FACTORS PREDICTIVE OF THE NEED FOR RENAL REPLACEMENT THERAPY IN CRITICALLY ILL PATIENTS WITH RHABDOMYOLYSIS AND THEIR OUTCOME

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ACS	Acute Coronary Syndrome
AIDS	Acquired Immunodeficiency Syndrome
APS	Acute Physiology Score
ADP	Adenosine Diphosphate
AKI	Acute Kidney Injury
APACHE	Acute Physiologic and Chronic Health Evaluation
ATP	Adenosine Triphosphate
BMI	Body Mass Index
CK	Creatine Kinase
CNS	Central Nervous System
CVA	Cerebral Vascular Accident
DM	Diabetes Mellitus
ESRD	End-Stage Renal Disease
GCS	Glasgow Coma Scale
HIV	Human Immunodeficiency Virus
HPT	Hypertension
HUSM	Hospital Universiti Sains Malaysia
ICD	International Classification of Diseases
ICU	Intensive Care Unit
MAP	Mean Arterial Pressure
RRT	Renal Replacement Therapy
SD	Standard Deviation
SOFA	Sequential Organ Failure Assessment

LIST OF SYMBOLS

%	Percent/ Percentage
&	And
/	Or
=	Equals to
<	Less than
≤	Equals to or less than
>	More than
≥	Equals to or more than
A:aDO_2	Alveolar-arterial oxygen tension difference
Ca^{2+}-ATPase	Calcium ATPase pump
°C	Degree Celsius
cm	Centimetre
H_0	Null hypothesis
IU/L	International unit per litre
FiO_2	Fraction of inspired oxygen
kDA	Kilodalton
kg	Kilogram
kgm-2	Kilogram per metre square
mmHg	Millimetre of mercury
mm^3	Cubic millimetre
mL/hour	Millilitre per hour
mL/kg/hour	Millilitre per kilogram per hour
mg/dL	Milligram per decilitre
mEq/L	Milliequivalent per litre

mmol/L	Millimole per litre
μmol/L	Micromole per litre
n	Number
Na/K-ATPase	Sodium/Potassium ATPase pump
$NaHCO_3$	Sodium bicarbonate
α	Significance level alpha value
p	Significance level p value
PaO_2	Partial pressure of oxygen
pH	Power of Hydrogen
vs	Versus

FAKTOR-FAKTOR RAMALAN YANG MENYUMBANG KEPADA RAWATAN DIALISIS DI KALANGAN PESAKIT-PESAKIT KRITIKAL YANG MENGHIDAPI PEYAKIT *RHABDOMYOLYSIS* DAN HASIL RAWATAN MEREKA.

ABSTRAK

Latar belakang

Komplikasi sistemik *Rhabdomyolysis* yang paling serius adalah kecederaaan buah pinggang akut yang menyebabkan keperluan untuk rawatan dialisis dan hasil rawatan yang teruk.

Objektif

Untuk mengenalpasti faktor-faktor ramalan yang menyumbang kepada rawatan dialisis di kalangan pesakit yang menghidapi penyakit *Rhabdomyolysis* dan hasil rawatan mereka.

Tatacara

Ini adalah kajian prospektif observasi yang dijalankan di unit rawatan rapi Hospital Universiti Sains Malaysia selama satu tahun. Pesakit-pesakit dewasa yang dimasukkan ke unit rawatan rapi dan memenuhi kriteria *Rhabdomyolysis* pada bila-bila masa ketika mereka menerima rawatan di unit rawatan rapi akan direkrut. Pesakit-pesakit yang meghidapi penyakit buah pinggang yang kronik dan pernah menerima rawatan dialisis akan dikecualikan. Maklumat tentang faktor-faktor yang meyumbang kepada rawatan dialisis akan dikumpulkan. Hasil akhir kajian adalah rawatan dialisis ketika berada di unit rawatan rapi dan hasil rawatan. Analisis univariat dilakukan untuk mengenalpasti faktor-faktor yang menyumbang kepada rawatan dialisis.

