EARLY INDENTIFICATION OF PERIOPERATIVE ACUTE KIDNEY INJURY UTILIZING NOVEL RENAL BIOMARKERS

By

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ABSTRACT

Acute kidney injury (AKI) is a complication of major surgery. Novel renal biomarkers have been identified that show good sensitivity for assessing the risk of AKI development much earlier than current diagnostic measures. These biomarkers were primarily studied in a specific cardiac surgical population. The gold standard diagnostic measure of AKI is a change in serum creatinine (SCr), which is a late marker of renal functional loss. The aim of this study is to utilize NephroCheck® urine assay for tissue inhibitor of metalloproteinase-2 and insulin-like growth factor binding protein 7 (uTIMP-2*IGFBP7), two novel renal inflammatory biomarkers, to assess the risk of developing an AKI after major intraabdominal surgery for adult surgical patients.

Keywords: acute kidney injury, renal inflammatory biomarkers, uTIMP-2*IGFBP7, major surgery

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By

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DEDICATION

To my mother,

my mentor, my biggest supporter, my favorite nurse, and my role model,

who gave up her PhD for me,

but never strayed in her course to guide me to my highest achievements.

This one is for you.

You have been my inspiration and strength.

Everything I am, I owe to you, Mom.

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We have no known conflict of interest to disclose.

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AKI	Acute kidney injury
ATP	Adenosine triphosphate
AUROC	Area under the operating curve
AVR	Aortic valve replacement
BUN	Blood urea nitrogen
CABG	Coronary artery bypass grafting
CKD	Chronic kidney disease
CPB	Cardiopulmonary bypass
CRNA	Certified Registered Nurse Anesthetist
CSA-AKI	Cardiac surgery-associated AKI
EMR	Electronic medical record
GFR	Glomerular filtration rate
ICU	Intensive care unit
MAP	Mean arterial pressure
MVR	Mitral valve replacement
NPV	Negative predictive value
PACU	Post-anesthesia care unit
POD	Postoperative Day
PPV	Pulse pressure variation
RRT	Renal replacement therapy
SCr	Serum creatinine
TAVI	Transcatheter aortic valve implantation
UOP	Urine output
uTIMP-2*IGFBP7	Urine tissue inhibitor of metalloproteinase-2 * insulin-like growth factor binding protein 7

CHAPTER 1: INTRODUCTION

Acute kidney injury (AKI) following a renal insult leads to a rapid decline in glomerular filtration rate (GFR), fluid and electrolyte disturbances (Gharaibeh et al., 2018), and retention of metabolic waste products (Yaqub & Molitoris, 2017). This injury occurs within hours to days of the insult (Gharaibeh et al., 2018). Giannopoulos et al. (2017, p. 326) report that "AKI is currently considered as a syndrome with a multivariate pathophysiologic substrate, rather than a single-factor-induced state". Previously termed acute renal failure, medical terminology for this injury has evolved reflecting that it no longer must end in renal failure but can be reversed if identified early and interventions are implemented (Okusa & Rosner, 2017). Being complex, multifactorial, and developed from a multitude of situations, Liu et al. (2016) find AKI to be poorly understood overall.

AKI can range on a continuum from mild renal dysfunction to the development of chronic kidney disease (CKD) requiring renal replacement therapy (RRT) such as hemodialysis (Gharaibeh et al., 2018). In a mild AKI, the injury causes a slight decrease in GFR and urine output (UOP) declines (Kidney Disease: Improving Global Outcomes [KDIGO], 2012). However, as the AKI severity increases, the consequences increase to functional kidney loss, possible anuria, development of CKD (KDIGO, 2012), and potential mortality (McKinlay et al., 2018). With prompt identification and intervention, this injury may be treatable before functional loss is sustained.

Development of AKI during the intraoperative period may lead to sepsis, coagulopathy, increased hospitalization, prolonged mechanical ventilation, and death (McKinlay et al., 2018). Okusa and Rosner (2017) also describe electrolyte disturbances that accompany development of AKI, including hyperkalemia, acidosis, and volume overload. In severe AKI, the patient may experience hypermagnesemia, hyperuricemia, and possible cognitive changes (Okusa & Rosner, 2017). There is a risk for requirement of RRT when a patient develops a severe AKI (Ishag & Thakar, 2016). Severe AKI also increases the risk of patient morbidity and mortality.

Kheterpal et al. (2007) report an 8-fold increased risk of mortality with developing AKI perioperatively. McKinlay et al. (2018) report a 12-fold increased risk of mortality associated with developing AKI after major abdominal surgery. Mortality following cardiac surgery, is estimated to range from 25% (Hoste et al., 2020) to 60% (Koyner et al., 2008) of patients with severe renal injury requiring RRT.

AKI claims the lives of 1.7 million patients per year globally (Thongprayoon et al., 2018). With the increased incidence of AKI and development of associated serious adverse outcomes, healthcare cost escalates, placing a burden on society (Thongprayoon et al., 2018). The risk-adjusted average cost of the patient without injury has been compared to the cost for the patient who sustains AKI; the estimated cost increase is $15,900 for a single episode of AKI (Hobson et al., 2017). Due to the estimated annual expenditure in excess of $10 billion for hospital-acquired AKI placing a burden on hospital reimbursement, the Centers for Medicare and Medicaid Services recently introduced AKI requiring in-patient hemodialysis as a 2020 cost measure for the Merit Based Incentive Payment System for providers (Centers for Medicare and Medicaid Services [CMS], 2020). In exploring this topic regionally, there is a 15.9% death rate attributed to kidney disease in North Carolina (CMS, 2022), despite a task force set by the NC General Assembly to combat this health care concern in 2008. These poor outcomes may be mitigated or avoided with proper early identification of risk for developing AKI using novel renal biomarkers and timely interventions.

Background

Azotemia, a common feature of AKI, is the abnormally high retention of nitrogenous waste products such as blood urea nitrogen (BUN) and serum creatinine (SCr) (Yaqub & Molitoris, 2017). With the retention of these toxic nitrogenous substances, SCr and BUN levels rise indicating renal impairment; while apoptosis occurs in the injured renal area leading to remodeling and recovery (Yaqub & Molitoris, 2017).

Acute tubular necrosis can occur when an AKI is associated with ischemia of the renal tissues (Butterworth et al., 2018, Chapter 57). With continued ischemia, the injured cells experience adenosine triphosphate (ATP) depletion and start to release vasoactive mediators, such as nitric oxide and endothelin, from endothelial cells. Under the influence of these mediators and damage, endothelial permeability increases and GFR is subsequently impaired (Yaqub & Molitoris, 2017). Depending on the severity of the injury or amount of tissue involved, GFR may start to recover during cellular repair (Yaqub & Molitoris, 2017).

The incidence of AKI is 5% to 7.5% for all patients who have acute care hospitalizations (Ishag and Thakar, 2016). AKI is a common, often unrecognized postoperative event occurring after major surgery. McKinlay et al. (2018) report that 30% to 40% of all hospital acquired AKI cases develop perioperatively, and the incidence is on the rise in the United States (Gharaibeh et al., 2018). As discussed previously, it is known that development of perioperative AKI may contribute to sepsis, coagulopathy, increased hospitalization, prolonged mechanical ventilation, and mortality (McKinlay et al., 2018). Perioperative AKI development is highly correlated with the type and urgency of the surgery (Hobson et al., 2017; Ishag & Thakar, 2016; Koyner et al., 2008; Romagnoli et al., 2018; Whitaker et al., 2015).

Common causes of AKI include embolic events, hypotension, mechanical ventilation, nephrotoxic medications, hyperglycemia, rhabdomyolysis (McKinlay et al., 2018), renal medullary ischemia, renal tubular obstruction, remodeling and metabolism changes of renal tubular epithelial cells, sepsis-associated, contrast-induced (Liu et al., 2016) and the use of cardiopulmonary bypass during surgery (Liu et al., 2016; Whitaker et al., 2015). Many of these factors are commonly associated with surgery. McKinlay et al. (2018) created a diagram of the potential pathophysiology of the perioperative AKI (see Appendix A) that includes hemodynamic factors, anesthetic factors, and surgical factors. Due to the multitude of causative factors resulting in AKI and related azotemia, they are often categorized as prerenal, intrarenal, or postrenal sources of injury.

Common prerenal causes of azotemia include hypotension, hypovolemia, abdominal compartment syndrome, and impaired cardiac output (Butterworth et al., 2018, Chapter 57). Hemorrhage, burns, diuretic therapy, dehydration, and gastrointestinal fluid loss can lead to intravascular volume depletion and reduced extracellular fluid volume (Yaqub & Molitoris, 2017). Cardiac tamponade, congestive heart failure, aortic stenosis, cirrhosis with concomitant ascites, and nephrotic syndrome can lead to decreased circulating volume and increased extracellular fluid volume (Yaqub & Molitoris, 2017). Renal blood flow can be impaired by venous thromboses, arterial stenosis, nonsteroidal anti-inflammatory drug (NSAIDs) use, and angiotensin-converting enzyme inhibitors (ACE-Is) (Yaqub & Molitoris, 2017). Lastly, sepsis, vasodilatory drugs, and many anesthetic agents cause systemic vasodilation which could result in prerenal azotemia (Yaqub & Molitoris, 2017). If recognized early and corrected, prerenal azotemia can be rapidly reversed (Yaqub & Molitoris, 2017); thus, early identification of risk for developing AKI is essential. There is a small and variable window of opportunity between the injury and functional loss to mitigate kidney damage (Ishag & Thakar, 2016). While researching major non-cardiac surgical patients, Gocze and colleagues (2015) found that early intervention for hypotension may reverse early cell cycle arrest and be renal protective.

Intrarenal causes of AKI can be subdivided into four categories according to Yaqub and Molitoris (2017): vascular disease, tubular disease, glomerular disease, and renal interstitial disease. Nephrotoxic medications, radiocontrast dyes, and heavy metals can all injure the renal interstitial tissues (Butterworth et al., 2018, Chapter 57). Thompson et al. (2020) report all the following medications as potential causative agents of AKI: ACE-Is, angiotensin receptor blockers (ARBs), chemotherapy (particularly cisplatin, carboplatin, and methotrexate), antiretrovirals, NSAIDs, cimetidine, contrast media dyes, illegal drugs (particularly heroin and methamphetamine), and antibiotics (particularly aminoglycosides, cephalosporins, amphotericin B, bacitracin, and vancomycin). These drugs induce renal injury by either direct cellular injury, vasoconstriction, or inducing tubular obstruction (Yaqub & Molitoris, 2017).

Finally, common postrenal causes of AKI include causes of urinary tract obstruction such as carcinoma, blood clots, kinked Foley catheters, ureteral obstruction, and benign prostatic hypertrophy (Yaqub & Molitoris, 2017). Occasionally, during abdominal surgery, ureteral obstruction is a complication of the procedure itself, for instance an inadvertently sutured ureter during gynecological surgery. Many of these discussed sources of AKI may occur during the perioperative period.

Significance

The current gold standard for AKI diagnosis is by measuring a rise in SCr and decline in urine output as defined by the 2012 Kidney Disease: Improving Global Outcomes Clinical Practice Guidelines (KDIGO, 2012). Diagnostic and staging criteria may be viewed in Appendix B (KDIGO, 2012). Using these standards for diagnosing AKI, it is estimated that 31% of hospital-acquired AKI were avoidable and 43% of patients experienced delays in treatment (National Confidential Enquiry into Patient Outcomes and Death Website [NCEPOD], 2009). Erdbruegger and Okusa (2021) refer to SCr as a “functional marker” as opposed to a “damage biomarker”. Despite being the gold standard in diagnosing AKI, elevated SCr alone does not lead practitioners to identify AKI in the early stages (McKinlay et al., 2018). The rise in SCr is often delayed and does not correlate with the severity of the injury (Koyner et al., 2008). After the renal insult occurs, SCr may not spike until 24 hours to 7 days later (van Duijl et al., 2019). There is a small and variable window of opportunity between the onset of injury and a spike in SCr for kidney damage mitigation (Ishag & Thakar, 2016). Once SCr increases by 0.3 mg/dL or 1.5 times the patient baseline SCr value, 50% of kidney function has already been lost (Ishag & Thakar, 2016).

During periods of stress, renal tubular cells will release the protein inflammatory biomarkers urinary tissue inhibitor of metalloproteinase-2 and insulin-like growth factor binding protein 7 (uTIMP-2*IGFBP7) (Massoth et al., 2019). The only U. S. Food and Drug Administration (FDA) approved device to measure these novel renal biomarkers is the

NephroCheck® urine assay. This assay provides a risk assessment score for the subsequent development of a Stage 2 or 3 AKI within the following 12 hours.

Purpose of the Study

Better predictive models are needed to reduce the patient health burden of AKI utilizing novel renal inflammatory biomarkers. The purpose of this study is to explore the association between major non-cardiac intraabdominal surgery and the early identification of risk for AKI development using the NephroCheck® urine assay to measure uTIMP-2*IGFBP7.

Conceptual Framework

AKI is a complex syndrome resulting from varied injuries that can lead to devastating outcomes (Ronco et al., 2019). A perioperative AKI nursing conceptual model is proposed using a derived renal-specific systems model based on Neuman's systems model (2002) synthesized with Orlando's deliberative nursing process (1961) to guide this research. Major surgery is a known risk factor for development of perioperative AKI (McKinlay et al., 2018). Certified Registered Nurse Anesthetists (CRNAs) play a vital role in patients' well-being and care throughout the perioperative period. Using Orlando's deliberative nursing process (1961), the CRNA is constantly assessing for perioperative stressors that could potentially impact the renal system throughout the entire perioperative period. The perioperative period extends from the preoperative workup, throughout the intraoperative period to the follow-up post-surgical visit. This perioperative AKI nursing conceptual model could aid CRNAs administering anesthesia to identify perioperative stressors that may lead to a harmful AKI. Using Orlando's nursing process, the actions of CRNAs either by identifying AKI earlier when ordering NephroCheck® urine tests or by implementing intraoperative renal protective measures could lead to reduced severity of AKI and long term sequalae for patients. The concepts of Neuman's systems model (2002) and Orlando's deliberative nursing process (1961) will be reviewed in relation to the aims of this study and subsequent proposal of a new perioperative AKI nursing conceptual model.

