THE DIAGNOSTIC AND PREDICTIVE VALUE OF PLASMA CYSTATIN C FOR ACUTE KIDNEY INJURY SECONDARY TO SEPSIS IN THE INTENSIVE CARE UNIT

BY

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A dissertation submitted in fulfilment of the requirement for the degree of Master of Medicine (Anaesthesiology)

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ABSTRACT

Introduction : Plasma Cystatin C (pCysC) is one of the functional biomarker for Acute Kidney Injury (AKI). Derivation of estimate of Glomerular Filtration Rate (eGFR) from pCysC has been developed for practical daily use in clinical practice for evaluating renal function. This study evaluates the utility of pCysC in diagnosing AKI, predicting death and its correlation with eGFR in septic critically ill patients.

Materials and method : This is a two centre, prospective observational study of septic critically ill patients. Inclusion criteria were patients older than 18 years old with sepsis, based on Sequential Organ Failure Assessment (SOFA) score of two or more and procalcitonin level greater than 0.5 ng/ml. Serum Creatinine and pCysC were measured at six time intervals (0, 4, 24, 28, 48, and 52 hours). AKI was defined based on creatinine criteria of the Kidney Disease : Improving Global Outcome (KDIGO) guideline.

Result : Seventy patients were recruited into this study, of which 32 (45.7%) had AKI and 15 (21.4%) died. pCysC diagnosed AKI in all six time intervals with AUC range of 0.859, 0.858, 0.876, 0.918, 0.887, and 0.879 for 0 hour, 4, 24, 28, 48, and 52 hours, respectively ($p < 0.0001$). It did not predict in-hospital mortality at any time interval, with AUC range of 0.053 to 0.608 ($p > 0.1$). pCysC showed strong negative correlation with all estimates of GFR, with best profile recorded at 28 hours. Correlation coefficient for $eGFR_{CG}$, $eGFR_{MDRD}$, $eGFR_{CKD-EPI}$ and keGFR were -0.778, -0.763, -0.808, and -0.781, respectively ($p < 0.0001$). There is no correlation between cardiac output and pCysC and GFR. Correlation coefficient were between -0.208 to 0.267 ($p > 0.1$)

Conclusion : Plasma Cystatin C diagnosed AKI in septic critically ill patients and strongly correlated with all estimates of GFR. However, plasma Cystatin C did not predict in-hospital death. In addition, it did not correlate with cardiac output.

APPROVAL PAGE

I certify that I have supervised and read this study and that in my opinion, it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Master of Medicine (Anaesthesiology).

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DECLARATION

I hereby declare that this dissertation is the result of my own investigations, except where otherwise stated. I also declare that it has not been previously or concurrently submitted as a whole for any other degrees at IIUM or other institutions.

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Firstly, it is my utmost pleasure to dedicate this work to my dear parents and my family, who granted me the gift of their unwavering belief in my ability to accomplish this goal: thank you for your support and patience.

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LIST OF ABBREVIATIONS

AKI	Acute Kidney Injury
ARF	Acute Renal Failure
CIAKI	Contrast Induced Acute Kidney Injury
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CNS	Central Nervous System
CPB	Cardio-Pulmonary Bypass
CVS	Cardiovascular System
eGFR	Estimate of Glomerular Filtration Rate
ICU	Intensive Care Unit
KDIGO	Kidney Disease : Improving Global Outcome
keGFR	Kinetic Estimate of Glomerular Filtration Rate
MDRD	Modification of Diet in Renal Disease
NIH	National Institute of Health
PAC	Pulmonary Artery Catheter
pCysC	Plasma Cystatin C
PiCCO	Pulse-induced Continous Cardiac Output
qSOFA	Quick Sequential Organ Failure Assessment
RRT	Renal Replacement Therapy
SOFA	Sequential Organ Failure Assessment
USCOM	Ultra-Sound Cardiac Output Monitoring