Keputusan

Sebanyak 30 pesakit yang memenuhi kriteria-kriteria kajian, 4 (13.3%) daripada mereka memerlukan rawatan dialisis dan 3 (10.0%) kematian dilaporkan. Skor median APACHE II dan SOFA adalah 9.0 (IQR=14.0) dan 3.5 (IQR=6.3), masing-masing. Kebanyakan pesakit *rhabdomyolysis* 28 (93.3%) dalam kajian ini adalah disebabkan trauma. Faktor-faktor klinikal yang didapati berkaitan dengan keperluan dialisis adalah skor SOFA (*P*=0.021), tahap puncak serum *creatine kinase* (*P*=0.026), tahap puncak *serum creatinine* (*P*=0.024), penggunaan natrium bikarbonat (*P*=0.037) dan tempoh kemasukan ke Unit Rawatan Rapi (*P*=0.026).

Kesimpulan

Skor SOFA yang tinggi, tahap puncak CK, tahap puncak *creatinine*, penggunaan natrium bikarbonat dan tempoh kemasukan ke Unit Rawatan Rapi yang panjang adalah faktor-faktor ramalan yang menyumbang kepada keperluan rawatan dialisis di kalangan pesakit-pesakit kritikal yang meghidapi peyakit *rhabdomyolysis.*

FACTORS PREDICTIVE OF THE NEED FOR RENAL REPLACEMENT THERAPY IN CRITICALLY ILL PATIENTS WITH RHABDOMYOLYSIS AND THEIR OUTCOME

ABSTRACT

Introduction

In rhabdomyolysis, the most serious systemic complication is acute kidney injury (AKI), which is associated with the need for renal replacement therapy (RRT) and poor outcome.

Objective

To identify the factors predictive of the need for RRT in critically ill patients with rhabdomyolysis and their outcome.

Methods

This was a prospective observational study conducted in the intensive care unit (ICU) of the Hospital Universiti Sains Malaysia over a 1 year period. Consecutive adult patients admitted to the ICU who fulfilled the criteria of rhabdomyolysis at any point during their ICU stay were recruited. Obvious cases of renal failure and pre-existing use of RRT were excluded. Data on factors that are known to predict the need for RRT were recruited. The end point of the study was initiation of RRT during the ICU stay and the outcome. Univariate analysis was performed to identify the factors that were significantly associated with the initiation of RRT.

Results

A total of 30 subjects fulfilled the study criteria, of which 4 (13.3%) of them required RRT and 3 (10.0%) death reported. The subject's APACHE II and SOFA median scores were 9.0 (IQR=14.0) and 3.5 (IQR=6.3), respectively. Majority of the rhabdomyolysis patients 28 (93.3%) were due to trauma. Factors that showed significant association with RRT include SOFA score (*P*=0.021), peak serum creatine kinase level (*P*=0.026), peak serum creatinine level (*P*=0.024), use of sodium bicarbonate (*P*=0.037), and length of ICU stay (*P*=0.026).

Conclusion

In this study, higher SOFA, peak CK level, peak creatinine level, use of sodium bicarbonate and longer length of stay ICU were the predictive factors leading to initiation of RRT in critically ill patients.

CHAPTER 1

INTRODUCTION

1.1 Introduction

Renal replacement therapy (RRT) has emerged as mainstay of treatment for acute kidney injury. Early initiation of RRT helps in the removal of uremic toxins, allow fluid and electrolyte balance and prevent life threatening complications such as metabolic encephalopathy, hyperkalemia and pulmonary oedema (1). Rhabdomyolysis indicates disintegration or destruction of the striated muscle. It can be caused by either traumatic or non-traumatic injury of muscle cell. Rhabdomyolysis is characterised by muscle injury and subsequent leakage of intracellular muscle contents (2). The release causes electrolytes imbalances, disseminated intravascular coagulation (DIC), AKI and multiorgan failure. The typical triad of rhabdomyolysis are muscle weakness, muscle ache and dark colour urine. Elevation of serum CK level to greater than 1000 IU/L (3), which is 5 times the upper limit of normal, is diagnostic. After commencement of muscle injury, serum CK starts to surge at approximately 2-12 hours, peaks within 1 to 3 days and later drops at a comparably constant rate of about 40% of the previous day's value. Level typically normalizes after 6-10 days (4). Etiology of rhabdomyolysis vary, dependent on the age. Common causes among adults are trauma, drugs and infections (5).

AKI is the most frequent systemic complication of rhabdomyolysis. Experimental evidence suggested that direct and ischemic tubular injury, intra-renal vasoconstriction and tubular obstruction are the main pathophysiology involved in AKI. Myoglobin from destructed muscle contributes significantly in the development of AKI. AKI occurs in 33-50% of patients with rhabdomyolysis (6), and it is the important cause of mortality.