Neuman's Systems Model

Betty Neuman first published her systems model in 1972. It was originally titled *A model for teaching the total person approach to patient problems* (Wills, 2019). The systems model appeared after multiple revisions (Wills, 2019). This conceptual model was deductively derived and based on a synthesis of her philosophical beliefs, nursing expertise, and knowledge from multiple disciplines including Lazarus' stress and coping, Selye's stress theory, von Bertanlanffy and Lazlo's general systems theory, and Chardin and Cornu's wholeness in systems (Neuman, 2002). Neuman's systems model reflects the interest of nurses in the human, either ill or well as an individual holistic client, the multiple environmental stressors that can influence health, and the partnership between patients and nurses in the pursuit of identifying prevention interventions (Freese & Lawson, 2010).

As seen in Figure 1, the model has concentric rings circling the basic structure of the human (Wills, 2019). These concentric rings depict lines of defense and resistance to stressors to the client (Wills, 2019). This systems model was meant to be a holistic model of the client to assist nurses with management of how patients' respond to stressors and to assess where they are on the continuum of health (Neuman, 2002). Five interacting variables exist simultaneously within the basic structure at the center of the concentric rings which include physiology, psychology, sociocultural, developmental, and spiritual variables (Wills, 2019). Neuman includes a nursing process with three steps: nursing diagnosis, negotiating nursing goals with the patient, and assessing nursing outcomes (Freese & Lawson, 2010). This conceptual model is extremely complex and can be used in multiple situations (Wills, 2019). Because of the widespread use of Neuman's model, the Neuman Systems Model Trustees Group, Inc monitors and gives permission for the use of the model in research, which was obtained for this research.

For the purposes of this study and proposal of a new perioperative AKI nursing conceptual model, Neuman's concepts of environment, client system, health, stressors, and nursing will be derived to a renal specific systems model. Due to the complexity of the systems

model, the original concepts are detailed first, before deriving them to a renal specific model and synthesizing them with Orlando's deliberative nursing process (1961).

Environment

Neuman intended this model to provide a holistic approach to a client, that is considered a unique whole, who is in dynamic interaction with the environment, stressors, and internal variables. She provided a systems approach to nursing care for identifying nursing problems, understanding the client in these dynamic interactions, and to aid in providing prevention as intervention (Freese & Lawson, 2010). Her open system is a concept to acknowledge that a system is in constant exchange of information and energy with elements within the system organization and the environment surrounding the system (Neuman, 2002). "Stress and reaction to stress are basic components of an open system" (Freese & Lawson, 2010, p. 311). Neuman used environment as a broad concept to define all external and internal factors surrounding the client system that may influence the stability of the system. The environment surrounding and affecting the client system is also dynamic, as it is influenced by the client as well (Neuman, 2002).

For the purpose of this study the environment surrounding the participant will be their internal baseline renal health and the external rigors of major surgery. Potential perioperative breaches to the renal system integrity frequently occur during major surgery such as bouts of hypotension, hypovolemia, and the use of medications that are noxious to the renal system among others (McKinlay et al., 2018).

Client System

Each client system is unique and includes a collection of internal native characteristics and response patterns. The client is a dynamic individual that exists on a continuum of wellness to illness and is impacted by the interrelationships of variables found throughout their basic client structure and additional concentric rings that help them react to stressors (Neuman, 2002). "Physiology, psychological, sociocultural, developmental, and spiritual variables occur

and are considered simultaneously in each client concentric ring" (Neuman, 2002, p.15). The client system can be further subdivided into the basic client structure and different lines of defense. In this study, the renal system is derived from Neuman's client system (Neuman, 2002). This shall focus specifically on the renal system, the protective layers of the renal system, and the reaction of the renal system to environmental stressors. This system shall still receive input from internal and external environments; particularly, perioperative stressors.

Basic Client Structure. The basic client structure is the center of the concentric rings in the client system, which represents the client's native genetic factors, innate factors of the species, and strengths or weaknesses of the system (Neuman, 2002). "Examples for the client as an individual are innate mechanisms for the maintenance of a normal temperature range, genetic response patterns, and the strength or weakness of body organs" (Neuman, 2002, p. 17). This central core is surrounded by different lines of resistance and defense.

Lines of Resistance and Defense. The lines of resistance depicted as dashed inner concentric circles around the basic core structure are activated by invading stressors that breach the normal line of defense and "contain certain known and unknown internal and external resource factors that support the client's basic structure and normal defense line, thus protecting system integrity" (Neuman, 2002, p. 18). The flexible line of defense is a dynamic accordion-like outer line of defense, depicted by a dashed line within the systems model (see Figure 1). As a protective buffer of the client system, "it ideally prevents stressor invasions of the client system, keeping the system free from stressor reactions, or symptomology" (Neuman, 2002, p. 17). When this flexible line is no longer capable of protecting the client system, the stressor will invade the normal line of defense. The normal line of defense is a solid concentric circle within the system, representing an adaptation level of health of the client system developed over time and considered normal for each patient individually. This line is used to judge deviation from wellness for each patient (Neuman, 2002).

Health

Neuman conceptualizes client health as a continuum with wellness or optimal system stability at one end and illness and death at the opposite end (Neuman, 2002). The dynamic client system is in constant contact with input from the environment, both internal and external, and must react to stressors. These reactions to stressors and interplay with the environment, in addition to basic structure changes that occur throughout a life span change the client's position on the health continuum. Stability within the client system leads to optimal wellness and the client's needs are met (Freese & Lawson, 2010). When a client's needs are unmet, the result is a reduced state of wellness and suboptimal health (Neuman, 2002). Needs may be met by positively reacting to interactions or invading stressors either by internal protective factors or with the assistance of nursing prevention as intervention (Neuman, 2002). Reconstitution represents the return to system stability which is an ideal balance of harmony during the varied energy exchanges occurring within the system. This concept "represents successful mobilization of energy resources" (Neuman, 2002, p. 324) to achieve maintenance of wellness.

Stressors

A stressor is any tension-producing force that interacts with the client in the internal or external environment that may lead to a negative or positive impact based on the client's perception of the force and their ability to negotiate the impact of the force (Neuman, 2002). Within a dynamic client system, multiple stressors may impact the system at any one time (Neuman, 2002). The degree of reaction of the system "represents system instability that occurs when stressors invade the normal line of defense" (Neuman, 2002, p. 322). For the purpose of this study, perioperative breaches will be derived from Neuman's concept of stressors.

Nursing

Neuman describes nursing as a unique profession concerned with assessing clients' needs, identifying variables in the environment that may affect clients, helping them to adjust to stressors, and caring for clients through preventive intervention using unique nursing knowledge

and science (Neuman, 2002). Nursing is concerned with the whole client wellbeing and that the nurse's perception will influence any care given to the client (Freese & Lawson, 2010). Both the perception of the nurse and that of the client must be assessed (Neuman, 2002). There are multiple stages of prevention as intervention provided by the nursing action and determinants. "*Primary prevention*: before a reaction to stressors occurs. *Secondary prevention*: treatment of symptoms following a reaction to stressors. *Tertiary prevention*: maintenance of optimal wellness following treatment" (Neuman, 2002, p. 323).

Neuman's complex systems model lays the foundation for deriving the renal specific systems model. The renal specific systems model has been synthesized with Orlando's deliberative nursing process (1961) in a newly proposed perioperative AKI nursing conceptual model as a framework to guide CRNA's assessment and intervention implementation when perioperative stressors are identified that could precede an AKI.

Orlando's Deliberative Nursing Process

Ida Jean Orlando's deliberative nursing process was part of the dynamic nurse-patient relationship she researched (Orlando, 1961). This process was meant to be reflective in nature to use nursing assessment of patients' needs and apply nursing knowledge for intervention to meet their needs (Orlando, 1961). Orlando described that nursing had its own distinct skill set and ability to address patients' needs (Schmieding, 2002).

Orlando's deliberative nursing process is a "specific theory about how nurses process observations and respond to patients based on inferences from the nurse-patient interaction" (Alligood, 2002, p. 52). Following this process, professional nurses use all the senses to collect data on the patient's condition, presenting behavior, and immediate needs. Then they respond to this assimilated data by reflectively moving through the five stages of the nursing process to address these needs (Schmieding, 2002). Orlando's deliberative nursing process was to give nurses, especially new to the profession, a framework for effective nursing practice and to clarify the nurse's professional role (Schmieding, 2002). This process has been adapted to multiple

uses including the nurse-patient and nurse-physician relationships (Fawcett, 2005). A published version of a figure depicting model concepts for the nursing process by Orlando has not been identified.

Patient's Need and Presenting Behavior

The patient's need "is situationally defined as a requirement of the patient which, if supplied, relieves or diminishes his immediate distress or improves his immediate sense of adequacy or well-being" (Orlando, 1961, p. 5). The patient's behavior indicates an immediate need; cues may manifest as verbal, non-verbal, or physical forms (Schmieding, 2002).

Patients are unique individuals with needs. They may display their needs in a myriad of ways including verbal requests, nonverbal forms (such as crying or silence), or in physical forms (such as disturbances in their blood pressure). The nurse will reflect upon, interpret, and react to this displayed presenting behavior (Schmeiding, 2002). When patients are unable to resolve their needs, they may become distressed. This interpretation is vital to the use of this theory in this research. Often under anesthesia, patient needs may only be reflected in vital sign changes or assessment of physical changes such as shivering or decreased urine output.

Deliberative Nursing Process

Nursing is a profession of caregivers with specific knowledge who make observations, react to input received by all the senses, and act upon them. "The purpose of nursing is to supply the help a patient requires in order for his needs to be met" (Orlando, 1990, p. 9). Orlando specifies the importance of deliberate reaction instead of automatic reaction of the nurse (Alligood, 2002). She describes this process as a dynamic, reflective model in which the patient's behavior affects the nurse and vice versa (Orlando, 1961). This reflection is the first step of the nursing process; mindful assessment (Sitzman & Eichelberger, 2011). The five steps of the nursing process are assessment, nursing diagnosis, planning, implementation, and evaluation (Sitzman & Eichelberger, 2011). CRNAs utilize this process each day in constant

cycle as they critically assess their patients' needs, implement interventions, and evaluate for further need throughout the perioperative period.

Perioperative AKI Nursing Conceptual Model

In the newly proposed perioperative AKI nursing conceptual model, the client system from Neuman's systems conceptual model (Neuman, 2002) was derived into a renal-specific systems model. This model will guide nursing research for perioperative AKI specific stressors and nursing interventions to aid lines of defense against these stressors. Neuman's wellness continuum (Neuman, 2002) was adapted to a renal wellness continuum. On this renal wellness continuum, renal wellness exists at one side with chronic renal failure at the other. AKI, as established earlier, is a dynamic process that has a wide range of effect on the renal system; therefore, Neuman's model is well suited to address the concerns of perioperative AKIs. The patient may sustain a reversible injury or a more robust injury that could lead to chronic renal failure and the need for hemodialysis (Gharaibeh et al., 2018). The choice to not include the Neuman systems model nursing process revolves around the second phase of this process that requires negotiation with the patient to determine nursing goals (Neuman, 2002). Therefore, this renal systems model is synthesized with Orlando's deliberative nursing process (Orlando, 1961). As the patient is anesthetized when a perioperative AKI may occur, the deliberative nursing process lends to more creative assessment and intervention on behalf of the patient. Orlando describes patient presenting behaviors as potentially displayed by verbal, nonverbal, or physiologic means (Schmeiding, 2002). Physiologic changes under anesthesia may alert providers to patient needs.

Following Walker and Avant's (2019, Chapter 9) method of theory synthesis, the aim of this synthesis was to overlay the deliberative nursing process (Orlando, 1961) on a renal-specific systems model to aid nursing research in prevention, early identification, and intervention related to perioperative AKIs. A brief literature search indicates that there is a gap in nursing knowledge on the application of Neuman's and Orlando's nursing models for surgical

patients or patients with AKI, therefore the merging of these two models will provide a framework for nursing research pertaining to the early identification and mitigation of surgical-associated AKI.

As seen in Figure 2, a newly derived perioperative AKI nursing conceptual model based on the synthesis of Neuman's (2002) systems model and Orlando's (1961) deliberative nursing process provides a framework to understand the complexity of perioperative AKIs and will guide this research. The environment remains unchanged from Neuman's environment (2002) surrounding the renal system. Having major surgery will lend great context to the potential perioperative stressors requiring adaption of the renal system to maintain stability and wellness.

The dynamic renal system will respond to stressors in either a positive or negative way. The renal system may be able to compensate for invading stressors or breaches. If compensation is overwhelmed, an injury pattern could occur. This injury may be in the form of an AKI. Within the renal system, internal resistance factors known as lines of resistance help to stabilize the system and return it to its baseline state. For example, if the kidney system perceives a decreased flow state, autoregulation of blood flow to compensate for this stress is enacted between mean arterial pressures (MAP) of 80 and 180 mmHg (McKinlay et al., 2018). Each patient has developed a normal line of defense over time that serves as a baseline of renal health to measure wellness deviation against. Each patient exhibits a different level of baseline health. Factors that may help determine this level of wellness include patient history, co-morbidities, response pattern to stressors, and organ strength or weakness.

Stressors to the renal system will vary and differ in the magnitude of disruption they bring to the system's stability. These perioperative stressors can result in a variety of AKIs ranging from mild disruptive injuries to more severe injuries that lead to the development of renal functional loss and chronic renal failure (Gharaibeh et al., 2018). It is known that perioperative AKI may lead to the development of sepsis, coagulopathy, increased hospitalization, prolonged mechanical ventilation, and mortality (McKinlay et al., 2018). As

perioperative breaches stress the lines of defense, AKI risk increases. Therefore, AKI development may worsen the stressed state of the renal system. As AKIs worsen, patient needs will increase.

