# Incidence and Factors Associated with Acute Kidney Injury (AKI) in Hyperchloremic Critically Ill Adult Patients

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**DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF MEDICINE ANAESTHESIOLOGY**


**UNIVERSITI SAINS MALAYSIA**

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**ACKNOWLEDGEMENTS**

In The Name of Allah, The most Beneficent, The Most Merciful. All praises and thanks (be) to Allah, the Lord of the universe.

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A special thanks and acknowledgements to Dr Tai Li Ling and the Malaysian Registry of Intensive Care for their contribution in sharing their knowledge for this study which has made it possible for me to complete this research in time where I would forever be in debt.

Last but not least, I would love to mention Tassha Hilda Adnan from National Institutes of Health (NIH), Malaysia and all my other colleagues in M.Med Anaesthesiology University Sains Malaysia programme which had helped me every step of the way in fulfilling this requirement.

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**LIST OF SYMBOLS, ABBREVIATIONS AND ACRONYM'S**

| | |
|---|---|
| ABG | Arterial Blood Gas |
| AG | Anion Gap |
| AKI | Acute Kidney Injury |
| AKIN | Acute Kidney Injury Network |
| BE | Base Excess |
| CCIS | Critical Care Information System |
| CKD | Chronic Kidney Disease |
| DKA | Diabetic Ketoacidosis |
| $HCO_3^-$ | Bicarbonate Ion |
| HIS | Hospital Information System |
| ICU | Intensive Care Unit |
| IQR | Inter Quartile Range |
| JEPeM | Jawatankuasa Etika Penyelidikan Manusia USM |
| SPSS | Statistical Package for the Social Sciences |
| ml | mililitre |
| mmol/L | mili mol per litre |
| MOH | Ministry of Health |
| MREC | Medical Research & Ethics Committee |
| MRIC | Malaysian Registry of Intensive Care |
| NMMR | National Medical Research Register |
| OR | Odds Ratio |
| ROC | Receiver Operating Characteristic |
| SAPS II | Simplified Acute Physiology Score II |

| | |
|---|---|
| SD | Standard Deviation |
| USM | Universiti Sains Malaysia |
| VIKI | Ventilator Induced Kidney Injury |
| $[Cl^-]_{max}$ | Maximum serum chloride concentration in 48 hours |
| $[Cl^-]_{min}$ | Minimum serum chloride concentration in 48 hours |
| $[Cl^-]_0$ | Serum chloride concentration on admission |
| $\Delta[Cl^-]$ | Changes of serum chloride concentration |

**ABSTRAK**

**KAJIAN PEMERHATIAN KELOMPOK SECARA RETROSPEKTIF DALAM INSIDEN DAN FAKTOR-FAKTOR YANG DIKAITKAN DENGAN KEGAGALAN GINJAL AKUT DI KALANGAN PESAKIT KRITIKAL DEWASA DENGAN KADAR KLORIDA TINGGI DALAM DARAH SEWAKTU DI UNIT RAWATAN RAPI**

*Latar Belakang*

Kandungan klorida tinggi dalam darah masih lagi merupakan ketidakseimbangan elektrolit di Unit Rawatan Rapi yang paling tidak diendahkan meskipun beberapa kajian dalam dekad terakhir telah membuktikan kaitannya dengan Kegagalan Ginjal Akut. Kajian ini bertujuan untuk melaporkan insiden dan faktor berkaitan dengan Kegagalan Ginjal Akut di kalangan pesakit dewasa yang kritikal yang mempunyai kandungan klorida tinggi dalam darah.

*Kaedah*

Dalam kajian kohort retrospektif yang diadakan di sebuah hospital besar berpakar, pesakit yang mempunyai tahap klorida tinggi berusia 18-65 tahun semasa kemasukkan akan dimasukkan kedalam kajian. Perkembangan Kegagalan Ginjal Akut menggunakan kriteria AKIN dalam masa 48 jam dijadikan sebagai hasil utama dan faktor-faktor yang berkaitan dengannya dianalisis.

*Keputusan*

248 (11.7%) daripada pesakit yang dimasukkan semasa kajian adalah berklorida tinggi semasa kemasukan. Daripada jumlah ini, 84 (34%) pesakit mendapat Kegagalan Ginjal Akut. Umur 56-65 tahun [OR = 2.598 (1.126-5.995); p = 0.025], skor SAPS II [OR = 1.04 (1.02-1.06); p <0.001], kegagalan pernafasan [OR = 2.516 (1.064-5.947); p = 0.036], kegagalan kardiovaskular [OR = 2.239 (1.083-4.626); p = 0.030], kandungan klorida tinggi terlampau [OR = 2.045 (1.176-3.557); p = 0.011], darah berasid terlampau [OR = 2.733 (1.269-5.886); p = 0.010] dan darah berasid akibat metabolik terlampau [OR = 2.003 (1.010-3.972); p = 0.047] didapati berkaitan dengan Kegagalan Ginjal Akut. Selepas penyesuaian dengan faktor yang bersabitan, skor SAPS II (adjusted OR, 1.032 [1.003-1.062]; p = 0.028) dan umur 56-65 tahun (adjusted OR, 2.506 [1.024-6.135]; p = 0.044) didapati boleh membayangkan Kegagalan Ginjal Akut.