Mortality rate among rhabdomyolysis patients who were admitted into the intensive care unit, was reported to be 59% with AKI and 22% without AKI. Patients with AKI who required RRT had higher in-hospital mortality than those with AKI but not requiring renal replacement, 40% vs 11.9% (7).

Patients with AKI requiring RRT have a substantially higher mortality rate and yet, there is a lacking of study on factors predictive of the need for RRT in critically ill patients with rhabdomyolysis and their outcome. If the predictive factors are known earlier, timely recognition and prevention of the associated factors for the need of renal replacement therapy may improve the survival rate of rhabdomyolysis patients.

Hence, this study was done to investigate factors predictive of the need for RRT in critically ill patients with rhabdomyolysis and their outcome.

1.2 Problem Statement and Study Rationale

Patients with AKI requiring RRT have a substantially higher mortality rate and yet, there is no study conducted to evaluate the associated factors for the need of RRT and survival among rhabdomyolysis patients admitted to the Intensive Care Unit of HUSM. Hence, by identifying the associated factors for the need of RRT through this study will be of great importance to predict survival among patients diagnosed with rhabdomyolysis.

If this study is found to be significant, early recognition and prevention of the associated factors for the need of RRT may improve the survival rate of rhabdomyolysis patients.

1.3 Literature Review

1.3.1 Definition

Over the last few decades, many definitions have been used to define AKI. In clinical practice, at least 44.2 umol/L increase of serum creatinine, a decrease in creatinine clearance of at least 50% or the need for RRT are the most common indices used to define AKI (8). Meanwhile, Risk, Injury, Failure, Loss of kidney function and End-stage kidney disease (RIFLE) and Acute Kidney Injury Network (AKIN) classification for AKI can easily be applied when the baseline serum creatinine is known. However, in reality, baseline serum creatinine remain unknown for many patients. In this study, we use serum creatinine to predict incidence of AKI. We follow up serum creatinine levels daily from admission until day 7 after the diagnosis of rhabdomyolysis.

1.3.2 Etiology

The clinical presentation of rhabdomyolysis varies. Acute kidney injury occurs in up to 50% of patients. Mortality rates was 59% in critically ill patients. Hypotension, trauma, electrolyte disturbances, drug abuse and sepsis are the common risk factors for rhabdomyolysis and can be found more readily in ICU patients (9).

1.3.3 Pathophysiology

Following muscle injury, myoglobin level increases in blood within a few hours, and might be used to detect rhabdomyolysis early. Based on study by Premru and co-workers, they suggested serum myoglobin level of more than 15–20 mg/L as an appropriate cut-off point in predicting myoglobinuric acute kidney injury (10). However, in clinical practice, myoglobin is not routinely used as the diagnostic marker. This is due to its short half-life of 2-3 hours, and its clearance can occur extra renal. Hence, serum myoglobin is not measured in our study.

In contrast to myoglobin, serum CK starts to surge at approximately 2-12 hours, peaks within 1 to 3 days and later normalizes 6-10days after muscle injury ceases. Serum half-life of CK is longer, about 1.5 days, due to relatively slow plasma clearance. Moreover, study has demonstrated that serum CK is as accurate as serum myoglobin in showing degree of muscle injury. Hence, CK is used routinely to diagnose and guide treatment of rhabdomyolysis.

CK is a dimer molecule with three distinct isoenzyme forms (termed MM, MB and BB), which can be differentiated electrophoretically. The highest concentration of CK is found in skeletal muscle. Skeletal muscle necrosis will bring about leakage of CK into the blood. Serum CK level of >1000 IU/L in the presence of skeletal muscle injury is diagnostic of rhabdomyolysis.

Studies show that serum CK >5000 IU/L is associated with higher risk of renal failure and the need for RRT (11). There are few smaller studies of rhabdomyolysis which showed that serum CK level is less likely to predict the need for RRT. However, a more

recent and larger retrospective cohort study done by Mc Mahon and colleagues has shown the association between serum CK and the need for RRT. Mc Mahon and colleagues have found that initial serum CK level in excess of 40000 IU/L has higher risk for RRT and/or in-hospital mortality. Another retrospective study done by Joanna and colleagues supports that peak CK of at least 5000 IU/L is sensitive but not specific for prediction of AKI requiring RRT in rhabdomyolysis (12).

