr>
<tr>
<td>Min – Max</td>
<td>13-92</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>138 (69.7)</td>
</tr>
<tr>
<td>Female</td>
<td>60 (30.3)</td>
</tr>
<tr>
<td><strong>Surgical</strong></td>
<td></td>
</tr>
<tr>
<td>Medical</td>
<td>108 (54.5)</td>
</tr>
<tr>
<td></td>
<td>90 (45.5)</td>
</tr>
</tbody>
</table>
7.2 ADMISSION DIAGNOSIS

Head trauma was the most common diagnosis among the surgical patients (66.7%). The three most common complications arising from the head trauma included intracerebral hemorrhage (21.3%), seizure (14%), and subdural / epidural hematoma (14%). Acute kidney injury, sepsis and neurologic infections contributed to 60% of the medical admissions. (Table 3 & 4). Due to the heterogeneous patient population in the critical care units and multiplicity of clinical events, there were overlaps in diagnostic labels. Hence, the primary admission diagnosis was used to categorize these patients into either surgical or medical patients.
### TABLE 3: MEDICAL DIAGNOSIS

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute kidney Injury</td>
<td>21</td>
<td>23.3%</td>
</tr>
<tr>
<td>Neurologic infections</td>
<td>18</td>
<td>20.0%</td>
</tr>
<tr>
<td>Sepsis</td>
<td>18</td>
<td>20.0%</td>
</tr>
<tr>
<td>Cerebral Vascular Accident</td>
<td>10</td>
<td>11.1%</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>8</td>
<td>8.9%</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>6</td>
<td>6.7%</td>
</tr>
<tr>
<td>Other metabolic diseases</td>
<td>5</td>
<td>5.6%</td>
</tr>
</tbody>
</table>

### TABLE 4: SURGICAL DIAGNOSIS

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head trauma</td>
<td>72</td>
<td>66.7%</td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>23</td>
<td>21.3%</td>
</tr>
<tr>
<td>Seizure</td>
<td>14</td>
<td>13.0%</td>
</tr>
<tr>
<td>Subdural/epidural hematoma</td>
<td>14</td>
<td>13.0%</td>
</tr>
<tr>
<td>Multiple trauma</td>
<td>6</td>
<td>5.6%</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>3</td>
<td>2.8%</td>
</tr>
</tbody>
</table>
7.3 ELECTROLYTES
The mean serum magnesium on admission was 0.9 Mmol/L (SD 0.4) with a range of 0.4-4.5 Mmol/L. Of this sample population, 137 patients (69.2%) had normal serum magnesium level, while 33 patients 16.7%(CI, 11.6 %-22.2%) had hypomagnesaemia and 28 hypermagnesemetic patients (14.1%). The mean serum calcium levels were 2.3 Mmol/L (SD 0.2), range of 1.4-2.7 Mmol/L, 181 subjects (91.4%) had normal serum calcium level, while 12 subjects (6.1%) had hypocalcemia and 5 patients (2.5%) had hypercalcemia. The mean serum potassium levels were 4.7 Mmol/L (SD 1.2), range of 2.5- 9.0 Mmol/L,121 subjects (61.1%) had normal serum potassium level, while 58 subjects (29.3%) had hyperkalemia and 19 patients (9.6%) had hypokalemia. (Table 5 & Figure 3)

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>MEAN (SD)</th>
<th>MEDIAN (IQR)</th>
<th>MIN-MAX</th>
<th>ELECTROLYTES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LOW n (%)</td>
<td>NORMAL n (%)</td>
<td>HIGH n (%)</td>
<td></td>
</tr>
<tr>
<td>Serum magnesium (Mmol/L) (N=0.7-1.1)</td>
<td>0.9 (0.4)</td>
<td>0.9 (0.7-1.0)</td>
<td>0.4-4.5</td>
<td>33(16.7)</td>
</tr>
<tr>
<td>Corrected Calcium (Mmol/L) (N=2.15-2.65)</td>
<td>2.3 (0.2)</td>
<td>2.3 (2.2-2.4)</td>
<td>1.4-2.7</td>
<td>12(6.1)</td>
</tr>
<tr>
<td>Serum potassium (Mmol/L) (N=3.5-5.0)</td>
<td>4.7 (1.2)</td>
<td>4.5 (4.0-5.2)</td>
<td>2.5-9.0</td>
<td>19(9.6)</td>
</tr>
</tbody>
</table>
7.4 APACHE II SEVERITY SCORE