*Kesimpulan*

Satu dari tiga pesakit yang berkadar klorida tinggi menghadapi Kegagalan Ginjal Akut selepas 48 jam kemasukkan ke Unit Rawatan Rapi. Markah SAPS II dan umur 55-65 tahun terbukti merupakan faktor yang meramalkan Kegagalan Ginjal Akut. Markah SAPS II adalah satu cara yang berguna yang boleh memberi jangkaan akan Kegagalan Ginal Akut di kalangan pesakit berkadar klorida tinggi.

**ABSTRACT**

**RETROSPECTIVE OBSERVATIONAL COHORT STUDY IN THE INCIDENCE AND FACTORS ASSOCIATED WITH ACUTE KIDNEY INJURY IN HYPERCHLOREMIC CRITICALLY ILL ADULT PATIENTS DURING THEIR STAY IN INTENSIVE CARE UNIT**

*Background*

Hyperchloremia is still the least looked at electrolytes imbalance in ICU despite a few studies in the last decade has proven its association with AKI. This study is aimed to report on the incidence and factors associated with AKI in hyperchloremic critically ill adult patients.

*Methods*

In this retrospective cohort study held in a tertiary hospital, hyperchloremic patients aged 18-65 years old on admission were included. Development of AKI using AKIN criteria within the next 48 hours was marked as the primary outcome and factors associated with it were analysed.

*Results*

248 (11.7%) of the patients admitted during the study were hyperchloremic on admission. Out of this, 84 (34%) patients developed AKI. Age 56-65 years [OR=2.598 (1.126-5.995); p=0.025], SAPS II score [OR=1.04 (1.02-1.06); p<0.001], respiratory failure [OR=2.516 (1.064-5.947); p=0.036], cardiovascular failure [OR=2.239

(1.083-4.626); p=0.030], severe hyperchloremia[OR=2.045 (1.176-3.557); p=0.011], severe acidemia [OR=2.733 (1.269-5.886); p=0.010] and severe metabolic acidosis[OR=2.003 (1.010-3.972);p=0.047] were found to be associated with AKI. After adjusting to confounding factors, SAPS II score (adjusted OR, 1.032 [1.003-1.062]; p=0.028) and age 56-65 years (adjusted OR, 2.506 [1.024-6.135]; p=0.044) were found to be predictive of AKI.

*Conclusions*

One-third of hyperchloremic patients developed AKI after 48 hours of ICU admission. SAPS II score and age group 55-65 years are proven to be predictive factors of later development of AKI. SAPS II score is a useful tool in predicting AKI in hyperchloremic patients.

# CHAPTER 1: INTRODUCTION

## 1.1 Background

Hyperchloremic metabolic acidosis is a subset of metabolic acidosis. It is characterised in patients having abnormally high serum chloride associated with metabolic acidosis and normal anion gap. Generally it can be caused by excessive gastrointestinal loss of bicarbonate, proximal real tubular acidosis, long term use of carbonic anhydrase, ingestion of excessive chloride acid, post treatment of Diabetic Ketoacidosis (DKA) or following resuscitation with chloride rich fluids such most commonly use 0.9% Normal Saline.

Metabolic acidosis has been known to be associated with higher incidence of mortality in Intensive Care Unit (ICU) patients while recent studies has shown that serum chloride level is associated with higher incidence of Acute Kidney Injury (AKI)(1, 2). The most common iatrogenic cause hyperchloremic metabolic acidosis is due to generous infusion of chloride rich solutions, mainly normal saline 0.9%. It has been the main crystalloid use in most clinical settings and almost always the first choice of crystalloid for maintenance or replacement of fluid loss.

It is also the recommended fluid in managing sepsis, dengue shock syndrome and DKA patients.Therefore the risk for hyperchloremic acidosis is always present in clinical settings especially in ICU settings. Thus this study may recognise the added risk of Hyperchloremic Metabolic Acidosis into developing Acute Kidney Injury.

### 1.2 Problem Statement and Study Rationale

Acute Kidney Injury is one of the main morbidity in ICU that is associated with high mortality and costly treatment (3, 4). Hyperchloremia on the other hand has been associated with higher incidence of AKI while metabolic acidosis is one of the major factor contributing to AKI and mortality (5-8). AKI is reported around 15% in Malaysian ICU, does hyperchloremia with metabolic acidosis has any significant contribution to AKI (9, 10)?

### 1.3 Research Objectives

#### 1.3.1 General Objective

To describe the incidence and factors associated AKI in hyperchloremic critically ill adult patients.

#### 1.3.2 Specific Objective

1. To determine the proportion of hyperchloremic patients with metabolic acidosis during the study period.
2. To identify the group difference in the incidence of AKI in patients with or without metabolic acidosis in ICU.
3. To determine the factors associated with AKI among hyperchloremic patients in ICU.

## 1.4 Research Hypotheses

### Null Hypothesis

Metabolic acidosis and other factors of age, SAPS II score, main organ failure, acidemia, chloride levels and hyperchloremic metabolic acidosis are not independently associated with AKI in hyperchloremic patients.

### Alternative Hypothesis

Metabolic acidosis and other factors of age, SAPS II score, main organ failure, acidemia, chloride levels and hyperchloremic metabolic acidosis are independently associated with AKI in hyperchloremic patients.