In this study, we followed up serum CK levels daily from admission until day 7 after the diagnosis of rhabdomyolysis. This is because although serum CK generally peaks at day 1, but it may peak later than 72 hours after admission in a considerable number of patients. Serum CK values were divided into following subgroups: 1) <1000 IU/L (more than five times the normal cut-off value); 2) between 1000-5000 IU/L; 3) between 5000-40000 IU/L; and 4) >40000 IU/L. These values were chosen because serum CK of more than 1000 IU/L is diagnostic of rhabdomyolysis, whereas CK value of 5000 IU/L and higher are found to have an increased risk of rhabdomyolysis-induced AKI. CK value of >40000 IU/L was chosen based on Mc Mahon risk score.

Beside initial and peak serum CK levels, we have incorporated the causes of rhabdomyolysis in this study to predict the risk of RRT and mortality in our rhabdomyolysis patients. This is supported by studies that show incorporation of causes of rhabdomyolysis will provide additional prognostic information. Mc Mahon and coworkers found that patients with low-risk causes (seizures, syncope, exercise, statins or myositis) has a lower risk of poor outcome (5.1%) compared with 21.1% poor outcome in those with other causes.

On the other hand, we also incorporate other variables including initial serum urea, serum potassium, serum calcium, serum phosphate, serum bicarbonate, and serum pH to predict the risk of RRT and mortality in our study. This is supported by a few studies (13). Mc Mahon and colleagues have developed a scoring system based on various factors calculated on admission, including the initial CK level together with other parameters such as hypocalcemia, hyperphosphatemia and acidosis and patient's variables such as age, gender and type of injury. Another retrospective cohort study done by Chun-Yu Chen and colleagues from 2006 to 2011, concludes that etiologies of rhabdomyolysis, peak blood urea nitrogen and creatinine levels are the risk factors for RRT in rhabdomyolysis (14).

In order to prevent AKI in rhabdomyolysis patients, after early recognition of risk factors that are being discussed earlier, timely aggressive fluid resuscitation should be initiated within 6 hours of admission to minimize the risk of AKI (15). Therefore, the timing of fluid initiation in this study is grouped into either ≤6 hours and >6 hours. The optimal choice of fluid and rate of repletion are unclear. There is no study that directly compared the efficacy and safety of different types and rates of fluid administration in this setting. Generally an initial rate of 100-200 mL/hour of crystalloids is suggested. Fluid repletion is titrated to achieve a urine output of 200-300 mL/hour and continued until plasma CK level decreases to <5000 IU/L.

Besides aggressive fluid resuscitation, some studies demonstrate that patients with rhabdomyolysis who are appropriately monitored may benefit from alkalinisation of urine using bicarbonate therapy. As long as the arterial pH is less than 7.5, serum bicarbonate is less than 30 mEq/L or hypocalcemia is not present, bicarbonate may be

given. The treatment aims to raise urine pH to above 6.5 and a serum pH between 7.40 and 7.45 (16). In theory, urine alkalinisation will prevent heme-protein precipitation with Tamn-Horsfall protein and therefore prevent intratubular pigment cast formation. Despite these potential benefits, clinical evidence is insufficient to prove that an alkaline diuresis is more effective than saline diuresis in preventing AKI. On the other hand, loop diuretics generally are not given unless volume overload is present. Therefore, these factors were also included in this research to study any possible significant association.

In summary, early recognition of those who are likely to have adverse clinical outcomes especially AKI in the course of rhabdomyolysis, allow early risk stratification, institution of aggressive prophylactic measures and prognostication.