Orlando's (1961) deliberative nursing process is synthesized with the newly derived renal system model. Patient's needs may be met by nurses who assess the presenting behavior and employ this process after reflecting on their immediate reaction to the presenting behavior. Patient needs should improve when using the deliberative process discipline. An inverse relationship is seen as patient needs resolve and are decreased, stability of the line of defense in the renal system increases.

Theoretical and Operational Definitions

For purposes of this study, the concepts that will be focused upon are the renal basic core structure of the renal system, perioperative breaches, and AKI. The theoretical and operational definitions of these concepts will follow. The theoretical definitions presented represent the basic meaning of the variable of interest. The operational definitions provide the method we plan to use to quantify these variables of interest.

Renal System

This renal derived system from Neuman's client system (Neuman, 2002) includes the renal basic core structure and all lines of resistance and defense. The renal system is dynamic just like Neuman's (2002) client system that interacts with internal and external environments, receiving input and responding either positively or negatively. The concentric rings that represent the lines of resistance and defense are conceptually unchanged from Neuman's (2002) systems model and are derived to a renal-specific systems model. These protective buffers of the renal system help prevent stressor invasions of the system, keeping the system free from reactions or symptomology. When this flexible line is no longer capable of protecting the renal system, the stressor will invade the normal line of defense. The normal line of defense represents an adaptation level of health of the renal system developed over time and

considered normal for each patient individually. This normal line of defense is used to judge deviation from wellness for each patient (Neuman, 2002). The lines of resistance are activated by invading stressors that breach the normal line of defense and act to help support the client's renal structure, thus protecting system integrity (Neuman, 2002). The different lines of defense in the renal system will not be measured in this study. However, the renal basic core structure will be measured. Also, the overall stability of this renal system will be operationalized by whether the patient exhibits the criteria for diagnosis of an AKI after their major surgery.

Renal Basic Core Structure

The theoretical definition of renal basic core structure is derived from Neuman's systems model (2002) as the basic factors of the patient's renal system and factors that may affect the renal system including organ strength or weakness, response pattern to stressors, the patient's health history, co-morbidities, spiritual beliefs, sociocultural influences, developmental factors, and psychological factors. All these factors intermingle and affect the renal system.

Major surgery impacts the environment surrounding the renal basic core. Major surgery is defined as "an operation upon an organ within the cranium, chest, abdomen, or pelvic cavity" (Merriam-Webster, n.d.). Participants enrolled in this study will be undergoing major non-cardiac intraabdominal surgery.

Renal basic core structure will be operationalized through investigation of the participant record and intake interview to gather data utilizing a standardized researcher-developed data collection tool (see Appendix C). Descriptive data will be gathered about their renal organ strength including previous AKI diagnoses, medical history, surgical history, medication history, previous labs, baseline vital signs, patient demographics, and anticipated procedure during the study.

Perioperative Breach

The second concept of interest in this study is perioperative breach. This is conceptually derived from Neuman's (2002) environmental stressors and is defined as potential perioperative

stressors that impact the renal system and could result in an AKI; whether of prerenal, intrarenal or postrenal origin. The renal system could endure more than one breach at any one time. Additionally, one breach may lead to another, such as a prerenal insult of the renal system resulting in an intrarenal injury that leads to a worsening AKI.

Perioperative breach is operationally defined as any of the following prerenal, intrarenal, or postrenal cause of AKI assessed in the perioperative record. Prerenal known causes investigated include hypotension and hypovolemia. Hypotension in this study is defined as a mean arterial blood pressure (MAP) less than 65 mmHg for more than 5 minutes. According to Sessler et al. (2021), MAPs less than 65 mmHg are known to be associated with perioperative renal and myocardial injuries. Hypovolemia is defined as a pulse pressure variation (PPV) greater than 13% (Bar-Yosef et al., 2017). MAPs and PPVs will be collected from the intraoperative electronic medical record (EMR). If PPV is not recorded in the record, blood pressures will be used to calculate the PPV during any breath cycle under hypotension as previously defined using the following calculation (Hussein et al., 2018): PPV = ((PPmax - PPmin)/((PPmax + PPmin)/2)) x 100. Known intrarenal causes of AKI (nephrotoxic drug use including contrast dye, antibiotics, and ACE-inhibitors) or postrenal causes (kinked catheter or obstructed ureter) will be collected from the EMR.

Acute Kidney Injury

The final concept of interest in this study is AKI and identification of the injury. AKI is an injury to the kidney within hours to days of the insult that results in a rapid decline in GFR, and fluid and electrolyte disturbances (Gharaibeh et al., 2018). AKI is theoretically defined as a complex syndrome that leads to renal dysfunction and exists on a wellness continuum from reversible injury to functional renal loss and chronic renal disease (Gharaibeh et al., 2018).

AKI will be operationally measured in two ways for this study, using both the standard and novel methods. For the standard method, SCr values will be recorded at baseline and each day postoperatively until discharge. Additionally, UOP will be assessed for the first 24 hours

postoperatively. We will note patients that meet the criteria for AKI diagnosis and staging utilizing the 2012 KDIGO Clinical Practice Guidelines (KDIGO, 2012) for AKI (see Appendix B). For the novel method for early identification of AKI, urinary TIMP-2*IGFBP7 levels utilizing NephroCheck® urine risk assessment assay will be measured at baseline, at 6 PM on the surgery day, and the morning of postoperative day one (POD 1). A risk score greater than 0.3 is indicative of high-risk for developing moderate to severe (Stage 2-3) AKI within the next 12 hours (Astute Medical, 2017).

Specific Aims and Research Questions

The **Specific Aims** are to:

Aim 1: **Explore the association between major non-cardiac intraabdominal surgery and incidence of AKI.** (N=81)

Research question 1a: What is the association between major non-cardiac intraabdominal surgery and incidence of AKI?

Research question 1b: How does this association compare to published cardiac surgery-associated AKI (CSA-AKI) incidence?

The null hypothesis of Aim 1 is that major non-cardiac intraabdominal surgery will not have a significant association with AKI.

Aim 2: **Evaluate the use of the NephroCheck® urine assay for uTIMP-2*IGFBP7 in early identification of risk for developing moderate to severe AKI in major non-cardiac adult surgical patients**. (N=81)

Research question 2a: What is the effectiveness of the NephroCheck® urine assay for early identification of risk for all true cases of Stage 2 and 3 AKI in our sample?

Research question 2b: Does NephroCheck® identify risk of AKI development earlier than SCr diagnosed episodes of AKI in our sample?

The null hypothesis of AIM 2 is that uTIMP-2*IGFBP7 will not provide early identification of those at true risk for development of perioperative moderate to severe (Stage 2-3) AKI in

adult patients requiring major non-cardiac intraabdominal surgical procedures compared to the gold standard of measuring serum creatinine.

Basic Assumptions

There are assumptions that underlie this research. For a perioperative AKI to occur, we must understand where the patient is on their health continuum and what breach or breaches during surgery led to an AKI. It is assumed that participants in this study will truthfully answer all questions in the preoperative interview to help establish and measure their renal core basic structure.

Summary

There is a small window of reversibility for kidney injury that is dependent upon prompt identification and early intervention before kidney function is lost (Ishag & Thakar, 2016). Novel methods of identifying risk of perioperative AKI development early will significantly reduce healthcare costs by reducing length of hospital stay, decreasing the development of CKD, and improving patient morbidity and mortality. My research will work towards Goal 1 of the United States Department of Health and Human Services' Advancing American Kidney Health Initiative: Reduce the risk of kidney failure (US Department of Health and Human Services [US DHHS], 2019). This proposed innovative way to identify risk of developing a perioperative AKI earlier utilizing uTIMP-2*IGFBP7 biomarkers may help mitigate injury severity before permanent damage occurs, improve patient outcomes, and reduce healthcare costs associated with treatment.

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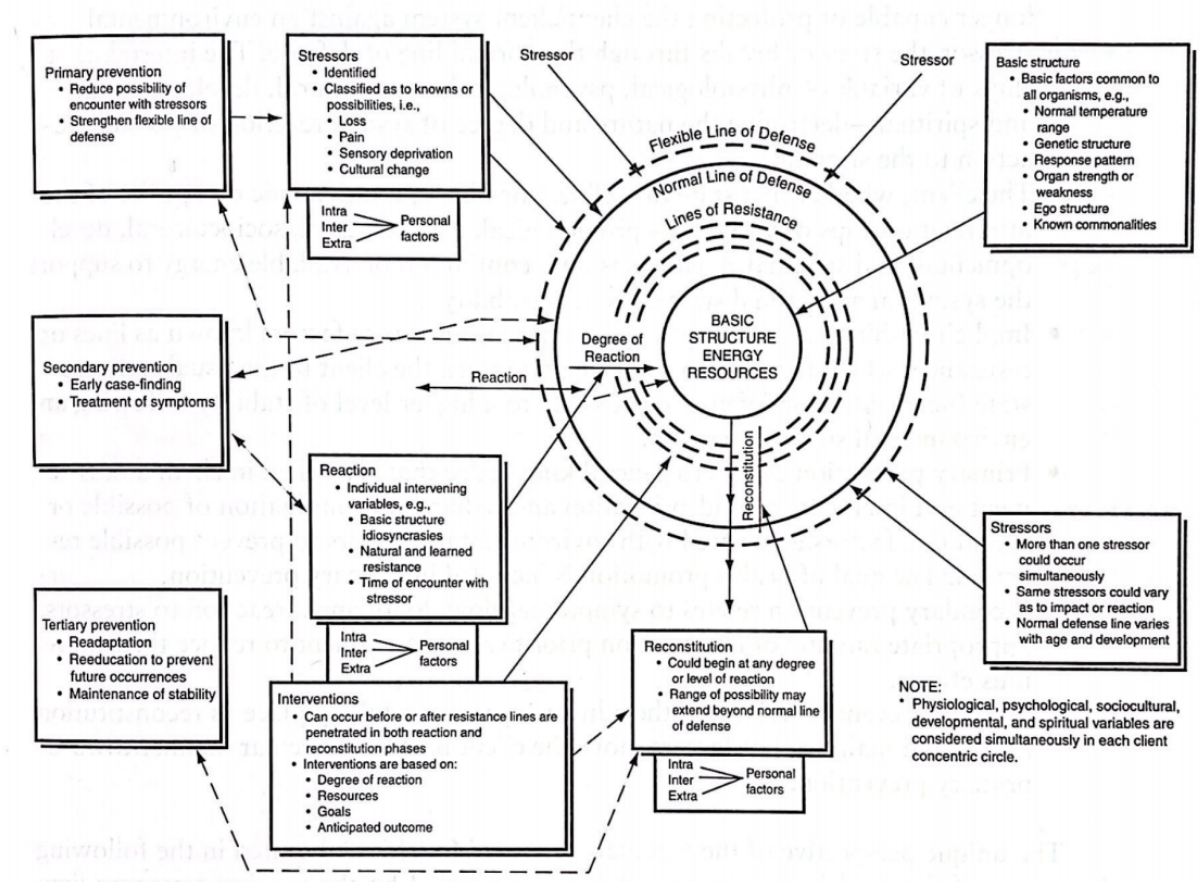
Figure 1

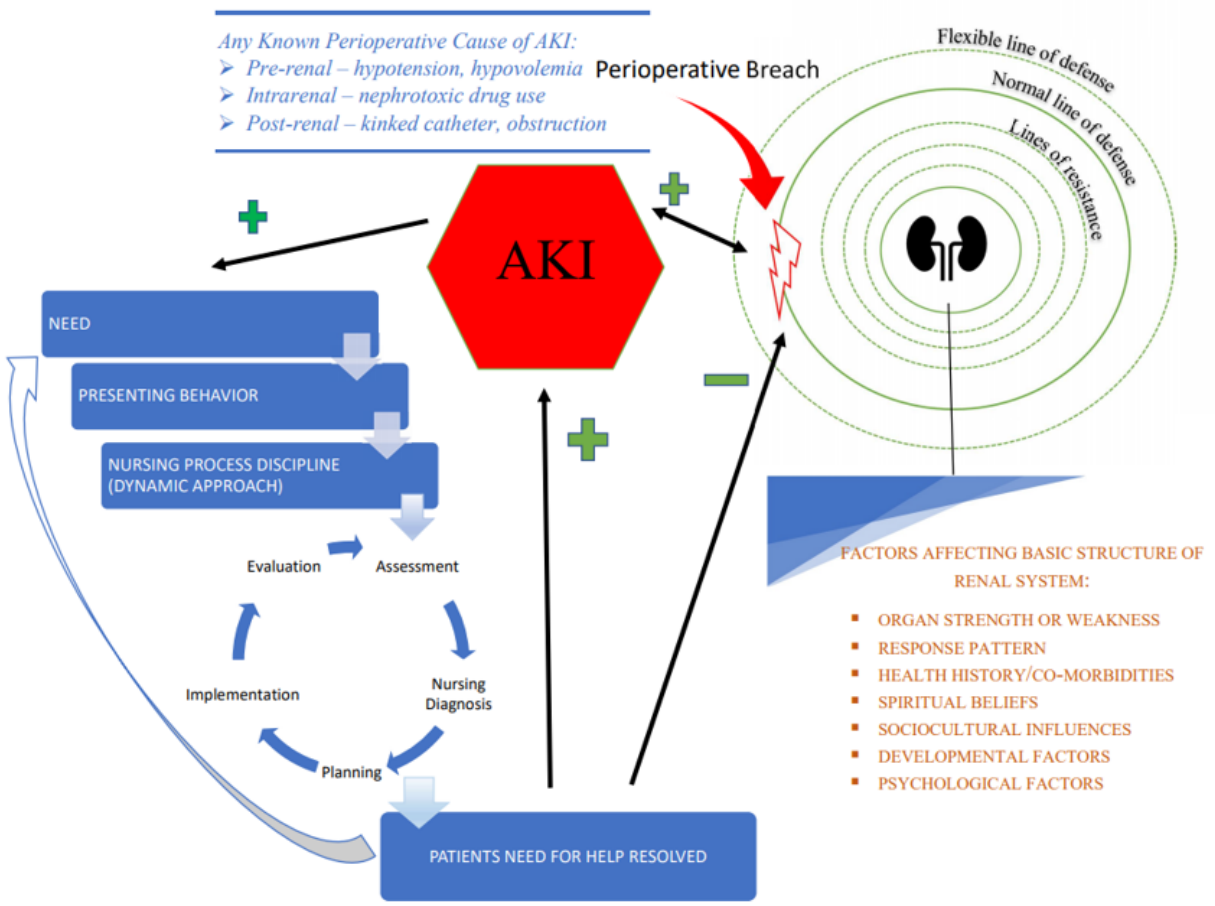
The Neuman Systems Model (Neuman, 2002, p.13)



Note. Original diagram copyright © 1970 by Betty Neuman.