## 1.5 Literature Review

### 1.5.1 Acute Kidney Injury

One of the largest and latest study on the epidemiology of AKI in critically ill patient was in 2007 by Bagshaw et al(3). It was a large observational surveillance cohort study done in 20 ICU from different Australian hospitals over a period of 10 years from 1996 to 2005. They have found that out of 91254 patients in the study, the incidence of AKI during the first 24 hours of ICU admission was 5.2% and it was with an increasing trend of 2.8% increments per year. Greater increment was seen in the last 5 years period of the study with difference of 5.6% to 4.8%. The study also pointed out that there is higher hospital mortality and longer median length of stay in ICU and hospital among patients with AKI versus non AKI (3).

Locally, incidence of AKI is reported in yearly Malaysian Intensive Care Registry. In the last 2 reports, the incidence of AKI within 24 hours of ICU admission was around 15%. This is 3 times of the incidence reported in Australia by the study mentioned previously(3). Another local study was done in 2015 by Ralib et al. (11) demonstrated that incidence of AKI in her ICU was 65% in 48 hours of ICU admission. This is more than triple of the incidence reported by MRIC in the same year(9). It seems that 24 hours time may be too short to see the real picture of AKI in ICU. This is then supported by a large multinational prospective study done by Hoste et al. (12) (AKI-EPI) which had observed 1032 out of 1802 (57%) had developed AKI within 1 week of ICU admission.

### 1.5.2 Hyperchloremia

In 2012, Yunos et al. has done a prospective, open-label, sequential pilot study of total 1533 patients in an ICU in Melbourne Australia over a period of 1 year to study the association between a chloride-liberal versus chloride-restrictive intravenous fluid administration strategy and acute kidney injury in critically adult. The study has found out that chloride restrictive therapy is associated with significantly lower increase of mean serum creatinine level during ICU stay of 14.8 versus 22.6 mmol/L. Furthermore, the study also stated that the chloride restrictive therapy was associated with significantly reduced incidence of patients in Injury and Failure class of RIFLE's AKI classification. The use of RRT was also associated with lower incidence in patients on chloride restrictive therapy compared to chloride liberal therapy by 6.3% versus 10% (2).

Zhang et al. in 2013 has suggested that a higher minimum chloride level is protective against AKI while the higher the chloride level above normal value is associated with a higher incidence of AKI in unselected critically ill patients. In his retrospective cohort study in an ICU over a period of just over 2 years, he has studied 1221 patients who were critically ill and finds out that 29.2% of them has developed AKI. Among those patients, he has correlated that the maximum and minimum chloride level before the onset of AKI is higher in patients who has developed AKI in contrast to those who did not. The study also points out that AKI group patients have higher fluid balance compared those who were not with the mean of 1245 ml versus 984 ml with p value of <0.001. The study has used AKIN staging of AKI and finds out that AKIN stage 1 patients has significantly higher Cl max level compared to non AKI patients while AKIN 3 stage has significantly higher Cl max compared to AKIN 2 stage patient.(6)

In a retrospective cohort study in duration from January 2011 to April 2015, Suetrong et al. instead has studied the association of hyperchloremia and moderate increase in serum chloride with the incidence of AKI in severe sepsis and septic shock patients. In this study, the incidence of AKI is higher in hyperchloremia group at 85.7% versus 47.9%.As supported by previous studies, higher level of maximum serum chloride is associated with higher incidence of AKI. This study also discovered that the higher the increase level of serum chloride is associated with higher incidence of AKI compared to maximum serum chloride alone. This is also true even in patients who were never hyperchloremic before (13).

A smaller scale study was done by Tani et al. in 2012 in Japan studying the incidence and prognostic value of hypochloremia in ICU patients. From this study they have laid out the incidence of hyperchloremia was 16.6% while the incidence of normochloremia and hypochloremia was 74.6% and 8.8% respectively in critically ill patients (14).

The most recent prospective observational study on relating serum chloride level and AKI was done by Marttinen et al. in 2016. In this study, they were looking for the correlation of plasma chloride values with AKI in the critically ill patients. They find out that total of 78.7% of their study sample has hyperchloremia with 10.8% of them having severe hyperchloremia with serum chloride of more than 114 mmol/L. Among this patients, 48.8% has developed AKI where 28.6% of them were diagnosed in the first 24 hours of ICU stay (15).

### 1.5.3 Metabolic acidosis

Metabolic acidosis is believed to be the consequences of hyperchloremia in the critically ill patients. Most likely cause is hyperchloremic metabolic acidosis caused by iatrogenic normal saline infusion given to the patients for treatment and replacement of fluids(16). Jung et al. in his 2011 (5) prospective observational multi centre study has reported that incidence of severe metabolic acidosis in his study was 6% but it was associated with 57% mortality rate in ICU.

Gunnerson et al. in 2006 (17) in his observational cohort study of patients with lactate and non lactate metabolic acidosis has found that patients with metabolic acidosis are twice more likely to die than patients without metabolic acidosis. This association of

high mortality shows the importance of understanding the risk carried in patients with metabolic acidosis in ICU.

Conversely, Hu in 2017 had studied the ABG of 4873 of patients admitted to his ICU(8). In this retrospective study, he found that metabolic acidosis is an independent risk factor of developing AKI and hospital mortality in the critically ill patients.