The mean APACHE II score was 24.1 (SD 6.5) with a range of 6-45 (Table 6). On stratification of the APACHE II score, 75% of the patients had an APACHE II score of 20 and above with majority (54%) having an APACHE II score of between 20-29. (Table 7)

TABLE 6 APACHE II SCORE

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>APACHE II score</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>24.1 (6.5)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>24 (19-28)</td>
</tr>
<tr>
<td>Min – Max</td>
<td>6-45</td>
</tr>
</tbody>
</table>
### TABLE 7 STRATIFICATION OF APACHE II SCORE

<table>
<thead>
<tr>
<th>APACHE II SCORE</th>
<th>FREQUENCY (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>10-19</td>
<td>51 (25.8)</td>
</tr>
<tr>
<td>20-29</td>
<td>107 (54.0)</td>
</tr>
<tr>
<td>30-39</td>
<td>35 (17.7)</td>
</tr>
<tr>
<td>&gt;=40</td>
<td>4 (2.0)</td>
</tr>
</tbody>
</table>

### 7.5 ECG FEATURES

Electrocardiographic evaluation was carried out in 198 patients. As illustrated in the table 8 above, 96% (n=190) of the patients were in sinus rhythm at the time of admission, 4 patients had Atrial fibrillation, 1 patient had supraventricular tachycardia (SVT) and 3 patients had Atrial flutter. The mean heart rate, mean PR interval, mean QTc and median QRS duration were all within normal ranges. T wave abnormality was detected in 11.1% (n=22) of the patients, the most common being flattened T wave at 63.6% (n=14), inverted T wave was found in 27.3% (n=6) while peaked T wave was found in 9.1% (n=2). Left ventricular hypertrophy was noted in 14.6% (n=29) of patients while right ventricular enlargement was noted in 1% (n=2). AV Nodal blockage was found in 4 patients, 3 of whom had 1st degree heart block and 1 patient with complete heart block. There were 3 patients found to have RBBB and 2 patients having LBBB.
<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>FREQUENCY (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RHYTHM</td>
<td></td>
</tr>
<tr>
<td>Sinus</td>
<td>190 (96.0)</td>
</tr>
<tr>
<td>SVT</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>4 (2.0)</td>
</tr>
<tr>
<td>Atrial flutter</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>Heart rate (mean+SD)</td>
<td>96.3 (29.2)</td>
</tr>
<tr>
<td>PR interval (mean+SD)</td>
<td>147.1 (31.5)</td>
</tr>
<tr>
<td>QRS duration (median/IQR)</td>
<td>84.0 (75.5-95.5)</td>
</tr>
<tr>
<td>QTc interval (mean+SD)</td>
<td>409.9 (38.5)</td>
</tr>
<tr>
<td>T-WAVE ABNORMALITY</td>
<td></td>
</tr>
<tr>
<td>Abnormality (n=22)</td>
<td>22 (11.1)</td>
</tr>
<tr>
<td>Peak T wave</td>
<td>2 (9.1)</td>
</tr>
<tr>
<td>Flattened T wave</td>
<td>14 (63.6)</td>
</tr>
<tr>
<td>Inverted T wave</td>
<td>6 (27.3)</td>
</tr>
<tr>
<td>Prominent U-wave</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>LVH</td>
<td>29 (14.6)</td>
</tr>
<tr>
<td>RVH</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>RBBB</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>LBBB</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>AV Nodal Block</td>
<td>4 (2.0)</td>
</tr>
<tr>
<td>AV NODAL BLOCK</td>
<td></td>
</tr>
<tr>
<td>1st degree AV block</td>
<td>3 (75.0)</td>
</tr>
<tr>
<td>Complete heart block</td>
<td>1 (25.0)</td>
</tr>
</tbody>
</table>
7.6 CLINICAL OUTCOMES

The median length of ICU stay was 3 days (IQR; 1.75-10.75) in this sample population. Mechanical ventilation was applied for 36.8% (n=73) of patients. The median length of mechanical ventilation was 48 hrs (IQR; 24-108). The mortality rate at 14 days was 55.1% (n=109).

