INCIDENCE OF PERIOPERATIVE ACUTE KIDNEY INJURY AND ITS OUTCOME IN GENERAL SURGICAL PATIENTS

BY

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ABSTRACT

Acute kidney injury (AKI) is known to complicate surgery in 13% of patients. It is associated with significant morbidity, increased costs and mortality. Surgery is a known risk factor, estimated to cause one-third of all in-hospital AKI. This study aims to determine the incidence of perioperative AKI among patients undergoing surgery and to identify the risk factors and associated adverse outcomes. It is a single-centre, prospective, observational study conducted among general surgical patients between March to September 2018. Adult patients who are admitted for more than 24 hours and who undergo surgery under general or regional anaesthesia are recruited, and those with pre-existing ESRF are excluded. We employed the KDIGO definition of AKI, which is an elevation of serum creatinine by more than 1.5 times baseline. Baseline creatinine level is obtained from previous records or, in its absence, is back-calculated using the MDRD formula, assuming a baseline GFR of 75 ml/min. The incidence of perioperative AKI is 20.2%. Factors that, on bivariate analysis, are associated with AKI include age ($p<0.001$), presence of diabetes mellitus ($p<0.001$), hypertension ($p<0.001$), chronic kidney disease (CKD) ($p<0.001$), sepsis ($p<0.001$) and shock ($p<0.001$). The length and type of surgery (emergency vs. elective) are also associated with AKI ($p<0.001$, $p=0.011$). A multivariate analysis using binary logistic regression showed that age ($p=0.010$), pre-existing CKD ($p=0.002$) and length of surgery ($p=0.010$) are independently associated risk factors. AKI is significantly associated with adverse outcomes namely mortality ($p<0.001$), permanent kidney damage ($p<0.001$), prolonged length of stay ($p<0.001$), need for acute dialysis ($p<0.001$), ICU admission ($p<0.001$), mechanical ventilation, ($p<0.001$) and inotropic support ($p<0.001$). In conclusion, a high proportion of patients undergoing surgery may develop perioperative AKI, which leads to poorer outcomes. Identifying those at risk is crucial to future stratify patients, enabling better prognostication and calculation of drug prescription.
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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 Surgery.

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DECLARATION

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This thesis is dedicated to my parents, whose support has always been unwavering, whose patience, endless and whose love, unconditional.

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LIST OF ABBREVIATIONS

ADQI	Acute Dialysis Quality Initiative
AKI	Acute Kidney Injury
AKIN	Acute Kidney Injury Network
CKD	Chronic Kidney Disease
ESRF	End-Stage Renal Failure
GFR	Glomerular Filtration Rate
ICU	Intensive Care Unit
KDIGO	Kidney Disease Improving Global Outcomes
MDRD	Modification of Diet in Renal Disease
RRT	Renal Replacement Therapy
sCr	Serum Creatinine
UO	Urine Output

CHAPTER ONE

INTRODUCTION

1.1 STUDY BACKGROUND

Acute kidney injury (AKI) is used to describe a rapid reduction in renal function, leading to failure of excretion of plasma waste products, including urea and creatinine. It is not uncommon among hospitalized patients and has a detrimental effect to patient outcome. AKI is associated with increased length of hospital stay, increased costs, significant morbidity and both short- and long-term mortality.

Patients are especially susceptible to develop AKI in the perioperative setting. Surgery is estimated to cause approximately one-third of all in-hospital AKI (Uchino et al., 2005a). This owes, in part, to the fact that surgery is a major stressor that depletes the body's physiological reserve. This figure is thought to be higher if they have pre-existing medical illnesses that complicate recovery, such as diabetes mellitus, hypertension, cardiovascular disease, chronic kidney disease and malignancy. In addition, patients undergoing surgery are prone to episodes of hypovolemia. This leads to renal hypoperfusion and in turn exacerbates the problem.

There are many published studies on perioperative AKI among critically-ill surgical patients. However, to our knowledge, none addresses the general surgical patient population at large, especially in the local setting. We aim to fill this gap in our current understanding of this problem, specifically addressing the incidence, risk factors, and outcomes of perioperative AKI.

The presence of AKI in the perioperative period will adversely impact recovery. Identifying patients at risk to develop AKI is therefore crucial to identify at-risk patients at an early stage, enabling better and more accurate prognostication, calculation of drug prescription, goal-directed fluid therapy and early nephrology consultation.

1.2 RESEARCH QUESTIONS

i. What is the incidence of acute kidney injury among patients undergoing surgery?

ii. What are the risk factors associated with perioperative acute kidney injury?

iii. What adverse outcomes are associated with perioperative acute kidney injury?