Inferring from the literature review and the most recent local study, we can come to conclusion that AKI is one of the major picture of illness in critical care settings. This study is designed to further evaluate the incidence of AKI in local ICU by looking for the association between 2 major contributing factors for AKI in ICU which is hyperchloremia and metabolic acidosis.

Currently to our knowledge, there is no similar study has yet been published from either local or abroad study looking at the association of these factors and their development of AKI. We are expecting to see the concentration of AKI lay in the exposed cases compared to the exposed control population.

## 1.6 Conceptual Framework

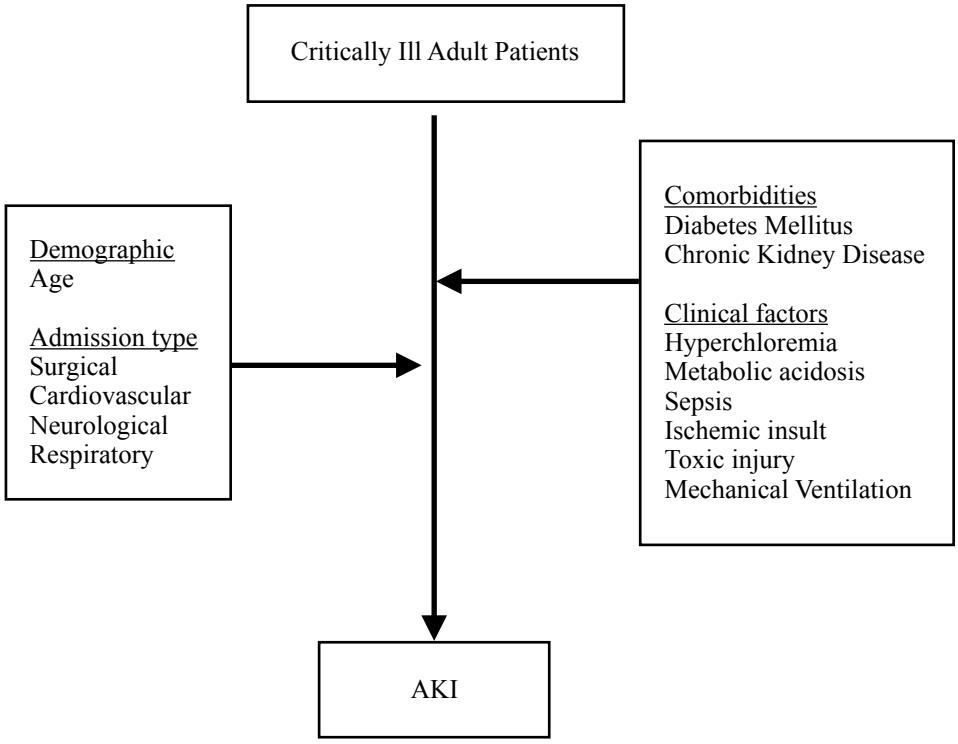


Figure 1.1 Conceptual Framework

## CHAPTER 2: STUDY PROTOCOL

### 2.1 Study Protocol submitted for Ethical Approval

#### 2.1.1 Research design

Retrospective observational cohort study in patient with hyperchloremia on developing AKI during stay in intensive care unit.

#### 2.1.2 Study area

Patients who were admitted to the Intensive Care Unit in Hospital Sultanah Nur Zahirah, Kuala Terengganu, Terengganu.

#### 2.1.3 Study population

Reference population - Critically ill patients in Terengganu

Target population- Critically ill adult patients in Terengganu whom were admitted to Hospital Sultanah Nur Zahirah, Kuala Terengganu, Terengganu.

Source population/sampling pool-Critically ill adult patients whom were admitted to Intensive Care Unit in Hospital Sultanah Nur Zahirah, Kuala Terengganu, Terengganu.

Sampling Frame-Critically ill adult patients whom were admitted to Intensive Care Unit in Hospital Sultanah Nur Zahirah between 1 September 2015 till 31 December 2016

### 2.1.4 Subject criteria

Inclusion Criteria

I. Age more than 18 and less 65 years old

II. Admitted to ICU

III. Hyperchloremia on admission

Exclusion Criteria

I. Patients who has missing data

II. Patients who did not have at least 2 renal profile investigations within 48 hours of admission

III. Patients who were readmitted to ICU during the study period

IV. Patients with preexisting Chronic Kidney Disease

### 2.1.5 Sample size estimation

Sample size calculation was done by using Sample Size for Unmatched Case - Control Study. Ratio of Controls to Cases was taken from a study by Marttinen et all in 2016 "Association of plasma chloride values with acute kidney injury in the critically ill, a prospective observational study" in Acta Anaesthesiologica Scandinavica (15) where he finds that out of 78.7% of his 445 patients has hyperchloremia on admission. From this, he finds out that the incidence of AKI and no AKI was 48.8% and 51.2% respectively. With this, we deduce that the Ratio of Controls to cases is 1.05. (15)

Libório et al. in 2014 (7) has done a large retrospective study in a university hospital in Boston looking at 18410 patients in 4 different units of intensive care from the year

2001 till 2008. In this study, he finds out that 12828 of this patients has metabolic acidosis on admission where 7985 of them developed AKI. Proportions of cases and controls with exposure were taken from this study for estimation.