CHAPTER ONE

INTRODUCTION

1.1 BACKGROUND OF THE STUDY

The incidence of Acute Kidney Injury (AKI) is high and increasing in patients admitted to the Intensive Care Unit (ICU) (Md Ralib & Mat Nor, 2015). In average about 30% to 60% of critically ill patients have AKI based on the RIFLE criteria (Md Ralib & Pickering, 2013). In Malaysian population, 65% of ICU patients had been reported to develop AKI, with almost half of those of the highest severity (Md Ralib & Mat Nor, 2015). AKI has been identified as one of the independent risk factors that contributed to morbidity and mortality in critically ill patients (Md Ralib & Pickering, 2013) (Bagshaw et al, 2009) (Patricia, Sakr, Reonhart, & Vincent, 2005). AKI has been a global public health concern, impacting approximately 13.3 million patients per year, with high morbidity and increased costs. Mortality occur in patients with AKI up to 33% (Iwagami, Mansfield, Quint, Nitsch, & Tomlinson, 2016), around 1.7 million deaths per year (Zuk & Bonventre, 2016).

Current consensus on definition of AKI are based on the surrogates of filtration function, which are serum Creatinine and urine output (International Society of Nephrology (ISN), 2012). These surrogates have limitations in term of temporal delay of Creatinine increment, lack of baseline measurement, lack of information on duration of increase, influence of fluid and use of diuretic which pose important issues in its use (Geok et al., 2013). Using serum Creatinine, estimate of Glomerular Filtration Rate (eGFR) and urine output in diagnosis of AKI results in delay in recognition and increased in cost of management and increased rate of mortality.

The development and discovery of new biomarkers for earlier AKI diagnosis has gained lot of interests over the past several years. Cystatin C is produced by all nucleated cells in the body, is completely filtered by the glomeruli and reabsorbed and catabolized in the proximal tubules (Charlton, Portilla, & Okusa, 2014). Its production is not affected by muscle mass, age less than 50 years old, sex, race and hydration status (Guillouet et al., 2011). Several studies showed that plasma Cystatin C predicted AKI earlier than serum Creatinine (Bennett & Devarajan, 2011) (Volpon, Sugo, & Carlotti, 2015) (Dai et al., 2015) (Aydogdu et al., 2013). These studies were conducted in Western countries, and to the best of our knowledge no study has been done in our Asian region. This study may support the implementation of the results from worldwide researches into local population.

High incidence of sepsis has contributed to increase development of AKI, known as sepsis-induced AKI (Md Ralib & Mat Nor, 2015). Geok et al. (2013) reported 13.7% overall incidence of AKI in first 24 hours of ICU admission with in-hospital mortality up to 43%. Severe sepsis patients complicated with AKI had higher in-hospital mortality around 60%, compared to No AKI which was around 40% (Malaysian Society of intensive Care, 2013) It is estimated that about 10% of ICU admissions in Malaysia were due to sepsis (Geok et al., 2013) (Malaysian Society of intensive Care, 2013). Sepsis may complicate AKI in up to 13.7% of patients, and together with AKI may cause in-hospital mortality up to 40% (Geok et al., 2013) (Malaysian Society of intensive Care, 2013).

Plasma cystatin C level varies with each individual's GFR and there is correlation between Cystatin C and GFR, even in the range where serum Creatinine could not detect changes in GFR of 60 to 90ml/min (Charlton et al., 2014), which showed Cystatin C superiority in detecting changes in GFR (Mårtensson, Martling,

Oldner, & Bell, 2012). Hassinger et al. (2012) demonstrated that the plasma Cystatin C is a good predictor for increased GFR.

An assessment of the new biomarkers beyond Creatinine, such as comparison with hard outcomes including mortality may offer a more valid assessment (Pickering & Endre, 2013). Several studies observed correlation between increased plasma Cystatin C with in-hospital mortality (Perianayagam, Seabra, Tighiourt, Liangos, & Jaber, 2009) (Bell et al., 2009). However, their further analysis showed that this association was affected by multiple co-founding factors including APACHE II score, sepsis, presence of liver disease and requirement for mechanical ventilation (Perianayagam et al., 2009). Increase in mortality rate in association with increase serum Cystatin C concentration may also be explained by systemic inflammation caused by sepsis (Mårtensson et al., 2012).

AKI secondary to sepsis is associated with the systemic hypotension (Umbro, Gentile, Tinti, Muiesan, & Mitterhofer, 2016) or changes in hemodynamics (Alobaidi, Basu, Goldstein, & Bagshaw, 2015). Measurement of cardiac output (CO) may give an idea on its relation with AKI. Methods of measurement of cardiac output had evolved from invasive Pulmonary Artery Catheter (PAC) to less invasive Pulse-induced Continuous Cardiac Output (PiCCO) monitoring to non-invasive Ultrasonic Cardiac Output Monitoring (USCOM) (Alobaidi et al., 2015).