1.3.4 Conceptual Framework:

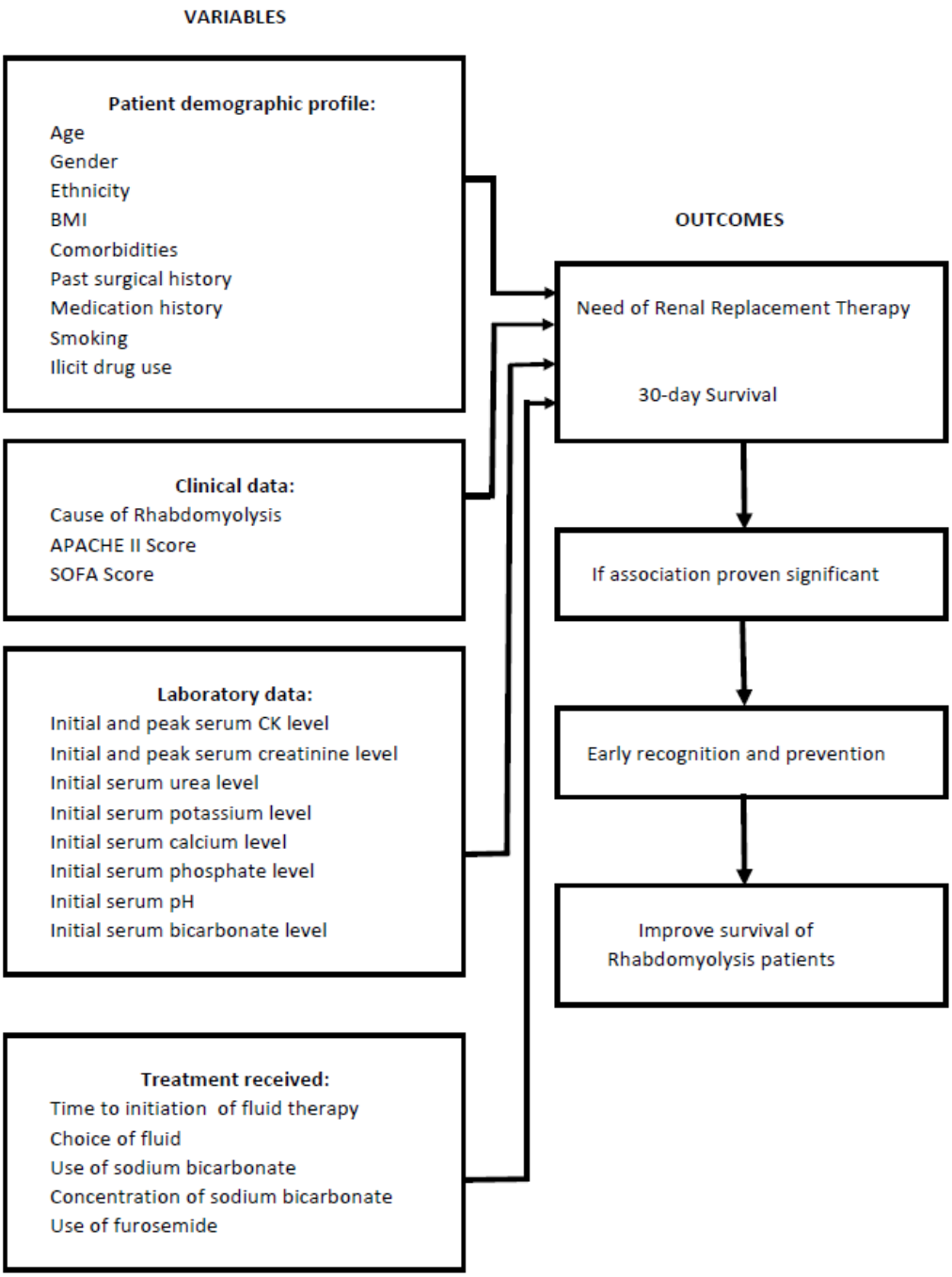

Figure 1: The conceptual framework of the importance of early recognition of factors influencing the need of renal replacement therapy that leads to improved survival among rhabdomyolysis patients.

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CHAPTER 2

STUDY OBJECTIVES

2.1 General Objective

To identify the associated factors of the need for RRT among rhabdomyolysis patients admitted to the ICU of HUSM.

2.2 Specific Objectives

1) To describe demographic data of rhabdomyolysis patients admitted to the ICU of HUSM.

2) To identify the associated factors for the need of RRT in rhabdomyolysis patients admitted to the ICU of HUSM.

3) To compare outcome in term of 30-day mortality

2.3 Research Hypotheses

1) Null hypothesis (H_0): There is no difference in demographic profile among rhabdomyolysis patients admitted to the ICU of HUSM with or without need for RRT.

2) Null hypothesis (H_0): There is no difference in associated factors between RRT and non-RRT patients admitted to the ICU of HUSM.