Table 2.1 AKI complications in patients with or without metabolic acidosis

| | | Exposed + | Exposed - | Total |
|---|---|---|---|---|
| | | AKI | No AKI | |
| Disease + | Metabolic Acidosis | 7985 | 4843 | 12828 |
| Disease - | No Metabolic Acidosis | 2268 | 3314 | 5582 |
| Total | | 10253 | 8157 | 18410 |

Table extracted from Libório, A. B., Leite, T. T., Neves, F. M. d. O., Teles, F. & Bezerra, C. T. d. M. (2014). AKI Complications in Critically Ill Patients: Association with Mortality Rates and RRT. *Clinical Journal of the American Society of Nephrology* (7)

Table 2.2 Sample Size for Unmatched Case-Control Study

For:

| | |
|---|---|
| Two-sided confidence level(1-alpha) | 95 |
| Power(% chance of detecting) | 80 |
| Ratio of Controls to Cases | 1.05 |
| Hypothetical proportion of controls with exposure | 26 |
| Hypothetical proportion of cases with exposure: | 43 |
| Least extreme Odds Ratio to be detected: | 2.15 |

| | Kelsey | Fleiss | Fleiss with CC |
|---|---|---|---|
| Sample Size - Cases | 120 | 119 | 130 |
| Sample Size - Controls | 125 | 124 | 136 |
| Total sample size: | 245 | 243 | 266 |

References: Kelsey et al., Methods in Observational Epidemiology 2nd Edition, Table 12-15
Fleiss, Statistical Methods for Rates and Proportions, formulas 3.18 &3.19

CC = continuity correction
Results are rounded up to the nearest integer.

From this calculation, the desired minimal sample size is 243 participants.

### 2.1.6 Sampling method and subject recruitment

Patients who were admitted during the study period will be identified from ICU registry. Patients will then be shortlisted using the inclusion criteria of age between 18 - 65 years old. Then by using "Hospital information Network (HIS)" software, renal profile investigation taken at the time of ICU admission will be reviewed and used to identify patients with hyperchloremia on admission.

Patients who fits in the exclusion criteria will then be listed out from the list before further data collection will be made.

From the registry census, 2120 patients were admitted to the ICU during the sampling period.

### 2.1.7 Research tool

Data collection sheet is used to collect data from HIS of the patients included into this study. This attached in appendix 1.

### 2.1.8 Operational definition

*Hyperchloremia* will be define as the blood serum chloride concentration of more than 110 mmol/L (18)

*Severe Hyperchloremia* is defined when serum chloride more than 114 mmol/L (15)

*Acidemia* is when serum ph less than 7.35 on admission to ICU

*Severe Acidemia* ph less than 7.20 on admission to ICU (5)

*Metabolic acidosis* is defined when serum BE is less than -2 on admission to ICU(17)

*Severe Metabolic acidosis* defined as when serum BE is less than -5 on admission to ICU (19)

*Normal anion gap* is the difference between the product of plasma sodium concentration and potassium with serum concentration of chloride and bicarbonate. Any value of less than 16 mmol/L is considered normal (20).

*Hyperchloremic Metabolic Acidosis* is define as patients with hyperchloremia with serum BE on admission of less than -2 and with normal anion gap.

*Acute Kidney Injury* is defined as any patients that fits in any of the 3 stages of AKI within 48 hours of ICU admission using the criteria given by Acute Kidney Injury Network (21).

*ICU Stay* is the length of stay of the patient in the ICU.

Table 2.3 Classification/staging system for Acute Kidney Injury

| Stage | Serum Creatinine criteria | Urine output criteria |
|---|---|---|
| 1 | Increase in serum creatinine of more than or equal to 0.3mg/dl (≥26μmol/l) or increase to more than or equal to 150% to 200% (1.5-to 2-fold) from baseline | less than 0.5mg/kg per hour for more than 6 hours |
| 2 | Increase in serum creatinine to more than 200% to 300% (>2 to 3 fold) from baseline | less than 0.5ml/kg per hour for more than 12 hours |
| 3 | Increase in serum creatinine to more than 300% (>3 fold) from baseline (or serum creatinine of more than or equal to 4mg/dl [≥354 μmol/l] with an acute increase of at least 0.5mg/dl [44μmol/l]) | less than 0.3ml/kg per hour for 24 hours or anuria for 12 hours |

Table extracted from Mehta et al. (21)

### 2.1.9 Data collection method

Patients who were admitted within the study duration will be identified from ICU registry. Patient's data then will be collected from "Hospital Information System (HIS)" software and "Critical Care Information System (CCIS)" using their Registration Number obtained from ICU registry. All the data will be collected according to data collection form (appendix A) and patients will be included and excluded according to the inclusions and exclusions criteria.

The data then will be used to determine incidence of AKI using AKIN's Criteria. All other statistical work in determining study objective will be done using SPSS.

All data collected using the data collection sheet will be kept in locked bag and given unique identification number that does not include any of patients sensitive data such as National Identity Card Number or Hospital Registry Number,

Data that is collected then will be keyed into a locked laptop that can only be assed by Principal Investigator.