1.3 OBJECTIVES

1.3.1 General Objective

i. To determine the incidence of perioperative acute kidney injury and its association with outcome in general surgical patients in Hospital Tengku Ampuan Afzan (HTAA)

1.3.2 Specific Objectives

i. To describe the socio-demographic characteristics of patients admitted to the general surgical wards
ii. To measure the incidence of perioperative acute kidney injury in patients admitted to the general surgical wards in HTAA
iii. To determine the risk factors associated with acute kidney injury
iv. To measure the outcome associated with the presence of acute kidney injury (mortality, length of stay, need for acute dialysis, mechanical ventilation, admission to ICU, and vasopressor therapy)

CHAPTER TWO

LITERATURE REVIEW

2.1 DEFINITIONS, DIAGNOSTIC CRITERIA AND EPIDEMIOLOGY

Studies on acute kidney injury (AKI) have historically been hampered by a lack of consensus definition and differing diagnostic criteria, and clinicians tended to rely on their own judgement to determine when a patient is said to develop AKI. These arbitrary definitions have incorporated, to varying extent, clinical conditions such as oliguria, anuria, or need for renal replacement therapy, as well as laboratory parameters such as serum urea, serum creatinine or metabolic acidosis. As a result, reported incidences varied widely from 1 to 31% between studies in patient populations of similar demography and risk factors (Hobson, Singhania, & Bihorac, 2016).

At the outset of the century, efforts have been made to standardize these myriad definitions and to come up with a single defining criterion. The primary aim was to standardize reporting of this particular morbidity without under- or overestimating its true prevalence.

In theory, there are several biomarkers that represent renal excretory function, to varying degrees of accuracy. These include serum creatinine, urea, cystatin C, β-trace protein, inulin, iohexol as well as several radioactive markers (Gowda et al., 2010). Not all, however, are suitable for routine use in daily clinical practice.

In 2002, the Acute Dialysis Quality Initiative (ADQI) was created and proposed the RIFLE criteria as a uniform definition of AKI (Bellomo et al., 2004). Though renal excretory function is best represented by measurement of glomerular filtration rate (GFR), the authors have suggested using serum creatinine (sCr) as a surrogate marker instead. It reliably predicts renal function, and more importantly is routinely measured and consistent across practices all over the world.

Table 1 RIFLE criteria for diagnosis and classification of Acute Kidney Injury

Category	**Serum Creatinine (sCr) Criteria**	**Urine Output (UO) Criteria**
Risk	Increased sCr x1.5 baseline	UO < 0.5ml/kg/h x 6H
Injury	Increased sCr x2 baseline	UO < 0.5ml/kg/h x 12H
Failure	Increased sCr x3 baseline	UO <0.3ml/kg/h or anuria x 12H
Loss	Persistent ARF = complete loss of kidney function > 4 weeks	
ESKD	End-stage Kidney Disease (>3 months)	

This was followed in 2007 by the Acute Kidney Injury Network (AKIN), which proposed another set of criteria that similarly uses serum creatinine and urine output as the main parameters (Mehta et al., 2007).

Table 2 AKIN criteria for classification and staging of Acute Kidney Injury

Stage	**Serum Creatinine (sCr) Criteria**	**Urine Output (UO) Criteria**
1	Increased sCr by ≥ 26.4µmol/l or 1.5-2.0 times baseline	UO < 0.5ml/kg/h for 6H
2	Increased sCr to 2.0-3.0 times baseline	UO < 0.5ml/kg/h for 12H
3	Increased sCr by ≥ 354µmol/l or ≥ 3.0 times baseline	UO <0.3ml/kg/h for 24H or anuria for 12H

Finally in 2012, the Kidney Disease Improving Global Outcomes (KDIGO) released a clinical practice guidelines for acute kidney injury (AKI), incorporating elements from the two previous definitions, with some minor modifications (Kellum et al., 2012).

Table 3 KDIGO staging for Acute Kidney Injury

Stage	**Serum Creatinine (sCr) Criteria**	**Urine Output (UO) Criteria**
1	Increased sCr by or 1.5-1.9 times baseline	UO < 0.5ml/kg/h for 6-12H
2	Increased sCr to 2.0-2.9 times baseline	UO < 0.5ml/kg/h for ≥12H
3	Increased sCr by ≥3.0 times baseline or Increase sCr to ≥353.6 μmol/l or Initiation of renal replacement therapy or Decrease in eGFR to <35ml/min/1.73m^2 (in patients <18 years old)	UO <0.3ml/kg/h for 24H or anuria for 12H

A validation study for all three criteria found that the AKIN criteria is inferior to the two, whereas the RIFLE and KDIGO criteria achieved similar discrimination (Fujii, Uchino, Takinami, & Bellomo, 2014). The KDIGO system is chosen for this study, incorporating the definition of AKI as an elevation of sCr by 1.5 times baseline. The KDIGO criteria stipulate that the diagnosis of AKI can be made with the sCr or urine output criteria. Since the study was conducted among general surgical patient population, where hourly urine output measurement is not routine, the urine output criteria is disregarded.

The clinical impact of AKI in cardiac and major vascular surgeries has been extensively studied, the incidence of which ranging between 11% and 31% (Robert et al., 2010). The incidence of AKI after abdominal surgeries varies much wider, quoted to be between 6.8% (Long et al., 2016) to 22.4% (Teixeira et al., 2014). This large discrepancy is likely due to the fact that abdominal surgeries tend to differ greatly in terms of length and complexity, as well as the lack of uniform definition of what constitutes a “major” abdominal surgery.