Figure 2

Perioperative Acute Kidney Injury Nursing Conceptual Model



CHAPTER 2: REVIEW OF LITERATURE

Introduction

Within the framework of the perioperative AKI nursing conceptual model (see Chapter 1, Figure 2), this chapter reviews the current state of the science regarding the complex syndrome of perioperative AKI and the comparison of available standard and novel techniques of identifying AKI. A review of the literature was conducted. Primary research studies with empirical data for adult surgical patients were included that assessed the ability of uTIMP-2*IGFBP7 to identify risk of surgical-associated acute kidney injury.

Databases searched included Cumulative Index to Nursing & Allied Health Literature (CINAHL), ProQuest Nursing and Allied Health Database, Scopus, and PubMed, in addition to reference review. Search terms included a combination of MESH terms, subject headings, and keywords as applicable for each database, including ‘acute kidney injury’, ‘AKI’, ‘renal injury’, ‘renal complication’, ‘surgical’, ‘surgery’, ‘operative’, ‘urinary tissue inhibitor of metalloproteinase-2 * insulin-like growth factor binding protein 7’, and ‘uTIMP-2*IGFBP7’. No date restraints were used in searching so all primary studies utilizing this urine assay for adult surgical patients could be identified. Article selection was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Moher et al., 2009). The PRISMA diagram for the initial search of literature in June of 2020 may be viewed in Chapter 4, Figure 1. This early review was submitted for publication in 2020, accepted and published in June 2022. The published manuscript is presented in Chapter 4. This state of the science literature search was updated as of February 2023. Only full-text, English, human studies found in peer reviewed journals were included. Literature containing pediatric populations (less than 18 years of age), mixed populations of surgical and other types of patients such as septic or cancer, and pilot studies were excluded. Low level articles such as review, commentary, interviews, editorials, abstracts, and posters were also excluded.

By searching four databases and using other methods such as reference list review, 540 records were identified. Duplicates were removed, and the remaining 503 records were screened for title and abstract. Based on the inclusion and exclusion criteria and by quality appraisal, an additional 436 records were removed. The remaining 67 full-text articles were assessed for eligibility, and 52 were excluded for various reasons including pediatric populations, pilot studies, investigations of other biomarkers, non-surgical populations, the use of uTIMP-2*IGFBP for non-identification purposes and lack of full text. Fifteen primary quantitative studies of adult surgical patients were identified and included in this review.

This review continues with an overview of the current science of the complex syndrome of surgical-associated AKI and the methods for AKI identification including the standard method utilizing SCr and the novel method utilizing the inflammatory renal biomarkers uTIMP-2*IGFBP7. A matrix was used for data extraction (see Appendix D). Finally, gaps in the scientific knowledge will be reviewed.

AKI

All fifteen studies evaluated a primary end point of AKI development postoperatively. However, some used the endpoint of any stage AKI, while others used only moderate to severe staged AKIs as an endpoint. Each used the NephroCheck® urine risk assessment assay to evaluate uTIMP-2*IGFBP7 novel renal biomarkers for indication of AKI development. All fifteen studies utilized KDIGO (2012) staging to define AKI (see Appendix B). AKI incidence rates across the studies may be viewed in Table 1 at the end of this chapter.

Cummings et al. (2019) studied 400 adult cardiac surgical patients from a previously published randomly controlled trial conducted in the United States (US). These patients underwent elective coronary artery bypass grafting (CABG), valve replacements, or ascending aortic surgery with a mix of utilizing cardiopulmonary bypass (CPB). The average age of the participants enrolled was 67 years. Cummings et al. (2019) reported 3.5% (n=14) of the sample met the primary endpoint of moderate to severe (Stage 2-3) AKI within 48 hours postoperatively.

NephroCheck® cut-off risk score of greater than 0.3, was used to assess the risk for this endpoint. They also reported that an additional 19.3% (n=77) developed a stage 1 AKI postoperatively. Across any AKI staging, 22.8% of the participants (n=91) developed a surgical-associated AKI. Cummings et al. (2019) incidence findings were the lowest of the fifteen studies regarding development of Stage 2-3 AKI. However, Kanchi et al. (2023) found the lowest incidence rate of development of any stage AKI at 14.4% in their off-pump CABG surgical cohort.

Gunnerson et al. (2016) studied a multinational, multisite cohort of patients from the US and Europe. This study combined 375 surgical patients from previously studied cohorts over 39 sites in the Sapphire study (Kashani et al., 2013) and Topaz study (Bihorac et al., 2014). These patients underwent a mix of cardiothoracic and non-cardiothoracic surgeries. They reported 9.3% (n=35) experienced the primary endpoint of moderate to severe (Stage 2-3) AKI within 12 hours of surgery, utilizing KDIGO staging criteria (2012). The average age of the participant experiencing moderate to severe AKI was 67 years, while the average age of the participant not experiencing AKI was 64 years. The prespecified cut-off risk score of 0.3, was used to attempt to identify moderate to severe AKI (Stage 2-3) patients with biomarkers.

Oezkur et al. (2017) studied 150 surgical patients in Germany. These patients underwent elective CABG, valvular surgeries both reconstructions or replacements, a combination of the former, or thoracic aortic surgery all involving CPB. The median age of this sample was 67 years old. They reported an incidence of 23.3% (n=35) experiencing an AKI within 48 hours of surgery. They further categorized this as 18% (n=27) and 5.3% (n=8) experiencing Stage 1 AKI or Stage 2-3 AKI respectively. Like Gunnerson et al. (2016), Oezkur et al. (2017) used the traditional cut-off risk score of 0.3 to identify at risk patients with the NephroCheck® tool.

Also studying German surgical patients, Gocze et al. (2015) enrolled 107 patients receiving major non-cardiac surgery including hepatobiliary, transplant, cancer, vascular, and

trauma procedures, with an average age of 60. They reported an incidence of 42.1% (n=45) that developed any stage AKI postoperatively. They further categorized this as 19.6% (n=21) experiencing a Stage 1 AKI and 22.4% (n=24) as experiencing a Stage 2-3 AKI using the KDIGO criteria (2012). In line with the previous two studies, Gocze et al. (2015) also used a cut-off risk score of 0.3 to identify at-risk patients for moderate to severe AKI (Stage 2-3).

Pilarcyzk et al. (2022) also studied 101 German patients requiring thoracic aortic surgery with moderate hypothermic circulatory arrest. Later in the chapter, another study by Pilarcyzk et al. (2015) with a smaller cohort is noted for patients requiring CPB. In this larger study (Pilarcyzk et al., 2022), the average age of no AKI or Stage I AKI patients was found to be 69; while the average age of moderate to severe AKI (Stage 2-3) patients was 73. Their primary endpoint was development of moderate to severe AKI (Stage 2-3) within 48 hours. Pilarcyzk et al. (2022) describe findings of 31.7% (n=27) incidence of any AKI. Using KDIGO staging criteria (2012), they further categorize this incidence as 13.9% (n=14) and 12.9% (n=13) for AKI Stage 1 and AKI Stage 2-3 respectively.

Finge et al. (2017) studied 93 French patients undergoing elective and non-elective CABG, valve replacement, and thoracic aortic procedures with CPB. The ages of this sample ranged from 62 to 81 years old. They reported an incidence of 36.6% (n=34) of patients experiencing any stage AKI within the first 48 hours postoperatively. In attempts to identify these at-risk patients, the researchers utilized different cut-off values (0.3, 0.5, and 2) for testing.

Also studying 93 patients, Waskowski et al. (2021) enrolled Swiss patients at a single site undergoing emergent or elective open abdominal aortic surgery with infra- or suprarenal clamping. The average age of this sample was 69 years old. They reported an incidence of 33.3% (n=31) any stage AKI postoperatively. Using KDIGO criteria (2012), they further categorized the patients into 21.5% (n=20), 6.5% (n=6), and 5.4% (n=5) experiencing Stage 1, 2, and 3 AKI respectively. Urinary TIMP-2*IGFBP7 biomarkers were used to identify these at-

risk patients utilizing the cut-off points of 0.3 and 2.0 for AKI Stage 1 and AKI Stage 2-3 respectively.

The most recent study included in this review was conducted in India by Kanchi et al. (2023) enrolling a 90-patient cohort requiring off-pump CABG. The average age of this surgical cohort was 53 years. As reported earlier, these researchers noted the smallest incidence of any stage AKI development at 14.4% (n=13) of the cohort. This incidence was further categorized as 6.7% (n=6) and 7.8% (n=7) for development of AKI Stage 1 and AKI Stage 2-3 respectively. Kanchi et al. (2023) employed a cut-off value of 0.3 for NephroCheck results indicating any stage AKI. Other studies included in this review utilized this same cut-off only to indicate development of moderate to severe AKI (Stage 2-3).

Zaouter, Priem et al. (2018) enrolled 62 patients in France undergoing transcatheter aortic valve implantation (TAVI) procedures. The average age of this cohort was 80 years old. They reported a 35.5% (n=22) incidence of any stage AKI development postoperatively. The majority of AKI development was Stage 2-3 with 33.9% (n=21) and only 1.6% (n=1) experiencing Stage 1 AKI.

Pilarczyk et al. (2015) studied 60 patients in Germany undergoing CABG utilizing CPB. The average age of this sample was 69 years for no-AKI or Stage 1 AKI and 76 years for Stage 2-3 AKI. They reported a 31.7% (n=19) incidence of any stage AKI within 48 hours postoperatively. The cut-off of 0.15 at 4 hours postoperatively and 0.89 on postoperative day 1 (POD 1) was used for NephroCheck® identification of the reported 10% (n=6) of patients that experienced a Stage 2-3 cardiac surgery-associated AKI (CSA-AKI).

In China, Wang et al. (2017) enrolled 57 patients undergoing mitral valve replacement (MVR), aortic valve replacement (AVR), CABG, or valvuloplasty procedures with or without the use of CPB. The average age of this sample was 60 years old. Within 7 days following surgery, Wang et al. (2017) reported an incidence of 35.1% (n=20) any AKI development. They further

categorized these patients as 24.6% (n=14) and 10.5% (n=6) as experiencing a Stage 1 AKI and Stage 2-3 AKI respectively.

Meersch et al. (2014) enrolled 50 patients in Germany undergoing cardiovascular surgery utilizing CPB. The average age of this cohort was 71 years old. They reported 52% (n=26) experienced any stage AKI postoperatively. Using the KDIGO staging criteria (2012), they found a 38% (n=19) incidence of Stage 1 AKI and 14% (n=7) incidence of Stage 2-3 CSA-AKI. NephroCheck® urine assay was used to measure the biomarkers with a cut-off point of 0.5 to indicate the potential for any stage AKI development.

Also studying a cohort of 50 patients, Zaouter, Potvin et al. (2018) enrolled patients in France undergoing elective CABG, AVR, MVR, aortic surgery, or a combination of these utilizing CPB. Zaouter, Potvin et al. (2018) found the highest incidence rate of 74% AKI development after elective cardiac surgery utilizing cardiopulmonary bypass, of all the studies. They reported 32% (n=16) experienced a Stage 2-3 CSA-AKI. These researchers used the traditional cut-off risk assessment score of 0.3 when utilizing NephroCheck®.

Enrolling 42 patients in Germany with an average age of 72 years old, Wetz et al. (2015) studied AKI development after elective and non-elective CABG utilizing CPB. They reported a 38.1% (n=16) incidence of any stage AKI development. They further reported a 31% (n=13) incidence of Stage 1 AKI development and 7.1% (n=3) development of Stage 2-3 CSA-AKI. This team evaluated two cut-off values of 0.3 and 2 for biomarker measurement.

Lastly, Dusse et al. (2016) enrolled 40 patients in Germany undergoing TAVI procedures either by transaortic or transapical approach. The average age of this sample was 81 years. They reported an incidence of 37.5% (n=15) development of any stage AKI within 48 hours postoperatively. They further categorized this incidence as 17.5% (n=7) Stage 1 AKI and 20% (n=8) incidence of Stage 2-3 AKI development. This team assessed both a 24 hour max value cut-off score of 0.91 and a cut-off score of 1.03 on POD 1 for measurement of uTIMP-2*IGFBP7 to indicate risk of AKI development.

AKI Identification

The universally accepted standard for AKI diagnostic criteria is the Kidney Disease: Improving Global Outcomes Clinical Practice Guidelines (KDIGO, 2012). These guidelines (see Appendix B) assess serum creatinine (SCr) values along with urine output for designating both the criteria for AKI diagnosis and staging. AKI is defined by any of the following: 1) an increase in SCr by greater than or equal to 0.3 mg/dL within 48 hours; 2) an increase in SCr to greater than or equal to 1.5 times the baseline SCr, which is known or presumed to have been drawn within the prior week; or 3) urine volume less than 0.5 mL/kg/h for 6 hours (KDIGO, 2012).