### 2.1.10 Study flow chart

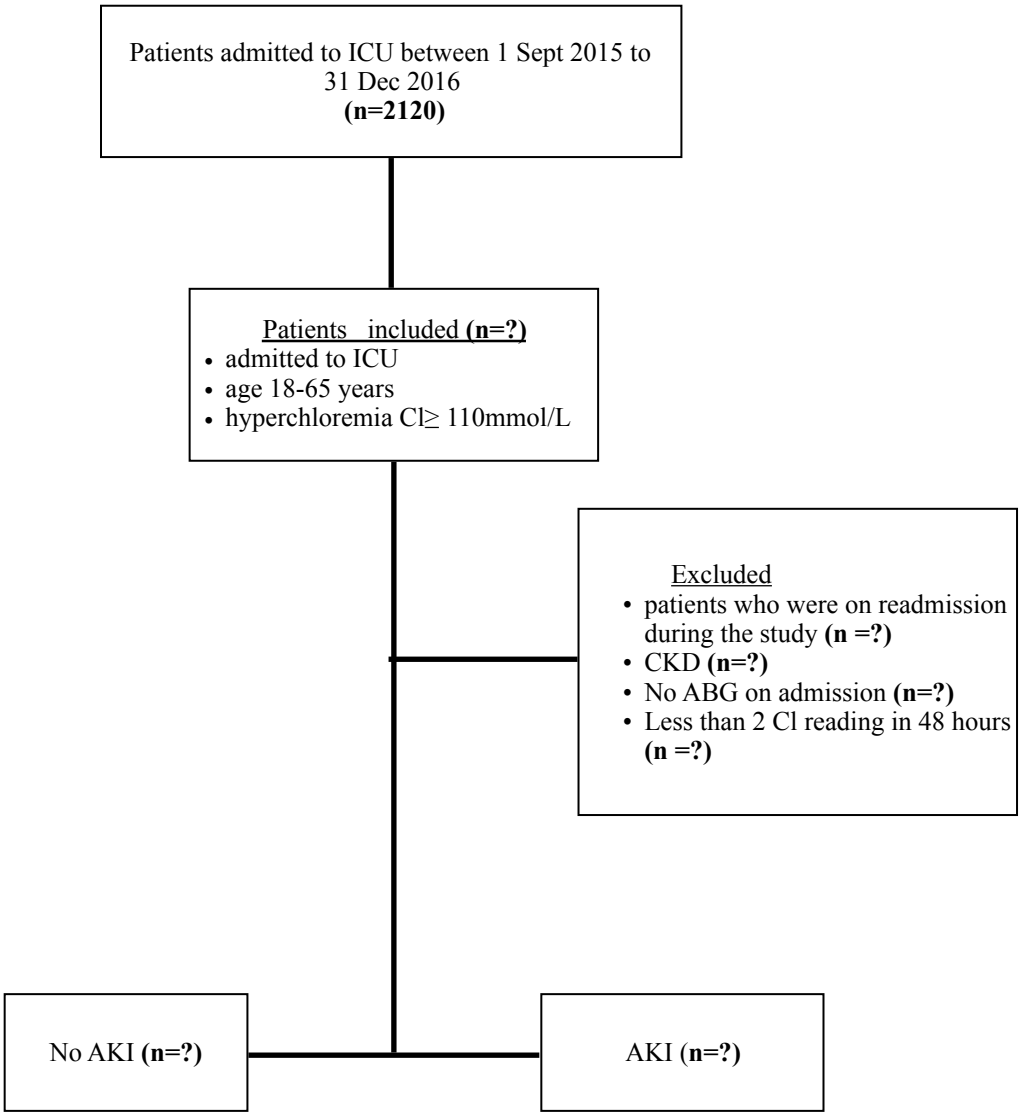


Figure 2.1 Study Flow Chart

### 2.1.11 Data analysis

Objective 1

Descriptive proportion of hyperchloremic patients with metabolic acidosis

Objective 2

Group difference in the incidence of AKI in patients with or without metabolic acidosis in ICU.

Objective 3

Factors associated with AKI among hyperchloremic patients in ICU.

### 2.1.12 Gantt chart & milestone

Table 2.4 Gantt chart & milestone

| Research Activities | 2016 | 2017 | | | | 2018 | | | | 2019 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Nov | Feb | May | Aug | Nov | Feb | May | Aug | Nov | Feb | May |
| Research proposal | X | X | | | | | | | | | |
| Ethics committee | | | X | X | X | X | | | | | |
| Data Collection | | | | | | X | X | X | X | | |
| Data Analysis | | | | | | X | X | X | X | | |
| Report Writing | | | | | | | | | X | X | X |
| Research submission | | | | | | | | | | X | X |

### 2.1.13 Budget proposal [If applicable]:

This is an investigator/self sponsored research and no grant was applied.

### 2.1.14 Ethical consideration(s) [if applicable]:

1. **Subject vulnerability**

As a retrospective cohort study involving data collections, the researcher also has applied for ethical approval from the National Medical Research and Ethics Committee (MREC) of the Ministry of Health (MOH), Malaysia via the National Medical Research Registry (NMRR).All data extractions from medical records and registry will be treated as confidential and details on the patients involved will not be compromised.

**2. Declaration of absence of conflict of interest**

This is an Investigator/Self sponsored research, there will be no direct benefit from the outcome of this study to any of the investigators involved that may influence our professional judgement.