TABLE 9: CLINICAL OUTCOMES

<table>
<thead>
<tr>
<th>OUTCOME VARIABLES</th>
<th>LENGTH OF STAY IN ICU (DAYS) n=198</th>
<th>DURATION OF VENTILATOR USE (HOURS) n=73</th>
<th>STATUS WITHIN 14 DAYS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay in ICU (Days)</td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td>FREQUENCY (%)</td>
</tr>
<tr>
<td></td>
<td>3 (1.75-10.75)</td>
<td>48 (24-108)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 hour - 14 days</td>
<td>1 hr - 336 hrs</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of ventilator use (hours)</td>
<td></td>
<td></td>
<td>Dead</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>109 (55.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Alive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>89 (44.9)</td>
</tr>
</tbody>
</table>
7.7 ASSOCIATIONS BETWEEN VARIABLES

7.7.1 ASSOCIATION BETWEEN HYPMAGNESEMIA AND OTHER ELETROLYTES

Bivariate analysis was then performed to explore associations between low magnesium levels (hypomagnesaemia) and electrolyte abnormalities. As illustrated in the table 10 below hypomagnesemic patients were three times more likely to have hypocalcaemia however this relationship did not reach statistical significance (p-value 0.104). Hypomagnesemic patients were 1.2 times more likely to have hypokalemia and this too was not statistically significant.

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>HYPMAGNESEMIA n (%)</th>
<th>NORMAL MG n(%)</th>
<th>OR (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYPOCALCEMIA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NORMAL CA $^{2+}$</td>
<td>4 (40.0)</td>
<td>6 (60.0)</td>
<td>3.0 (0.8 – 11.4)</td>
<td>0.104</td>
</tr>
<tr>
<td></td>
<td>29 (18.1)</td>
<td>131 (81.9)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>HYPOKALEMIA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NORMAL K$^{+}$</td>
<td>4 (28.6)</td>
<td>14 (71.4)</td>
<td>1.2 (0.4 – 4.0)</td>
<td>0.755</td>
</tr>
<tr>
<td></td>
<td>29 (19.1)</td>
<td>123 (80.1)</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

7.7.2 ASSOCIATION BETWEEN HYPMAGNESEMIA AND CLINICAL APACHE II SCORE

The mean APACHE II score of the hypomagnesemic patients was 26.5 (SD 7.6) and was higher compared to the mean of the normomagnesemic patients (26.5±7.6 Vs 23.7±6.1 p= 0.03).
7.7.3 ASSOCIATION BETWEEN HYPOMAGNESEMIA AND ECG FEATURES
The mean QTc intervals among the hypomagnesemic and the normomagnesemic patients were normal at 434.8 (SD 39.9) and 408.8 (SD 29.8) respectively. The hypomagnesemic patients had a longer QTc interval compared to the normomagnesemic patients (434.8±39.9 Vs 408.8 ± 29.8 p< 0.001).

7.7.4 ASSOCIATION BETWEEN HYPOMAGNESEMIA AND CLINICAL OUTCOMES
There was no statistically significant difference in the length of stay in CCU in hours between hypomagnesaemic patients and the patients who had normal magnesium (72 hrs Vs 96 hrs p=0.083). There was also no statistically significant difference in the duration of ventilation use in hours between the hypomagnesaemic patients and the patients with normal magnesium (48hrs Vs 72hrs p=0.2). There was no statistically significant difference in the CCU discharge status between the hypomagnesaemic patients and the patients who had normal magnesium, this was evidenced by an odds ratio of 1 and a p value of 0.965. (Table 11 below)
Table 11: ASSOCIATION BETWEEN HYOMAGENESAEMIA AND CLINICAL OUTCOMES