Given this uncertainty and the value to the clinician of a marker which would facilitate timely intervention which to prevent progression to severe AKI and reduce mortality, we aimed to evaluate the utility of plasma Cystatin C for AKI in sepsis patients. We also evaluated the performance of Cystatin C for prediction of mortality, and its association with all estimates of GFR (eGFR) by various equations. The association of Cystatin C with cardiac output measurement was also explored.

1.2 STATEMENT OF THE PROBLEM

The process of diagnosing AKI has been relying on serum Creatinine for the past decade. This caused delay in diagnosis with subsequent increase in health burden and economic impact (Zuk & Bonventre, 2016).

1.3 PURPOSE OF THE STUDY

The purpose of this study is to evaluate the diagnostic ability of plasma Cystatin C for AKI and its predictive ability for in-hospital mortality. Apart from that, this study assessed the correlation of plasma Cystatin C with eGFR and kinetic estimate of GFR (keGFR) and cardiac output.

1.4 RESEARCH OBJECTIVES

The study aimed to achieve the following objectives:

1. To determine the diagnostic ability of the plasma Cystatin C level for AKI diagnosed by serum Creatinine criteria of KDIGO Guideline.
2. To measure correlation of calculated estimate of GFR and keGFR with plasma Cystatin C level.
3. To determine predictive ability of plasma Cystatin C level with in-hospital mortality.
4. To determine association of the changes of eGFR, keGFR and plasma Cystatin C with changes of cardiac output as measured by ultrasonic cardiac output monitoring (USCOM).

1.5 RESEARCH QUESTIONS

This study was conducted to search for answers of the following questions :

1. What is the diagnostic ability of plasma Cystatin C level for AKI based on the current consensus definition?
2. How do eGFR estimated using Cockcroft-Gault, MDRD, CKD-EPI and keGFR equations correlate with Cystatin C level?
3. What is the predictive ability of plasma Cystatin C level for in-hospital mortality?
4. How do plasma Cystatin C level, eGFR estimated using Cockcroft-Gault, MDRD, CKD-EPI and keGFR equations associate with changes in cardiac output as measured by USCOM?