**3. Privacy and confidentiality**

All forms are anonymous and will be entered into SPSS software. Only research team members can access the data. Data will be presented as grouped data and will not identify the patients individually.

**4. Community sensitivities and benefits**

There is no expected interaction with the community to cause any distress or anxiety to the community and its sensitivity.

**5. Honorarium and incentives**

No honorarium or incentives will be given out in this study

**6. Other ethical review board approval [if applicable]**

I. National Medical Research and Ethics Committee (MREC) of the Ministry of Health (MOH), Malaysia via the National Medical Research Registry (NMRR)

A. Status of application-approved (NMRR-17-2360-37081)

## 2.2 Ethical Approval Letter (JEPEM USM)

UNIVERSITI SAINS MALAYSIA

JAWATANKUASA ETIKA PENYELIDIKAN MANUSIA

**Jawatankuasa Etika**
**Penyelidikan Manusia USM (JEPeM)**
*Human Research Ethics Committee USM (HREC)*

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**28th February 2018**

**Dr. Wan Mohd Hafidz Wan Hisham**
Department of Anaesthesiology
School of Medical Sciences
Universiti Sains Malaysia
16150 Kubang Kerian, Kelantan.

**JEPeM Code : USM/JEPeM/17100538**
**Protocol Title : Incidence and Association of Hyperchloremia and Development of Acute Kidney Injury (AKI) in Critically Ill Adult Patients with or without Metabolic Acidosis.**

Dear Dr.,

We wish to inform you that your study protocol has been reviewed and is hereby granted approval for implementation by the Jawatankuasa Etika Penyelidikan Manusia Universiti Sains Malaysia (JEPeM-USM). Your study has been assigned study protocol code **USM/JEPeM/17100538**, which should be used for all communication to the JEPeM-USM related to this study. This ethical clearance is valid from **28th February 2018** until **27th February 2019.**

Study Site: Hospital Sultanah Nur Zahirah, Kuala Terengganu, Terengganu.

The following researchers also involve in this study:

1. Assoc. Prof. Dr. Saedah Ali
2. Dr. Laila Ab Mukmin
3. Dr. Mohd Ridhwan Mohd Noor

The following documents have been approved for use in the study.

1. Research Proposal

In addition to the abovementioned documents, the following technical document was included in the review on which this approval was based:

1. Data Collection Sheet

Attached document is the list of members of JEPeM-USM present during the full board meeting reviewing your protocol.

While the study is in progress, we request you to submit to us the following documents:

1. Application for renewal of ethical approval 60 days before the expiration date of this approval through submission of **JEPeM-USM FORM 3(B) 2017: Continuing Review Application Form.** Subsequently this need to be done yearly as long as the research goes on.
2. Any changes in the protocol, especially those that may adversely affect the safety of the participants during the conduct of the trial including changes in personnel, must be submitted or reported using **JEPeM-USM FORM 3(A) 2017: Study Protocol Amendment Submission Form.**
3. Revisions in the informed consent form using the **JEPeM-USM FORM 3(A) 2017: Study Protocol Amendment Submission Form.**

CERTIFIED BY: National Pharmaceutical Regulatory Agency (NPRA) | Forum for Ethical Review Committees in Asia & Western Pacific Region

4. Reports of adverse events including from other study sites (national, international) using the **JEPeM-USM FORM 3(G) 2017: Adverse Events Report.**
5. Notice of early termination of the study and reasons for such using **JEPeM-USM FORM 3(E) 2017.**
6. Any event which may have ethical significance.
7. Any information which is needed by the JEPeM-USM to do ongoing review.
8. Notice of time of completion of the study using **JEPeM-USM FORM 3(C) 2017: Final Report Form.**

Please note that forms may be downloaded from the JEPeM-USM website: **www.jepem.kk.usm.my**

Jawatankuasa Etika Penyelidikan (Manusia), JEPeM-USM is in compliance with the Declaration of Helsinki, International Conference on Harmonization (ICH) Guidelines, Good Clinical Practice (GCP) Standards, Council for International Organizations of Medical Sciences (CIOMS) Guidelines, World Health Organization (WHO) Standards and Operational Guidance for Ethics Review of Health-Related Research and Surveying and Evaluating Ethical Review Practices, EC/IRB Standard Operating Procedures (SOPs), and Local Regulations and Standards in Ethical Review.

Thank you.

**"ENSURING A SUSTAINABLE TOMORROW"**

**PROF. DR. HANS AMIN VAN ROSTENBERGHE**
Chairperson
Jawatankuasa Etika Penyelidikan (Manusia) JEPeM
Universiti Sains Malaysia

Jawatankuasa Etika
Penyelidikan Manusia USM (JEPeM)
Human Research Ethics Committee USM (HREC)

19th December 2018

012-2650042
**Dr. Wan Mohd Hafidz Wan Hisham**
Department of Anaesthesiology
School of Medical Sciences
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www.usm.my

**JEPeM USM Code: USM/JEPeM/17100538**

**Study Protocol Title: Incidence and Association of Hyperchloremia and Development of Acute Kidney Injury (AKI) in Critically Ill Adult Patients with or without Metabolic Acidosis.**

Dear Dr:

We wish to inform you that the Jawatankuasa Etika Penyelidikan Manusia, Universiti Sains Malaysia (JEPeM-USM) approved the proposed amendments in your study entitled, **"Incidence and Association of Hyperchloremia and Development of Acute Kidney Injury (AKI) in Critically Ill Adult Patients with or without Metabolic Acidosis" [USM/JEPeM/17100538]** during its meeting on 6th December 2018.