Stage 1 AKI is defined as a SCr 1.5 to 1.9 times the baseline value or greater than or equal to 0.3 mg/dL (greater than or equal to 26.5 μmol/L) increase in the SCr value along with a decline of urine output (UOP) of less than 0.5 mL/kg/h for 6 to 12 hours (KDIGO, 2012). Moderate (Stage 2) AKI is defined as SCr 2 to 2.9 times the baseline value and decreased UOP of less than 0.5 mL/kg/h for more than 12 hours (KDIGO, 2012). Lastly, a severe (Stage 3) AKI is defined as 3 times the baseline SCr, an increase in SCr to greater than or equal to 4.0 mg/dL (greater than or equal to 353.6 μmol/L), or initiation of renal replacement therapy along with severely decreased UOP (less than 0.3 mL/kg/h for more than 24 hours) or anuria for greater than 12 hours (KDIGO, 2012).

The novel method for identification of risk for developing moderate to severe (Stage 2-3) AKI involves assessing novel renal inflammatory biomarkers. Urine tissue inhibitor of metalloproteinase-2 and insulin-like growth factor binding protein 7 (uTIMP-2*IGFBP7) are the two renal biomarkers assessed in the FDA-approved NephroCheck® urine assay. These two biomarkers are expressed by renal tubular epithelial cells during periods of stress. Their expression indicates early tubule injury (Massoth et al., 2019), results in G1 cell cycle arrest to help prevent potentially damaged cells from dividing and helps to spread the alarm to nearby cells of possible injury (Kashani et al., 2013).

Novel Biomarker Utilization

Of the fifteen studies identified in this review, only one study was conducted solely in the United States (Cummings et al., 2019). A second study was a mixed site study of the US and Europe (Gunnerson et al, 2016). Both studies had large cohorts, 400 and 375 respectively. Cummings et al. (2016) studied a mix of on and off pump cardiovascular surgical participants while Gunnerson et al. (2016) studied a larger variety of surgeries admitted to the ICU including cardiovascular and non-cardiovascular procedures. The remaining thirteen studies were conducted across Germany, France, Switzerland, China, and India (see Appendix D).

All studies used a prospective cohort design of adult surgical patients. Samples ranged from 40 to 400 patients, with a mean of 118 patients. Overall, the mean age of the samples was greater than 60 years of age with participants in the studies age ranging from 44 to 87 years. Thirteen of the fifteen studies focused only on cardiac surgery-associated AKI. Procedures categorized in the review as cardiac surgery include either transcatheter aortic valve implantation (TAVI) procedures (Dusse et al., 2106; Zaouter, Priem et al., 2018), emergency or elective abdominal aortic surgery with clamping (Waskowski et al., 2021), and mixed cohorts of CABG, MVR, AVR, valvuloplasty, thoracic aortic repair, and ascending aortic repair with or without the use of CPB (Cummings et al., 2019; Finge et al., 2017; Kanchi et al., 2023; Meersch et al., 2014; Oezkur et al., 2017; Pilarczyk et al., 2015; Pilarczyk et al., 2022; Wang et al., 2017; Wetz et al., 2015; Zaouter, Potvin et al., 2018). As stated previously, Gunnerson et al. (2016) studied a mix of cardiovascular and non-cardiovascular surgeries. The only study in this review that focuses on non-cardiac surgery was conducted on 107 participants for hepatobiliary, transplant, cancer, vascular, or severe trauma surgeries (Gocze et al., 2015).

All studies used KDIGO 2012 guidelines for diagnosing AKI by SCr and urine output, as well as NephroCheck® to assess uTIMP-2*IGFBP7 levels. The NephroCheck® is the only FDA test approved device to assess these renal biomarkers. Usefulness of the novel renal biomarkers uTIMP-2*IGFBP7 are categorized into marginal and good usefulness. In ROC

analysis, the area under the curve (AUC) is an index of the performance of a screening measure, relating sensitivity and specificity (Polit & Yang, 2016). This method of analysis is commonly used when assessing a measure compared to a gold standard. Marginal usefulness will include both poor and fair performance. For studies utilizing area under the operating curve (AUROC) to assess this usefulness, poor validity is found when the curve is close to the diagonal (AUROC of 0.5) whereas, a score of 1.0 is the most desirable (Polit & Beck, 2017). For this review poor to fair performance is defined as AUROC values of 0.5 to 0.79 and good to excellent performance is defined as AUROC values of 0.8 or greater.

uTIMP-2*IGFBP7 Usefulness

Seventeen different time points or time ranges were assessed across these fifteen studies for uTIMP-2*IGFBP7 biomarker levels (see Figure 1). These seventeen time points included either preoperatively or at induction of general anesthesia, 30 minutes after the start of CPB intraoperatively, at the end of CPB intraoperatively, at intensive care unit (ICU) or post anesthesia care unit (PACU) admission postoperatively, at 1 hour, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 10 hours, 12 hours, 24 hours postoperatively, twice daily every 12 hours postoperatively, POD 1, POD 2, and POD 3. The most frequently assessed time points were preoperatively or upon induction of general anesthesia, admission to the ICU or PACU after surgery, 4 hours postoperatively, 12 hours postoperatively, 24 hours postoperatively, and on POD 1.

The studies varied with regards to a primary endpoint. Some only included advanced Stage 2 or 3 AKI, based on KDIGO (2012) guidelines, while others included development of any stage AKI after surgery. There was also great variation in the cut-off values for the NephroCheck® risk score evaluation and interpretation. The FDA intended use of NephroCheck® is to use a cut-off value of greater than 0.3 to indicate risk of developing a Stage 2 or 3 AKI (Astute Medical, 2017). Characteristics of the studies included in the review can be found in Appendix D.

Marginal Usefulness of uTIMP-2*IGFBP7. As seen in Table 2, eight studies found uTIMP-2*IGFBP7 to have poor or fair usefulness for identifying risk of AKI development at individual time points on the day of surgery with AUROC values ranging from 0.52 to 0.78 (Cummings et al., 2019; Dusse et al., 2016; Finge et al., 2017; Kanchi et al., 2023; Pilarczyk et al., 2022; Waskowski et al., 2021; Zaouter, Potvin et al., 2018; Zaouter, Priem et al., 2018). Cummings et al. (2019) found a performance of 0.71 intraoperatively at the completion of CPB to identify Stage 2-3 AKI. Waskowski et al. (2021), Zaouter, Priem et al. (2018), and Cummings et al. (2019) all studied performance at post-procedure or admission to ICU time points. Waskowski et al. (2021) found the lowest AUROC performance of uTIMP-2*IGFBP7 postoperative at 0.52 following elective or emergency open abdominal aortic surgery. Zaouter, Priem et al. (2018) and Cummings et al. (2019) reported performance of 0.66 and 0.68 respectively at this same assessment time point. In looking at postoperative time periods of 2 hours, Pilarczyk et al. (2022) found performance of 0.74. At 3 hours postoperatively, Finge et al. (2017) found performance of the biomarkers to be 0.73. At 4 hours postoperatively Dusse et al. (2016), Kanchi et al. (2023), and Pilarczyk et al. (2022); performance was noted as 0.65, 0.6, and 0.72 in cardiac surgical patients. At 6 hours (Cummings et al., 2019), and 12 hours (Zaouter, Potvin et al., 2018); performance was noted as 0.78, and 0.69 respectively. Despite Pilarczyk et al. (2022) reporting marginal performance at 2 and 4 hours postoperatively (0.74 and 0.72), the ability of uTIMP-2*IGFBP7 to marginally identify those at risk of AKI development still outperformed SCr (AUROC 0.69).

Additionally, five studies found uTIMP-2*IGFBP7 to have marginal usefulness on POD 1; however, the exact times are not known. On POD 1 Wetz et al. (2015) and Zaouter, Priem et al. (2018) both identified AUROC values of 0.71 and Waskowski et al. (2021) found 0.60. These three studies all assessed the same endpoint of any AKI. Whereas Cummings and colleagues (2019) and Pilarczyk et al. (2022) assessed only Stage 2-3 AKI on POD 1 and found a

performance value of 0.75 and 0.54 respectively. Wetz et al. (2015) showed the markers could not predict the occurrence of AKI or discriminate between mild and advanced stages of AKI.

Good Usefulness of uTIMP-2*IGFBP7. As seen in Table 3, eight studies found the biomarkers to have good performance within the first 24 hours after surgery with AUROC values ranging from 0.8 to 0.98 (Cummings et al., 2019; Dusse et al., 2016; Gocze et al., 2015; Gunnerson et al., 2016; Meersch et al., 2014; Pilarczyk et al., 2015; Wang et al., 2017; Waskowski et al., 2021). Oezkur and colleagues (2017) reported odds ratio findings that further demonstrated good performance of these biomarkers.

One strategy that researchers utilized was to accept the max value of uTIMP-2*IGFBP7 across serial testing to ascertain risk scores. Four studies utilized this method. Cummings et al. (2019) found a performance of 0.82 using the patient's max value of biomarkers between intraoperative and 6 hours postoperative serial testing in a 400-participant mixed cardiac surgical cohort. Pilarczyk et al. (2015) reported an AUROC value of 0.84 for the max value of biomarkers within 24 hours for a 60-participant cohort undergoing CABG utilizing CPB. Dusse et al. (2016) found a performance of 0.87 utilizing the max value in a 24-hour period postoperatively in 40 patients undergoing TAVI procedures. Lastly, Meersch et al. (2014) studied 50 cardiac surgical patients utilizing CPB and found the highest performance of 0.90 utilizing this method assessing the max value of biomarker expression over a 24-hour period postoperatively. These four studies were all conducted in cardiac surgery cohorts.

In looking at individual time points of 4 hours after CPB (Meersch et al., 2014) and admission to ICU (Gocze et al., 2015), performance values were found as 0.81 and 0.85 respectively. Gocze and colleagues (2015) was the only study out of the fifteen included in this review that utilized a non-cardiac surgical sample, including 107 participants receiving hepatobiliary, transplant, cancer, vascular, and trauma procedures, with an average age of 60. Assessing 4 hours postoperatively, Wang et al. (2017) found performance to be 0.80 for any AKI stage and 0.83 for moderate to severe (Stage 2-3) AKI in a cohort of 57 mixed valvular and

CABG patients. Pilarczyk et al. (2015) also evaluated 4 hours postoperative biomarker levels in 60 CABG patients and found performance to be 0.86. They compared this finding to the traditional method of using SCr at 4 hours postoperatively, which revealed a much lower diagnostic accuracy with a performance of only 0.36 this early in the inflammatory process supporting the finding that SCr is a late marker (Pilarczyk et al., 2015). Lastly, at 12 hours postoperatively, Gunnerson and colleagues (2016) found biomarker performance to be 0.84. In expanding the assessment time points to POD 1, Pilarczyk et al. (2015), Dusse et al. (2016), and Waskowski et al. (2021), found performance values of 0.87, 0.97, and 0.98 respectively. Pilarczyk and colleagues (2015) again demonstrate the poor ability of SCr to early identify advanced stage AKI on POD 1 in contrast to the novel biomarkers with a performance of only 0.69. Dusse and colleagues (2016) also reported poor performance of SCr on POD 1 of only 0.63. Additionally, not assessing AUROC values, Oezkur et al. (2017) reported odds ratio findings that further support the biomarker having accurate predicting abilities for AKI following cardiac surgery at ICU admission.

In summary, the three studies reporting the highest performance include Waskowski et al. (2021), Dusse et al. (2016), and Cummings et al. (2019). Waskowski et al. (2021) found POD 1 marker performance to be the highest at 0.98 for Stage 3 AKI only; however, they caution the high risk of bias in a sample of only 5 participants. Biomarker performance was noted to be lower when including lesser staged AKIs. Dusse et al. (2016) also found POD 1 marker performance to be high (AUROC 0.971) with 100% specificity to predict advanced stage AKI; compared to serum creatinine (AUROC 0.629). Cummings et al. (2019) demonstrated 100% sensitivity in marker performance among cardiac patients post CPB, meaning all true AKI cases were identified by NephroCheck®. Dusse et al. (2016) also demonstrated findings of 100% sensitivity in marker performance following TAVI cardiac procedures. Cummings and colleagues (2019) reported a 100% negative predictive value (NPV), indicating the biomarkers can also be used to accurately predict patients that will not experience AKI at this given threshold. These

findings further indicated that uTIMP-2*IGFBP7 could detect AKI stage 2-3 (KDIGO, 2012) at admission to ICU, while SCr could not (Cummings et al., 2019). The biomarker was more useful than SCr and urine output at predicting moderate to severe AKI (Stage 2-3) development within 12 hours of surgery (Gunnerson et al., 2016) and within 72 hours of transapical or transaortic aortic valve implantation (Dusse et al., 2016).

Gaps in the Literature

Overall findings from this review of the literature suggest these biomarkers have good sensitivity for indicating risk of developing AKI between 4 to 24 hours postoperatively. Although limitations of this review include small sample size, single site studies, and utilization of different end points such as any AKI or only advanced Stage 2-3 AKI. Additionally, the seventeen studied time points across these studies overlap. For some patients, depending on the end of their surgery, the 12 hours postoperative time point may have occurred on POD 1. This overlap may confound findings.

There is an abundance of data supporting the use of these early risk assessing biomarkers in adult surgical populations. There is an even split among the included studies showing marginal or good usefulness of uTIMP-2*IGFBP7 at different time points, indicating the need for further research in additional populations of surgical patients. Eight studies utilized AUROC values and found performance scores from 0.80 to 0.98 at various time points (Cummings et al., 2019; Dusse et al., 2016; Gocze et al., 2015; Gunnerson et al., 2016; Meersch et al., 2017; Pilarczyk et al., 2015; Wang et al., 2017, & Waskowski et al., 2021) and one study reported odds ratio findings that supported good performance (Oezkur et al., 2017). However, the literature was lacking in funded research in the US conducted through the lens of anesthesia impacting perioperative AKI and any anesthetic-related confounding variables.