A meta-analysis was conducted in 2014 and found that from 19 previous studies involving a total of 82,514 patients, the pooled incidence of perioperative AKI in major abdominal surgery is 13.4% (O’Connor, Kirwan, Pearse, & Prowle, 2016), which constitutes both ICU and the general wards’ patients. The authors also found that perioperative AKI further leads to increased non-renal post-operative complications, prolonged hospital stay and mortality.

Within the local setting, the incidence, risk factors and outcome of AKI have been studied in various patient populations in Malaysia. The incidence of AKI in an intensive care unit was reported to be 65% (Md Ralib & Mat Nor, 2015), which includes critically-ill patients of both medical and surgical specialities. Another study reported the incidence of AKI is 14.2% among dengue patients (Mallhi et al., 2015). However, to date, no local study has been conducted to specifically address the burden of AKI among surgical patients.

The definition of perioperative period encompasses the entirety of the length of stay from admission until time of death or discharge (Jacobs et al., 2007). This includes any point during the hospitalization, be it the pre-operative, intra-operative or post-operative periods within the same admission.

2.2 RISK FACTORS FOR PERIOPERATIVE ACUTE KIDNEY INJURY

Various factors predispose one to develop AKI. These include age, pre-existing diabetes mellitus and hypertension, chronic kidney disease, cardiovascular disease, hypovolemia and sepsis (Kane-Gill et al., 2015). Importantly, patients who undergo surgery are at increased risk for AKI, especially in prolonged and emergency surgeries.

The patient's comorbidities are important predictive factors for the development of perioperative AKI. Slankamenac et. al. developed a predictive model for post-operative AKI, and found that pre-existing chronic diseases independently predicts the likelihood of developing AKI, with cardiovascular disease, chronic renal failure, and diabetes being the strongest predictors (Slankamenac et al., 2009). It is thought that these diseases cause chronic insults to the nephrons over the years, compromising the kidneys' excretory ability when the patient faces an acutely stressful event such as surgery.

The have also been demonstrable evidence that older age and higher body mass index is associated with higher incidence of AKI (Teixeira et al., 2014). Older patients, who have less robust cardiovascular reserve, are prone to states of low cardiac output, such as cardiac failure and hypovolemia, which in turn predispose to AKI.

The same can be said for sepsis, shock and emergency surgeries, where patients are less likely to be able to tolerate and compensate for these acute stress events. This problem is further compounded whenever surgery is complex and prolonged, particularly when it is also associated with episodes of intraoperative hypotension, the need for the transfusions of blood and blood products, as well as hemodilution as a result of large colloid infusion during surgery (Sun, Wijeysundera, Tait, & Beattie, 2016). In addition, inadequate tissue oxygen delivery, and the use of various medications such as diuretics and nephrotoxic antibiotics, vasopressors and inotropes are also found to predict the development of perioperative AKI (Hobson, Ruchi, & Bihorac, 2017).

2.3 OUTCOMES OF PERIOPERATIVE ACUTE KIDNEY INJURY

Perioperative AKI is associated with adverse outcomes and morbidity, the most obvious being the need for acute dialysis and ICU admission. In addition, AKI is also associated with increased length of hospital stay, increased mortality, and permanent kidney damage, with partial or no renal recovery (Doyle & Forni, 2016).

A large observational study in 2016 demonstrated that the development of postoperative AKI after major operation is associated with longer hospital stay (15.8 vs. 8.6 days) and higher rates of 30-day hospital readmission (21 vs. 13%) (Grams et al., 2016). Another study involving patients who underwent liver resection surgery showed that perioperative AKI is correlated with increased mortality (14.1 vs. 2.3%), as well as prolonged hospital stay, reintubation, increased rates of mechanical ventilation and requirement for acute dialysis (Tomozawa, Ishikawa, Shiota, Cholvisudhi, & Makita, 2015). A study of more than 4000 patients who underwent gastric cancer surgery reported an increase in in-hospital mortality, longer hospital stay and an increased rates of ICU admission in patients who was diagnosed with perioperative AKI (Kim et al., 2013).

AKI also independently predicts the likelihood of patients developing permanent kidney damage. A large systematic review and meta-analysis of 13 studies involving more than 1.4 million subjects was conducted in 2012 found a strong correlation between AKI and the development of chronic kidney disease (CKD) and end-stage renal failure (ESRF). The likelihood of developing permanent kidney damage proportionally increases with increasing severity of AKI (Coca, Singanamala, & Parikh, 2012).

CHAPTER THREE

MATERIALS AND METHODS

3.1 STUDY DESIGN

3.1.1 Study Type

This was a single-centre, prospective, observational study conducted among general surgical patients in the male and female general surgical wards.

3.1.2 Study Area

This study was conducted in Hospital Tengku Ampuan Afzan, Kuantan, Pahang.

3.1.3 Study Period

The study period was from March 2018 to September 2018.

3.2 SELECTION CRITERIA

3.2.1 Target Population

Patients with acute kidney injury in Pahang.

3.2.2 Study Population

Patients with acute kidney injury admitted to the general surgical wards who underwent surgical procedure at Hospital Tengku Ampuan Afzan.