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>HYOMAGENESAEMIA</th>
<th>NORMAL MAGNESIUM</th>
<th>OR (95% CI)</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of ICU stay (hrs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>72 (24-120)</td>
<td>96 (48-336)</td>
<td>-</td>
<td>0.083</td>
</tr>
<tr>
<td>Duration of ventilation (hrs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>48 (24-72)</td>
<td>72 (24-144)</td>
<td>-</td>
<td>0.222</td>
</tr>
<tr>
<td>CCU discharge status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alive: n (%)</td>
<td>16 (48.5)</td>
<td>67 (48.9)</td>
<td>1.0 (0.5-2.2)</td>
<td>0.965</td>
</tr>
<tr>
<td>Dead: n (%)</td>
<td>17 (51.5)</td>
<td>70 (51.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
8.0 DISCUSSION
In this observational clinical cohort of critically ill admissions, we set out to determine the prevalence of serum hypomagnesaemia and related clinical outcomes. Our study sample was young in age and predominantly male. Slightly less than half of the study samples were medical patients. Medical admissions diagnoses were mainly due to sepsis and acute kidney injury. A slight majority were surgical patients who had a history of trauma. In this work we report a prevalence of hypomagnesaemia of 16.7% with associated hypokalemia of 9.6% and hypocalcaemia of 6.1%. The mean APACHE II score in the study sample was high at 24.1 (SD 6.5). Patients with hypomagnesaemia had a statistically significant higher APACHE II score and a longer mean QTc interval compared to the patients with normal magnesium levels. Our study did not find a statistically significant association between hypomagnesaemia and two weeks clinical outcomes with regards to morbidity as measured by length of stay in CCU and duration of ventilator use and mortality.

The significance of hypomagnesaemia is that it’s common and more so in the severely ill patients. In our study, one in every five patients was found to have hypomagnesaemia. Hypomagnesaemic patients have been shown to have a poorer outcome with regards to mortality and morbidity\textsuperscript{14, 17, 80}. However, our study did not show a statistically significant relationship between hypomagnesaemia and two week clinical outcomes. We were however not powered to test these associations due to limitation in patient’s numbers and duration of follow up.

Reports on prevalence of hypomagnesaemia in critically ill patients ranges from 14-66\%\textsuperscript{16}. A plausible explanation for this wide range could be the differences in patients clinical categories. Our study compares favorably with Rubeiz et al\textsuperscript{80} who reported a prevalence of 20% on evaluating 381 acutely ill patients admitted to the emergency department CCU and medical ICU. This similarity may be due to shared baseline patient characteristics, majority of the admissions to the emergency CCU were due to trauma, in patients who were previously healthy. Majority were acutely ill patients whose baseline physiology may not be altered to a large extent. In contrast, Chernow et al\textsuperscript{14} reported a prevalence of 61%, they studied 193 post cardiac surgery patients. The high prevalence found by Chernow and colleagues could be attributed to the sample of patients studied. Post cardiac surgery patients are at a higher risk of magnesium depletion due to the large volumes of hypotonic fluid resuscitation infused which may shift
magnesium. These patients also tend to have blood transfusion hence citrate in blood may chelate magnesium. Limaye C.S et al 66 in India studied 100 medical ICU patients and found a prevalence of 52%. This high prevalence could be attributed to the fact that Limaye and colleagues did their study in an entirely medical ICU as opposed to our study where we had a mix of patients. Our study therefore had a heterogeneous patient population in terms of diagnostic labels.

STRENGTHS AND LIMITATIONS
To the best of our knowledge, this is the first study on prevalence of admission hypomagnesaemia among the critically ill, in Sub Saharan Africa. The sample population included patients of various disease labels, giving a broad picture of the magnitude of the problem in patients with critical illnesses. However, potential limitations do exist in our estimation of prevalence of hypomagnesaemia. Selection criteria for admission into CCU of the KNH, favors disease states that would require ventilation. Being a developing country with scarcity of resources for health care, our CCU bed capacity is limited; one would expect prioritization in admission criteria. This introduces a selection bias, which may have underestimated the prevalence, as most of the admissions were prioritized based on ventilation need as opposed to the need for multi-organ support.