Thirteen of the fifteen studies included in this review conducted research in cardiac surgical patients, some involving CPB, a known inflammatory process. There is limited research utilizing NephroCheck® risk assessment to identify AKI in other major surgical categories. Of

the nine studies that show good usefulness of uTIMP-2*IGFP7, only two included non-cardiac surgical patients; Gocze et al. (2015) with a complete cohort of non-cardiovascular surgical participants and Gunnerson et al. (2016) with a mixed surgical population including some cardiothoracic surgeries.

During this review it was also noted that there is limited data on adult patients from 20 to 50 years of age. Most of the studies were conducted with older aged samples and the results may not be generalizable based on the probability of older patients having increased numbers of confounding comorbidities.

Summary

This review of the literature identified fifteen primary quantitative studies utilizing urine TIMP-2*IGFBP7 via the NephroCheck® as an early risk assessment for development of perioperative AKI in adult surgical patients. Comparative incidence rates between non-cardiac and cardiac surgery associated AKI were found in the review. Study results were categorized either as marginal or good usefulness of renal biomarkers to identify AKI at seventeen different perioperative time points. However, primary endpoints and cut-off risk scores varied greatly across the studies. This review demonstrates the renal tissue specificity of uTIMP-2*IGFBP7 and that the biomarkers have high sensitivity for identifying AKI like the gold standard SCr.

The timeliness of identifying AKI is crucial. Nine studies included in this review found good performance of these biomarkers indicating injury more quickly than the gold standard SCr. Additional studies exploring ideal time points for the measurement of uTIMP-2*IGFBP7 to identify surgical-associated AKI in other major non-cardiac surgical populations are warranted.

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Table 1

AKI Development in Sample Populations from Articles Reviewed

Study	Sample n	Any AKI n	Stage 1 AKI n	Stage 2-3 AKI n
Cummings, 2019	400	91 (22.8%)	77 (19.3%)	14 (3.5%)
Dusse, 2016	40	15 (37.5%)	7 (17.5%)	8 (20.0%)
Finge, 2017	93	34 (36.6%)		
Gocze, 2015	107	45 (42.1%)	21 (19.6%)	24 (22.4%)
Gunnerson, 2016	375			35 (9.3%)
Kanchi, 2023	90	13 (14.4%)	6 (6.7%)	7 (7.8%)
Meersch, 2014	50	26 (52.0%)	19 (38.0%)	7 (14.0%)
Oezkur, 2017	150	35 (23.3%)	27 (18.0%)	8 (5.3%)
Pilarczyk, 2015	60	19 (31.7%)	13 (21.7%)	6 (10.0%)
Pilarczyk, 2022	101	27 (26.7%)	14 (13.9%)	13 (12.9%)
Wang, 2017	57	20 (35.1%)	14 (24.6%)	6 (10.5%)
Waskowski, 2021	93	31 (33.3%)	20 (21.5%)	11 (11.8%)
Wetz, 2015	42	16 (38.1%)	13 (31.0%)	3 (7.1%)
Zaouter, Potvin, 2018	50	37 (74.0%)	21 (42.0%)	16 (32.0%)
Zaouter, Priem, 2018	62	22 (35.5%)	1 (1.6%)	21 (33.9%)

Note. AKI = acute kidney injury; stages based on KDIGO (2012) guidelines.

Table 2

*Marginal Usefulness of uTIMP-2*IGFBP7 in Reviewed Articles*

Study	Time Point	Performance (AUROC)	Assessing
Cummings, 2019	Post CPB	0.71	AKI Stage 2-3
	ICU admission	0.68	AKI Stage 2-3
	6 hr postoperative	0.78	AKI Stage 2-3
	POD 1	0.75	AKI Stage 2-3
Dusse, 2016	4 hr postoperative	0.65	AKI Stage 2-3
Finge, 2017	3 hr postoperative	0.73	All AKI
Kanchi, 2023	4 hr postoperative	0.60	All AKI
Pilarczyk, 2022	2 hr postoperative	0.74	AKI Stage 2-3
	4 hr postoperative	0.72	AKI Stage 2-3
	POD 1	0.54	AKI Stage 2-3
Waskowski, 2021	ICU admission	0.52	All AKI
	POD 1	0.60	All AKI
Wetz, 2015	POD 1	0.71	All AKI
Zaouter, Potvin, 2018	12 hr postoperative	0.69	All AKI
Zaouter, Priem, 2018	Postprocedure	0.66	All AKI
	POD 1	0.71	All AKI

Note. AUROC = area under the operator curve; CPB = cardiopulmonary bypass; POD = post-operative day.

Table 3

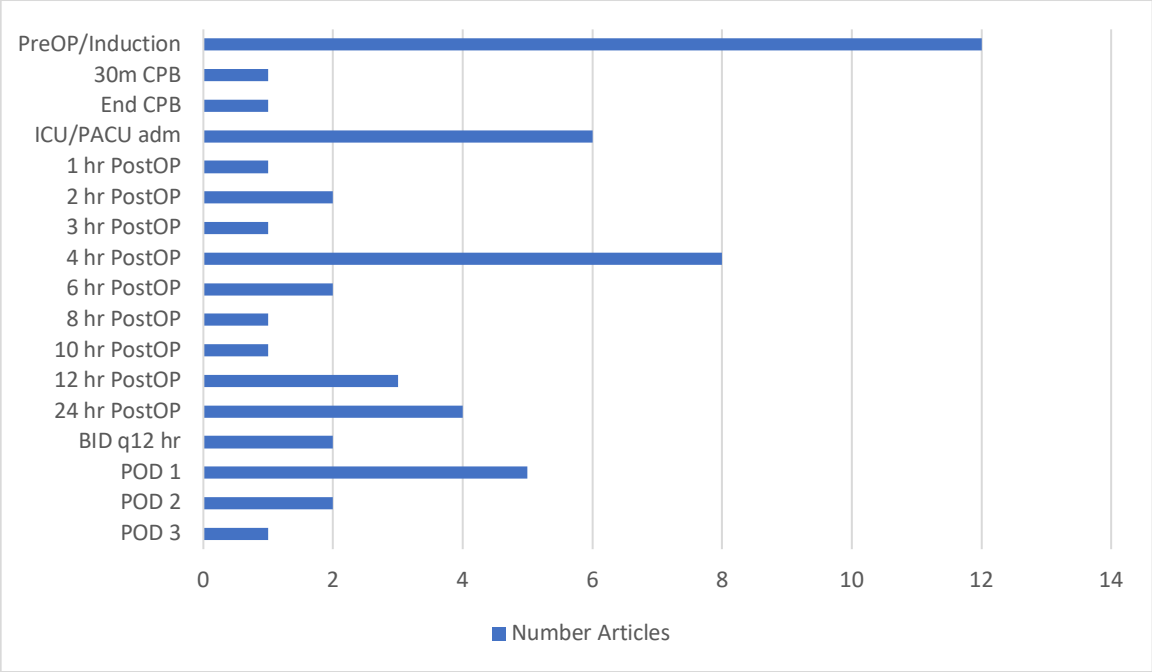
*Good Usefulness of uTIMP-2*IGFBP7 in Reviewed Articles*

Study	Time Point	Performance (AUROC)	Assessing
Cummings, 2019	Max value between intraoperative and 6 hr PostOP	0.82	AKI Stage 2-3
Dusse, 2016	Max value in 24 hr	0.87	AKI Stage 2-3
	POD 1	0.97	AKI Stage 2-3
Gocze, 2015	Admission to ICU	0.85	All AKI
Gunnerson, 2016	Within 12 hr PostOP	0.84	AKI Stage 2-3
Meersch, 2014	4 hr after CPB	0.81	All AKI
	Max value in 24 hr	0.90	All AKI
Pilarczyk, 2015	4 hr PostOP	0.86	AKI Stage 2-3
	POD 1	0.87	AKI Stage 2-3
	Max value within 24 hr	0.84	AKI Stage 2-3
Wang, 2017	4 hr PostOP	0.80	Any AKI
	4 hr PostOP	0.83	AKI Stage 2-3
Waskowski, 2021	POD 1	0.98	AKI Stage 3

Note. AUROC = area under the operator curve; PostOP = postoperatively; POD = postoperative day; CPB = cardiopulmonary bypass.

Figure 1

*uTIMP-2*IGFBP7 Measurement Time Points Across the Reviewed Studies*



Note. PreOP = preoperatively; CPB = cardiopulmonary bypass; PostOP = postoperatively; BID = twice daily; POD = post-operative day.

CHAPTER 3: METHODS

Introduction

Chapter three reviews the methodology to study the association between major non-cardiac intraabdominal surgeries and the early identification of risk for AKI development using the NephroCheck® urine assay for urinary tissue inhibitor of metalloproteinase-2 and insulin-like growth binding protein 7 (uTIMP-2*IGFBP7). This includes the study design, setting, sample, protection of human subjects, instruments, enrollment and data collection procedures, and data management and analysis procedures. A discussion of limitations is included along with a concluding summary.

Design

A cross-sectional, nonexperimental (observational) descriptive correlational design was used to investigate the aims of this study. The first aim of this study is to explore the association between major non-cardiac intraabdominal surgery and the incidence of AKI. The second aim of this study is to evaluate the effectiveness of the NephroCheck® urine assay for uTIMP-2*IGFBP7 in early identification of risk for developing moderate to severe AKI in major non-cardiac intraabdominal adult surgical patients. According to Polit and Beck (2017), an observational correlation design is suited to studying the association between AKI development and major intraabdominal surgery, as this design is primarily used to examine relationships among variables of interest.

Setting

The site of this research is a level I trauma center with 974 beds in the southeastern US. There are 26 operating room suites in the main surgical area of this facility. Once enrolled in the study, the participants underwent intraabdominal surgery and were followed by the principal investigator (PI) during their postoperative recovery. All NephroCheck® urine specimen preparation and lab testing were completed in a locked research wet lab in the College of Nursing (CON) at East Carolina University (ECU). The PI and Faculty Advisor had completed

safety training and had keyed access to this lab. All research was conducted at a private bench space with private supplies and tools.

Sample

After obtaining the appropriate Institutional Review Board (IRB) approval (see Appendix E), a convenience sample of adult patients undergoing major non-cardiac intraabdominal surgical procedures was recruited from the partnering clinical agency. This included an aggregate sample of participants which are patients of multiple surgical groups who were scheduled to undergo major non-cardiac intraabdominal surgery across different specialties.

Inclusion criteria were patients greater than or equal to 21 years of age, based on FDA approval for intended use of the measure (Astute Medical, 2017); participants undergoing major non-cardiac intraabdominal surgery, English speaking, and cognitively intact and able to consent for participation. Major non-cardiac surgery was defined as an operation upon an organ within the chest, cranium, abdomen, or pelvic cavity (Merriam-Webster, n. d.). Exclusion criteria included trauma and emergency surgical patients, those with history of renal transplantation, any currently COVID-19 positive patients, patients undergoing current chemotherapy, and those with significant proteinuria (urinary albumin greater than 125mg/dL), hyperbilirubinuria (urinary bilirubin greater than 7.2 mg/dL), or elevated methylene blue concentrations (urine concentration greater than 0.49mg/L).

In considering sample size, Gocze et al. (2015) reported a 22.4% Stage 2-3 AKI incidence rate in major non-cardiac surgical patients. Using this prevalence value with a 5% margin of error, and a confidence level of 80%, the sample size was calculated to be a minimum of 113 participants (Maple Tech International LLC, 2021). Careful observation of operating room schedules and the PI's availability as the sole collector for samples were used to estimate enrollment. Each NephroCheck® test kit was estimated to cost $100. Due to the constraints of cost associated with a statistically powerful sample, this pilot study planned to enroll 80 participants. No incentives were offered during the study.

Human Subjects Protection

The PI and all members of this dissertation committee have completed the CITI modules on research ethics and compliance prior to the start of this research. After committee approval of the research proposal, this research was approved under expedited review by the UMCIRB (see Appendix E). This research involved no more than usual risk, as urine samples were drawn from a foley catheter that was placed as part of the patients' routine surgical care. A time extension was granted by the IRB in the Spring of 2023. Additionally, during the world-wide COVID-19 pandemic, this research plan was subject to a required COVID-19 risk assessment for human subject research review (see Appendix F). Due to direct patient contact it was deemed a medium exposure risk; however, we plan to exclude any COVID-19 positive patients.

Instruments

To evaluate the variables of interest in this study a researcher-developed data collection tool was used to collect data from the intake interview and for a thorough postoperative chart review (see Appendix C). Serum creatinine (SCr) lab values were drawn as part of the participants' routine surgical care. These values were reviewed as the gold standard for meeting criteria of AKI diagnosis (KDIGO, 2012), along with postoperative urine output. Lastly, the NephroCheck® urine assay for uTIMP-2*IGFBP7 was utilized to assess urine samples drawn from the patients' foley catheters at three time points perioperatively. This risk assessment tool was used as the novel method of assessing risk for developing moderate to severe AKI (Stage 2-3). These three instruments will be discussed in greater detail.

Data Collection Tool

This tool encompasses collection of socio-demographics, preoperative assessment of vital signs, medication history, health history, surgical history, perioperative record to assess for known causes of AKI, post-operative record, and laboratory data. These were ascertained from intake interviews and chart review by the PI using the researcher-developed data collection tool (see Appendix C). Preoperative history and physicals documented by attending physicians were

reviewed, along with preoperative nursing, anesthesia, and recovery nursing documentation the day of surgery and throughout the patient admission in the electronic medical record (EMR).

Serum Creatinine

AKI was measured in a traditional diagnostic way and a novel risk identification way. The traditional operational definition of AKI utilizes the 2012 KDIGO Clinical Practice Guidelines to diagnose AKI. Criteria for AKI diagnosis is defined by any of the following: 1) an increase in SCr by greater than or equal to 0.3 mg/dL within 48 hours; 2) an increase in SCr to greater than or equal to 1.5 times the baseline SCr, which is known or presumed to have been drawn within the prior week; or 3) urine volume less than 0.5 mL/kg/h for 6 hours (KDIGO, 2012). The three stages of AKI severity are also defined by the KDIGO guidelines (2012) (see Appendix B).