1.6 THEORETICAL FRAMEWORK

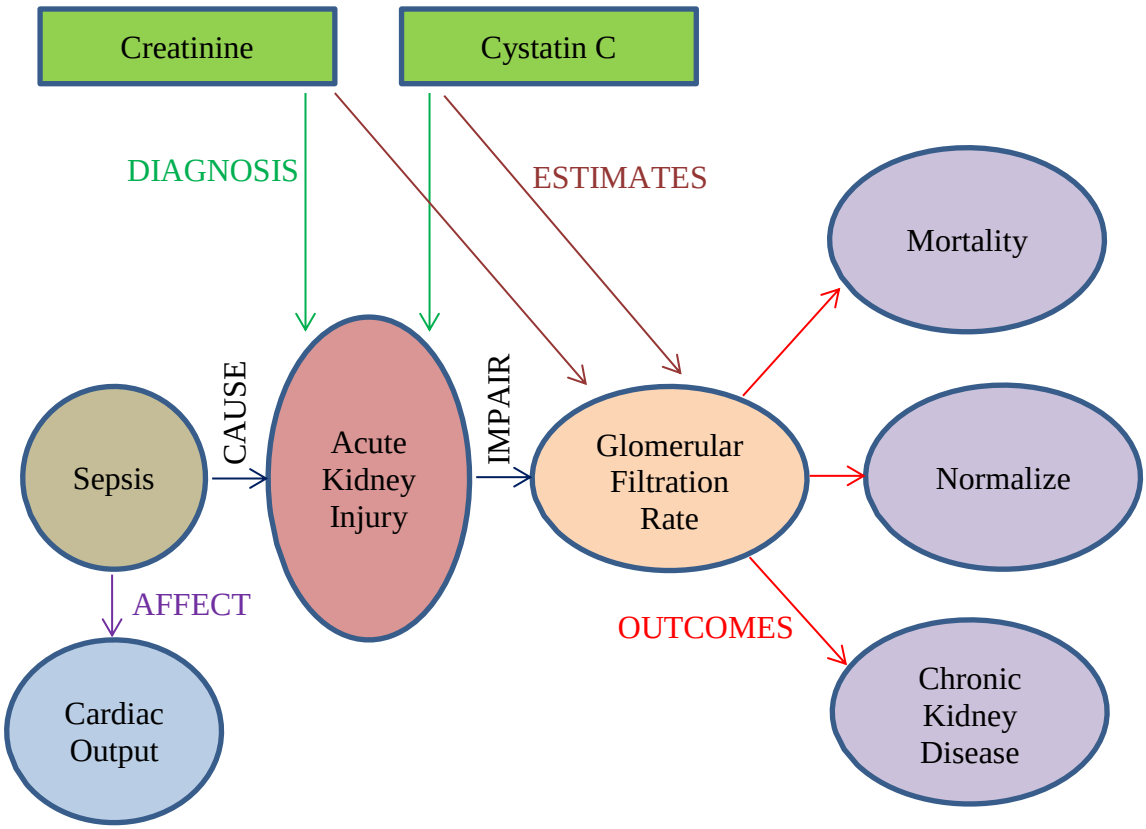

Figure 1.1 Theoretical Framework

1.7 RESEARCH HYPOTHESES

It is hypothesized that plasma Cystatin C has diagnostic ability for AKI, and predictive of in-hospital mortality. It also correlates with eGFR and keGFR, and cardiac output

1.8 SIGNIFICANCE OF THE STUDY

This study is significant in improving diagnosis of AKI and promotes earlier diagnosis of AKI, which will reduce health burden and economic impact to the government.

1.9 LIMITATIONS OF THE STUDY

There are few limitation to this study, which are :

1. Small sample size.
2. Two centre within same locality.

1.10 DEFINITIONS OF TERMS

Sepsis

A life-threatening organ dysfunction caused by a dysregulated host response to infection (Opal, Rubenfeld, Poll, Vincent, & Angus, 2016).

Acute Kidney Injury (AKI)

AKI is defined as any of the following (Kellum, Lameire, Aki, & Work, 2013) :

1. Increase in serum Creatinine level by ≥ 26.5 μmol/L within 48 hours.
2. Increase in serum Creatinine to ≥ 1.5 times baseline, which is known or preseumed to have occurred within the prior seven (7) days.
3. Urine volume < 0.5 ml/kg/hour for 6 hours.

Sepsis-associated AKI

A spectrum of AKI that has been associated with all spectrums of sepsis and septic shock.

Diagnosis of AKI

AKI is diagnosed using the serum Creatinine criteria of the KDIGO guideline.

Biomarker

A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention

USCOM

Ultrasound Cardiac Output Monitoring using ultrasound technique to measure cardiac output.

1.11 CHAPTER SUMMARY

This chapter introduced to the reader regarding problems that this research intended to investigate and solve. It also outlines the theoretical framework for better understanding of issues addressed by this study. Apart from that, it outlines study objectives, research questions and hypotheses.

CHAPTER TWO

LITERATURE REVIEW

2.1 INTRODUCTION

Since this study aimed to look at plasma Cystatin C and its diagnostic ability for AKI, correlation with eGFR, predictive ability for in-hospital mortality, and correlation with cardiac output, few subtopics need to be well understood. This literature review covers basic knowledge on AKI and its related topic, namely sepsis-associated AKI, diagnosis of AKI, mortality in AKI, sepsis, eGFR, and USCOM. In regards to biomarker and Cystatin C, this literature review explains in depth for better understanding of this study.

2.2 ACUTE KIDNEY INJURY (AKI)

The incidence of AKI is high and increasing in patients admitted to the ICU. In average about 30 to 60% of critically ill patients have AKI based on the RIFLE criteria (Md Ralib & Pickering, 2013). In Malaysian population, 65% of ICU population had been reported to develop AKI, with almost half of those of the highest severity (Md Ralib & Mat Nor, 2015).

AKI, previously known as Acute Renal Failure (ARF), is referred to a clinical syndrome characterized by rapid (hours to days) decrease in renal excretory function with accumulation of products of nitrogen metabolism such as creatinine and urea and other unmeasured waste products (Bellomo, Kellum, & Ronco, 2012). This change in term has a significant impact on emphasizing the earlier occurrence of renal excretory