Upon review of JEPeM-USM FORM 3(A) 2017: Study Protocol Amendment Submission Form, the following amendments have been approved:

1. Rephrasing of study title to 'Incidence and Factors Associated with Acute Kidney Injury (AKI) in Hyperchloremic Critically Ill Adult Patients.
2. Research Question V added.
3. Gantt chart and Milestone – Gantt chart adjusted to current time line.

Thank you.

**"ENSURING A SUSTAINABLE TOMORROW"**

**(PROF. DR. HANS AMIN VAN ROSTENBERGHE)**
Chairperson
Jawatankuasa Etika Penyelidikan (Manusia), JEPeM
Universiti Sains Malaysia

**c.c** Secretary
Jawatankuasa Etika Penyelidikan (Manusia), JEPeM
Universiti Sains Malaysia

JEPeM
JAWATANKUASA ETIKA
PENYELIDIKAN MANUSIA

## 2.3 Ethical Approval Letter (NMRR/MREC)

**JAWATANKUASA ETIKA & PENYELIDIKAN PERUBATAN**
***(Medical Research & Ethics Committee)***
KEMENTERIAN KESIHATAN MALAYSIA
d/a Institut Pengurusan Kesihatan
Jalan Rumah Sakit, Bangsar
59000 Kuala Lumpur

Tel.: 03-2287 4032/2282 0491/2282 9085
03-2282 9082/2282 1402/2282 1449
Faks: 03-2282 0015

**DR WAN MOHD HAFIDZ BIN WAN HISHAM**
**HOSPITAL SULTANAH NUR ZAHIRAH, KUALA TERENGGANU**

YBhg. Dato' / Tuan / Puan,

**SURAT KELULUSAN ETIKA: NMRR-17-2360-37081 (IIR)**
**INCIDENCE AND ASSOCIATION OF HYPERCHLOREMIA AND DEVELOPMENT OF ACUTE KIDNEY INJURY (AKI) IN CRITICALLY ILL ADULT PATIENTS WITH OR WITHOUT METABOLIC ACIDOSIS.**

**Lokasi Kajian:**
**HOSPITAL SULTANAH NUR ZAHIRAH, KUALA TERENGGANU**

Dengan hormatnya perkara di atas adalah dirujuk.

2. Jawatankuasa Etika & Penyelidikan Perubatan (JEPP), Kementerian Kesihatan Malaysia (KKM) tiada halangan, dari segi etika, ke atas pelaksanaan kajian tersebut. JEPP mengambil maklum bahawa kajian tersebut hanya melibatkan pengumpulan data melalui:

**i. Rekod perubatan**

3. Segala rekod dan data subjek adalah **SULIT** dan hanya digunakan untuk tujuan kajian ini dan semua isu serta prosedur mengenai *data confidentiality* mesti dipatuhi.

**4. Kebenaran daripada Pegawai Kesihatan Daerah/ Pengarah Hospital dan Ketua-Ketua Jabatan atau pegawai yang bertanggungjawab disetiap lokasi kajian di mana kajian akan dijalankan mesti diperolehi sebelum kajian dijalankan. YBhg. Dato' / Tuan / Puan perlu akur dan mematuhi keputusan tersebut. Sila rujuk kepada garis panduan Institut Kesihatan Negara mengenai penyelidikan di Institusi dan fasiliti Kementerian Kesihatan Malaysia (Pindaan 01/2015) serta lampiran *Appendix 5* untuk templet surat memohon kebenaran tersebut.**

.../2-

5. Adalah dimaklumkan bahawa kelulusan ini adalah sah sehingga **08-November-2018**. YBhg. Dato'/ Tuan/ Puan perlu menghantar dokumen-dokumen seperti berikut selepas mendapat kelulusan etika. Borang-borang berkaitan boleh dimuat turun daripada laman web Jawatakuasa Etika & Penyelidikan Perubatan (JEPP) (http://www.nih.gov.my/mrec).

i. ***Continuing Review Form*** selewat-lewatnya dalam tempoh 1 bulan (30 hari) sebelum tamat tempoh kelulusan ini bagi memperbaharui kelulusan etika.

ii. ***Study Final Report*** pada penghujung kajian.

iii. Mendapat kelulusan etika sekiranya terdapat pindaan keatas sebarang dokumen kajian/ lokasi kajian/ penyelidik.

6. Sila ambil maklum bahawa sebarang urusan surat-menyurat berkaitan dengan penyelidikan ini haruslah dinyatakan nombor rujukan surat ini untuk melicinkan urusan yang berkaitan.

Sekian terima kasih.

**"BERKHIDMAT UNTUK NEGARA"**

Saya yang menurut perintah

Pengerusi
Jawatankuasa Etika & Penyelidikan Perubatan
Kementerian Kesihatan Malaysia
mrecsec@nih.gov.my
03-2282 9085

s.k.: HRRC Hospital Sultanah Nur Zahirah

Hz/Approval2017/MRECshare