NephroCheck®

The novel operational definition of AKI utilizes the NephroCheck® urine assay test for urinary tissue inhibitor of metalloproteinase-2 and insulin-like growth factor binding protein 7 (uTIMP-2*IGFBP7). When exposed to stress, renal tubular epithelial cells that normally undergo a cell-cycle will arrest for a short period as a self-protection mechanism and will express uTIMP-2*IGFBP7 into the urine (Massoth et al., 2019). NephroCheck® urine assay is the only FDA approved test using novel renal biomarkers for identifying risk of developing moderate to severe AKI. A risk assessment score of greater than 0.3 is indicative of a high risk for developing moderate to severe (Stage 2-3) AKI within the next 12 hours (Astute Medical, 2017).

The validity of the clinical performance of NephroCheck® was evaluated over two studies conducted in the United States at various geographical locations. The evaluation enrolled intended use patients only; with a cohort of 408 for Study A and 126 for Study B (Astute Medical, 2017). Urine specimens from each subject in Study A were measured at three independent labs during the evaluation; however, each laboratory was missing an AKI Risk Score from one subject, thus 407 participants were evaluated in total (Astute Medical, 2017). Table 1 displays the test operating characteristics of clinical performance reported by Astute

Medical. Despite an average 50% false positive rate, this instrument was FDA approved for use to identify risk of moderate to severe AKI development.

Procedures

Enrollment

Eighteen attending physicians that routinely complete major non-cardiac intraabdominal surgeries were identified, informed about the study, and gave their signature of consent for their patients to be approached about the study (see Appendix G). The attending surgeons identified appropriate type cases for the study and alerted their staff to potential participants. The procedure for enrollment began with the surgical nursing staff, nurse practitioner (NP), physician assistant (PA), medical fellows, or the surgeon approaching eligible participants prior to their surgery. For the purpose of this study, they will be identified as the surgical team providers (STP). The PI trained all participating STPs prior to enrollment on how to approach potential patients (see Appendix H) and gave them an introduction script to follow (see Appendix I). After reading this script, the STPs gave interested potential participants an informational flyer describing the study (see Appendix J). This study flyer contained information about the planned research, provided details that the research would not alter their care in any way, would not cost them any money, described how collected data would remain protected, and provided contact information for the PI.

Once participants gave their assent for the PI to contact them, their contact information was documented by the STP on the participant communication log (see Appendix K). STPs stored these logs in a secured locked location in their office. The PI communicated with STPs and collected these logs regularly. The logs were stored safely with other study materials in a double locked lab, as noted in the following data management section. The PI contacted each potential participant either verbally by phone or in person to validate eligibility and to answer questions about the study prior to their scheduled surgery. The eligibility questionnaire may be viewed in Appendix L. The PI also kept a communication log with all potential participants (see

Appendix M). When a patient expressed interest in participating, the PI met with them the day of surgery to obtain written informed consent for participation in the study (see Appendix N) per the requirements of the IRB committee. Electronic consent forms were not currently permitted by the committee at the beginning of this research. This process occurred in the preoperative setting the day of their surgery prior to the administration of any sedative medications. After informed consent was obtained, a study flag was added to the patient's EMR and a hard copy placed in the physical surgical folder chart to alert care providers to the process (see Appendix O).

Prior to data collection the PI received hands-on training with the ECU Department Chair of the Clinical Lab Science Department pertaining to proper specimen handling, testing, and storage (see Appendix P). The PI also received training from Biomerieux at the point of installation of the NephroCheck® meter, including quality control checks for the device and specimen testing procedures. The meter was verified and calibrated according to industry standards prior to any patient sample testing using verified samples from another regional agency (see Appendix Q). Quality control checks were completed regularly and documented, in accordance with acceptable procedures.

Data Collection

Data collection encompassed a presurgical phase, a perioperative phase, and a postoperative phase, which included an intake interview, collection of urine samples and testing, and a thorough review of the patients' EMR. The procedure workflow diagram for this study can be seen in Figure 1.

Written informed consent was obtained from each willing participant, followed by an intake interview. This interview regarding the patient's medical history was conducted by the PI prior to surgery. Sterile 10 mL urine samples for NephroCheck® uTIMP-2*IGFBP7 assays were collected at induction of general anesthesia after the urine foley catheter was placed, at 6 PM on the day of surgery, and between 6 AM and 7 AM postoperative day 1 (POD 1). These urine

samples were collected by the PI in the operating room and in-patient care units postoperatively. They were collected using sterile syringes from the sterile sample port site of the foley catheter after cleansing with an alcohol pad.

The samples of urine collected by the PI were labeled and deidentified for transportation in a marked biohazard cooler with ice pack to the locked research wet lab in the CON. Each urine sample was tested for high levels of protein and bilirubin by chemistry dipstick. These two substances in high concentrations are known to interfere with the test results (Astute Medical, 2017). If high levels of either were detected, the urine sample was considered ineligible for the study and was excluded. Urine chemstick controls were completed regularly.

Urine sample collection and preparation procedures according to the test package insert may be viewed in Appendix R. The manufacturer requires that the fresh urine samples be centrifuged within one hour of collection, unless kept on ice (Astute Medical, 2017). The PI mixed the urine samples by inverting the collection syringe 8 to 10 times. The sample was transferred to a labeled centrifuge tube and capped. In a refrigerated centrifuge set to “an rcf of 1000 x g and temperature of 4°C (39.2°F)” (Astute Medical, 2017, p. 4); each sample was centrifuged for 10 minutes. Once completed, the supernatant was transferred to a clean specimen 1.7 mL microtube and allowed to reach room temperature for testing or immediately refrigerated or frozen. Prior to NephroCheck® testing, supernatant samples may be stored for 5 hours at room temperature or 20 hours in the refrigerator. Due to these constraints, specimen collection times, centrifuge times, and testing times were entered onto the data collection tool (see Appendix C).

The testing procedures are described in the NephroCheck® package insert (Astute Medical, 2017) and may be viewed in Appendix S. The clinical lab scientist member of this committee oversaw meter installation and was integral to the planning of proper procedures. Test cartridges were stored at 2 to 8°C in the locked research lab refrigerator. The cartridge package was opened and allowed to reach the operating temperature of 18 to 25°C (64 to 77°F)

while the sample was prepared. After thawing, each sample was mixed again on a Vortex mixer for 8 to 10 seconds. With the use of a calibrated precision pipette, the PI added 100 µL of the NephroCheck® test buffer solution to the test conjugate vial supplied with the test kit, thus reconstituting the conjugate bead found in the vial. Then the PI used a new pipette tip to add 100 microliter (µL) of centrifuged urine supernatant to the liquid in the conjugate vial. After mixing thoroughly three times, a 100 µL sample was introduced to the NephroCheck® test cartridge. The PI then placed the test cartridge into the NephroCheck® meter drawer and closed the drawer to initiate the test. In approximately 20 minutes, the NephroCheck® meter produced a risk assessment score as noted previously in the instrument section (Astute Medical, 2017). Testing supplies were then discarded in accordance with lab regulations.

As part of the participants routine surgical orders, daily SCr levels were drawn until discharge. These results were obtained from the patient's EMR. Serum creatinine and NephroCheck® lab values were entered onto the data collection tool at each time point (see Appendix C).

In the postoperative phase, a thorough review of the patient's EMR was completed by the PI for each participant. Each participant was followed for 30 days postoperatively. Patient data extracted from the EMR as previously described in the instruments section was deidentified and entered into a secure electronic data base within ECU guidelines for proper data security. Raw data was entered into REDCap. Nursing, physician, and anesthesia records were all reviewed. If an arterial line was present, these blood pressures were documented, for all other cases non-invasive blood pressures were documented. The results tab of the EMR was reviewed for lab data, electrocardiograms, and imaging such as MRIs and CT scans.

A clinical vignette was developed for each participant detailing the course of events during admission but excluding the NephroCheck® risk scores. Adjudication by the board-certified Nephrologist member of this research team was performed for each participant to

determine whether an AKI was sustained and the injury was leveled using KDIGO guidelines (2012).

Data Management and Analysis

Data was transferred from REDCap into and analyzed with IBM SPSS (Version 27) predictive analytics software, in collaboration with the statistician of this committee. Data was stored on a password protected school-approved drive and in REDCap. REDCap data is stored on a secure server which is HIPAA and FERPA protected (ECU, 2021). All data was screened and checked for accuracy, as well as for any missing data and outliers.

In Chapter 5, descriptive statistics will be shared about patients' renal core structure including co-morbidities, history of AKI, patient demographics, anticipated surgery type, and any perioperative stressors.

To answer AIM 1, frequencies will be shared revealing incidence rates of AKI related to different major intraabdominal surgeries. Fisher's Exact test will identify any predictor variables that have a relationship to development of perioperative AKI.

To answer AIM 2, descriptive statistics will be analyzed to compare the traditional (SCr) and novel (NephroCheck®) methods of AKI identification by studying sensitivity, specificity, positive predictive value, and negative predictive value to assess the accuracy of our traditional and novel methods of identifying AKI.

After the conclusion of the study, the data will be transferred to the secured nursing research drive in the CON. REDCap data will then be wiped by ECU Information Technology and Computing Services (ITCS). Data will be stored for six years to allow for dissemination of research. Any paper data will be stored in a locked cabinet in the locked wet lab in the CON for 6 years and then will be cross shredded, in accordance with IRB requirements.

Limitations

One limitation related to external validity in this research design may be that inferences made about the observed relationship between type of surgery and incidence of AKI may not be

generalizable to all patients having that type of surgery. There are many variations in persons, settings, and time that confound these relationships. Anesthesia providers manage their cases in a variety of ways which was not controlled in this study, other than by use of the Colorectal Enhanced Recovery After Surgery (ERAS) Protocol for one surgery group at the partner institution for patient management. However, other tracts of intraabdominal surgeries are also included in this aggregate sample. It is known that many risk factors for development of AKI occur directly from anesthetic actions (McKinlay et al., 2018).

Another limitation of this study may be statistical conclusion validity, meaning reaching false statistically significant relationships between the independent and dependent variables or Type I error. To control for low statistical power, an increased confidence interval could be considered; however, this would also increase the sample size. Due to the constraints of cost associated with an increased sample size, this was not feasible. Small sample size lowers the statistical rigor of the study.

Surgical case volume is ever changing during the COVID-19 world pandemic with over filled hospitals and lack of ability to admit elective surgical patients. This had the potential to impact participant enrollment greatly, potentially extending the data collection phase of this research. Since COVID infections have been independently linked to AKI (Hardenberg et al., 2021), COVID positive patients were excluded.

Lastly, due to the PI being the sole collector of samples there is concern for lost data points of urine collection or testing. The PI made every attempt possible in her schedule to contact each eligible participant and gather each data point to limit missing data.

Discussion

The inception of this project began with the support of five attending surgeons, as seen in Appendix G, fifteen additional surgery teams were added to improve early low enrollments. These additions were reported to the IRB committee and approved. As PI, I went to each surgical office to provide the same educational training prior to any enrollment of patients from

those offices. In some cases, there were partnering surgeons within the same office that shared recruiting nursing staff. This approach broadened our population variety to include colorectal, gynecological, urological, bariatric, nephrology, transplantation, general, and oncology tracks of service.

During the study time frame, the process changed for submission of informed consent documents to the partnering clinical agency. The original process required the PI to scan each consent document and send to the medical records so the scanned document and a flag may be placed on the patient EMR. Part way through the study, this process was changed, and the PI was notified. I attended training to properly tag each EMR myself and upload the scanned consent form as a media document.

Thirty surgical days were used for patient enrollment between May 9th and October 25th of 2022. During this time, as stated earlier in the limitations, the world was experiencing the COVID-19 pandemic. Eleven of the 30 specific enrollment dates (37%) were deemed as either Yellow or Red capacity situations by the hospital. During the May to October time frame, 74 days (44%) were designated as Yellow capacity, Red capacity, or on two occasions Emergency Operations for the facility. Capacity and bed space most definitely affected surgery schedules and the ability to continue elective procedures that would subsequently require postoperative admission. This also broadened where in the hospital patients would be admitted postoperatively. It became impossible for the PI to educate each nurse that may encounter a study patient in the perioperative course. I conducted continuous study process improvement throughout enrollment with known regular nursing staff. After a series of foley catheters were removed from patients enrolled in the study prior to 24 hours, I met with a sample of nursing staff in both the Ambulatory Stay Unit (ASU) and the Post Anesthesia Care Unit (PACU). After meeting with these staff members, suggestions were employed that lead to success with retention of participants. These included moving the bright yellow study flag from inside the chart to the front cover to allow greater visibility to receiving nurses, to come educate the PACU

nurses and create a study highlights sheet to be posted in the unit (see Appendix T), and to round with the PACU charge nurse and the ASU charge nurse daily on enrollment days to keep clear lines of communication with staff. Each of these strategies improved retention throughout the study.

Sampling time frame also became a concern as the PI was the sole collector of all samples. CRNAs caring for the enrolled patients communicated with the PI to alert them to foley placement in the operating room for first samples. On high enrollment days, with 4 to 6 patients, the day of surgery (DOS) 6 PM and POD 1 6 AM samples became challenging as these patients were all admitted to different units depending on bed capacity issues. Often, the sampling time extended outside of the hour originally planned. All samples were iced immediately to avoid any issues with sample integrity.

Additionally, in communication with ASU staff, the attending surgeons were requesting foley removal prior to 6 AM on the morning after surgery to expedite discharge of these patients from the observational unit. Through the improved process of rounding with the ASU charge nurse in the evening of enrollment days, I noted which patients to visit first on the morning of POD 1 and she made the various nursing staff aware to pull those foley catheters only after making contact with me. Ultimately, there was a lot of room for error solely based on clear communication lines. Our process improvement strategies mitigated these errors.

On the last day of enrollment, six patients had been approached about the study across multiple surgical offices. This led to the enrollment of a total of 81 participants. It was unclear as to which patients had been approached first, so the PI decided to enroll one above the planned cohort size.