CONCLUSION
In conclusion this study found that hypomagnesaemia is common in the critical care setting and more so in the severely ill patients.

RECOMMENDATIONS
In view of our study findings, it is therefore highly recommended that routine monitoring of serum magnesium and clinical assessment of patients at risk for Mg deficiency remains vital for making a timely diagnosis of magnesium depletion. More studies need to be done to determine serial magnesium changes during the patients stay in the critical care units.
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APPENDICES:

1. Appendix i- Study explanation for consent
2. Appendix ii- Consent form
3. Appendix iii- Transcription form
   a. Admission taxonomy
   b. Cormobid disease taxonomy
   c. APACHE II SEVERITY SCORE
   d. Lab measurements
   e. ECG findings
4. Appendix iv- Serum magnesium lab estimation
5. Appendix v- Serum Calcium laboratory estimation
6. Appendix vi- Serum potassium laboratory estimation
7. Appendix vii- Serum albumin laboratory estimation
8. Appendix viii- Arterial blood gas analysis
9. Appendix ix- Full Hemogram estimation
APPENDIX I

Study Explanation form

Introduction and objective of study

I am Dr Wanjiku Kagima, a masters student in internal medicine at the university of Nairobi. I am conducting a study on the magnesium levels on critically ill patients. Magnesium is a cation in the human body which serves as a co factor in more than 300 enzymatic reactions. The magnesium levels may be compromised due to many processes and this is especially true in patients admitted to critical care units. This study is intended to establish how common low magnesium levels are in our local setup among the critically ill patients. Early detection and intervention of low magnesium levels reduces the days of admission and also the risk of death. Those participating found to be having low magnesium will be referred to their primary physician for further management.

This study aims to,

i. Determine the prevalence of hypomagnesemia in critically ill patients in Kenyatta National Hospital.

Benefits and risks to you:

By participating in this study, you benefit by,

- Having examinations and laboratory tests done on you at no extra costs.
• A copy of the results will be availed to your file and the doctor informed of these results
• Those with low magnesium will be advised on modalities of management according to accepted standards of practice.

Risks:

History taking, physical examination and an Electrocardiogram (ECG) have no risks.

6 cc venous blood will be drawn from the antecubital vein and some level of minor discomfort will be experienced during blood withdrawal. This will be done on the day of admission only. ECG will be done also on the day of admission. Thereafter, daily follow-up for the duration of the study, i.e. 14 days, from the day of enrollment, for documentation of outcomes for those who are found to have low magnesium levels.

If you consent to participate in this study, you will:

1. Sign a consent form (Appendix ii)
2. Undergo a general physical examination
3. Have 6cc of blood taken for analysis
4. Have an ECG performed.
5. Be followed up for 14 days

Participation in this study is voluntary and you are allowed to withdraw at any time. Any information obtained by us in the process of the study remains confidential. You are free to ask questions regarding this study now and at any time during the study.

In case you have any questions concerning the study, kindly contact:

Dr. Wanjiku Kagima 0721889048 (primary investigator)
Chairman, KNH/UON-ERC 020726300-9 Ext. 44102
APPENDIX II

CONSENT FORM

I ………………………………………………………………………………. the (patient/ parent/ guardian) of ………………………………………………. After reading and having the study purpose explained to me by Dr. Wanjiku Kagima, do hereby give informed consent to participate in the STUDY ;HYPMAGNESEMIA IN CRITICALLY ILL PATIENTS UPON ADMISSION TO THE CRITICAL CARE UNITS AT KNH

I am aware that I can withdraw from this study without having any benefits or quality of management of my medical condition interfered with.

Signed: …………………………………………………………………………

Thumb print: ……………………………………………………………… Date: ………………………………………

Signature of questionnaire administrator: (Dr. Wanjiku Kagima) ……………………………………………

Witness: ……………………………….. Date: ………………………………..