Lastly, there was a push during this study by the hospital administration to decrease the amount of unnecessary ‘routine’ lab testing. This did impact the study in a few cases, where subsequent daily SCr values were not available after study participation. These patients were assessed by the Nephrologist member of this committee using their postoperative urine output

alone for qualification of AKI development according to the KDIGO guidelines (2012), but this was not as ideal as having all points of data for reference.

Summary

In review, a final sample of eighty-one participants undergoing major non-cardiac intraabdominal surgery in a southeastern Level I trauma hospital were approached and enrolled in this study. The STPs initially approached potential participants, shared a study informational flyer, and collected contact information. The PI arranged to speak or meet with each potential participant prior to their surgery to confirm eligibility and obtain written informed consent for participation. For this cross-sectional, nonexperimental (observational) descriptive correlational study, 81 adult participants were enrolled. Data was collected for the variables of interest of this study within the framework of the perioperative AKI nursing conceptual model (see Chapter 1, Figure 2). Using a researcher-developed data collection tool (see Appendix C), the PI conducted an intake interview reviewing the patient's health history after informed written consent was obtained for participation in the study. Urine samples were collected from foley catheters at three points during the perioperative period (baseline at foley catheter placement, 6 PM day of surgery, and between 6 AM and 7 AM POD 1) to test for uTIMP-2*IGFBP7 novel renal biomarkers. Serum creatinine lab values were reviewed in the patients' EMR daily during their admission. A comprehensive review of the patients' EMR was conducted by the PI to obtain additional data as previously described. To answer the aims of this study, frequency distributions were obtained, and descriptive analysis conducted. All study materials will be stored in a secure location or on an approved storage device according to university guidelines. The results of this study will be shared with participating surgeons and a manuscript was prepared for wider dissemination within the medical community. This manuscript may be viewed in Chapter 5.

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Table 1

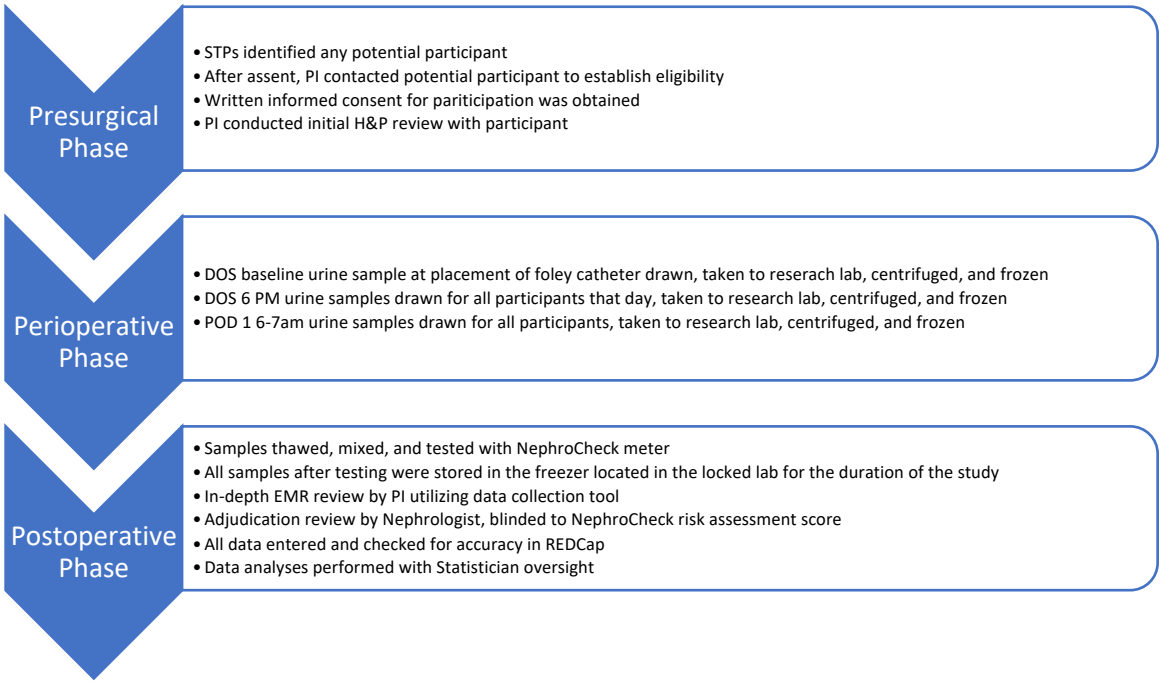
NephroCheck® Test Operating Characteristics (Astute Medical, 2017)

	Study A Lab 1 (n = 407)		**Study A Lab 2 (n = 407)**		**Study A Lab 3 (n = 407)**		**Study B (n = 126)**	
Statistic	**Value**	**95% CI**	**Value**	**95% CI**	**Value**	**95% CI**	**Value**	**95% CI**
Sensitivity (TPR)	0.92	0.85, 0.98	0.90	0.83, 0.97	0.93	0.87, 0.99	0.76	0.60, 0.91
Specificity (TNR)	0.46	0.40, 0.51	0.49	0.43, 0.54	0.45	0.39, 0.50	0.51	0.41, 0.60
FPR (1-Specificity)	0.54	0.49, 0.60	0.51	0.46, 0.57	0.55	0.50, 0.61	0.49	0.40, 0.59
FNR (1-Sensitivity)	0.08	0.02, 0.15	0.10	0.03, 0.17	0.07	0.01, 0.13	0.24	0.09, 0.40
NPV	0.96	0.93, 0.99	0.96	0.93, 0.99	0.97	0.94, 1.00	0.88	0.79, 0.96
PPV	0.26	0.21, 0.32	0.27	0.21, 0.33	0.26	0.21, 0.32	0.31	0.21, 0.42

Note. TPR= true positive rate; TNR= true negative rate; FPR= false positive rate; FNR= false negative rate; NPV= negative predictive value; PPV= positive predictive value.

Figure 1

Study Procedure Workflow Diagram



CHAPTER 4: PERIOPERATIVE URINARY TIMP-2*IGFBP7 AND ACUTE KIDNEY INJURY: A SYSTEMATIC REVIEW[1,2]

ABSTRACT

Background: Acute kidney injury (AKI) is a common post-operative outcome after major surgery. Many studies strive to improve the timeliness of identifying a surgical-associated AKI using novel renal biomarkers. However, there are limited studies focusing on the intraoperative phase of adult patient populations.

Purpose: The purpose of this review is to identify, evaluate and summarize the current literature for use of the novel renal biomarker urinary tissue inhibitor of metalloproteinase-2 * insulin-like growth factor binding protein 7 (uTIMP-2*IGFBP7) for early identification of AKI during the perioperative period for adult patients having major surgery.

Methods: Databases searched include CINAHL, ProQuest, Scopus, and PubMed. One additional article was found through reference review. The literature search followed the PRISMA guideline[9]. Twelve articles were reviewed and synthesized regarding the ability of uTIMP-2*IGFBP7 to early identify AKI during the perioperative period.

Results: The majority of studies reviewed report high sensitivity of uTIMP-2*IGFBP7 to identify surgical-associated AKI (AUROC >0.8); however, there is no consensus regarding the ideal time point for measurement or the cut-off values.

Conclusion: This novel renal biomarker shows promise of early identification of AKI in the adult surgical patient compared to current standard models. Future studies are warranted.

Keywords: Acute kidney injury, AKI, surgical, urinary tissue inhibitor of metalloproteinase-2*insulin-like growth factor binding protein 7, uTIMP-2*IGFBP7

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[1] The current chapter is also published in the American Association of Nurse Anesthesiology Journal: Ciuca, A. M., Bolin, L. P., & Horne, C. (2022). Perioperative urinary TIMP-2*IGFBP7 and acute kidney injury: A systematic review. AANA Journal, 90(3), 171-179.

[2] According to the author guidelines, this chapter is presented using the required AMA formatting.

INTRODUCTION

Acute kidney injury (AKI) is described as an insult to the kidney that leads to a rapid decline in glomerular filtration rate. This injury occurs within hours to days of the insult and leads to an abrupt deterioration in renal function along with fluid and electrolyte disturbances.[1] AKI can range from mild dysfunction to the development of chronic kidney disease requiring renal replacement therapy such as hemodialysis.[1]

Ishag and Thakar[2] report the incidence of AKI from 5% to 7.5% for all acute care hospitalizations. Of all hospital acquired AKI cases, 30% to 40% develop during the perioperative period[3] with cases increasing in the United States[1]. It is known that development of AKI during the intraoperative period may contribute to sepsis, coagulopathy, increased hospitalization and prolonged mechanical ventilation.[3] These poor outcomes may be mitigated or avoided with proper early identification of AKI and timely management of the injury.

Erdbruegger and Okusa[4] refer to serum creatinine (SCr) as a “functional marker” as opposed to a “damage biomarker”. Despite being the gold standard in diagnosing AKI, SCr lacks the ability to define AKI in the early stages.[3] The delayed rise in SCr does not accurately portray the development or the severity of the injury.[5] SCr may not spike until 24 hours to 7 days later.[6]

When exposed to stress, renal tubular epithelial cells that normally undergo a cell-cycle will arrest for a short period as a self-protection mechanism.[7] Urine tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7) are both protein biomarkers of this particular cell-cycle arrest phenomenon, their expression indicating early tubule injury.[7] Cells of the proximal tubule, loop of Henle and distal tubule may become stressed by ischemia, inflammation or toxicity.[6] With known surgical factors, such as hypotension, major vessel clamping, use of toxic medications, blood loss, and cardiopulmonary bypass[6] that lead to renal tubular stress and injury, this combination of cell-cycle arrest markers may identify AKI just as sensitively but earlier compared to later-rising serum creatinine as a

marker for renal function in surgical patients. There may be a small window of reversibility for kidney damage that is dependent upon prompt identification and early intervention.[2] During the perioperative period, the certified registered nurse anesthetist (CRNA) may employ point of care testing using novel renal biomarkers to detect AKI earlier than standard models.

The purpose of this review is to summarize the current state of the science for use of the novel renal biomarker uTIMP-2*IGFBP7 for early identification of AKI during the perioperative period for adult patients having major surgery. Subsequently, the integrated literature findings will be applied in designing a quantitative study for the evaluation of using uTIMP-2*IGFBP7 in a rural Level I hospital for surgical patients in the southeastern United States.

METHODS

Design. A project plan was developed, including identifying databases and key words as well as setting inclusion and exclusion criteria. Strategies were developed for data extraction and analysis. The methodology described by Whittenmore and Knafl[8] informed the review. All searches and evaluations were completed by the PI. Article selection was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[9].

Data Sources and Searches. Four databases were searched including CINAHL, PubMed, ProQuest and Scopus. Search terms included a combination of MESH terms, subject headings (MH or su), and keywords as applicable for each database, including ‘acute kidney injury’, ‘AKI’, ‘renal injury’, ‘renal complication’, ‘surgical’, ‘surgery’, ‘operative’, ‘urinary tissue inhibitor of metalloproteinase-2 * insulin-like growth factor binding protein 7’, and ‘uTIMP-2*IGFBP7’. No date restraints were used in the search. Searches were limited to full text, peer-reviewed, and English language. The CINAHL search query included (((MH “Kidney Failure, Acute”) OR “Acute kidney injury” OR AKI OR “renal injury” OR “renal complication”) AND (“TIMP-2” OR “IGFBP7” OR “urinary tissue inhibitor of metalloproteinase-2” OR “insulin like growth factor binding protein 7”) AND (MH “Surgery, Operative”) OR “surgery” OR “surgical”)). The PubMed search query included (((Acute kidney injury[MeSH Terms]) OR “AKI” OR “Acute kidney injury” OR “renal

injury” OR “renal complication”) AND ((timp2[MeSH Terms]) OR “IGF binding protein 7” OR “TIMP-2” OR “IGFBP7” OR “urinary tissue inhibitor of metalloproteinase-2” OR “insulin like growth factor binding protein 7”) AND ((surgery[MeSH Terms]) OR (operative surgical procedures[MeSH Terms]) OR “surgery” OR “surgical”)). The ProQuest search query included (((su(acute kidney injury)) OR "acute kidney injury" OR AKI OR "renal injury" OR "renal complications") AND ((su(timp-2)) OR (su(igfbp7)) OR "TIMP-2" OR "IGFBP7" OR "urinary tissue inhibitor of metalloproteinase-2" OR "insulin like growth factor binding protein 7") AND ((su(Surgery)) OR "surgery" OR "surgical")). The Scopus search query included (("acute kidney injury" OR "AKI" OR "renal injury" OR "renal complication") AND ("TIMP-2" OR "IGFBP7" OR "urinary tissue inhibitor of metalloproteinase-2" OR "insulin like growth factor binding protein 7”) AND (“surgery” OR “surgical")).

Inclusion and Exclusion Criteria. Primary research studies with empirical data for adult surgical patients that met inclusion criteria were included in the review. These studies would assess the ability of uTIMP-2*IGFBP7 to identify surgical-associated acute kidney injury. Only full-text, English, human studies found in peer reviewed journals were included. Literature containing pediatric populations (aged < 18 years of age), mixed populations of surgical and other types of patients such as septic or cancer, and pilot studies were excluded. Low level articles such as review, commentary, interviews, editorials, abstracts and posters were excluded.

Search Results. By searching four databases and using other methods such as reference list review, 213 records were identified. Duplicates were removed, and the remaining 184 records were screened for title and abstract. Based on the inclusion and exclusion criteria and by quality appraisal, an additional 145 records were removed. The remaining 39 full-text articles were assessed for eligibility, and 27 were excluded for various reasons including pediatric populations, pilot studies, investigations of other biomarkers, non-surgical populations and the

use of uTIMP-2*IGFBP for non-identification purposes. A final count of 12 articles were included in this integrative review. Details of the search are displayed in a PRISMA diagram (Figure 1).

Data Extraction and Synthesis. A matrix was developed to extract data from the articles to include location, study population, purpose, design, measurement, primary endpoint, cut-off points and main findings of each study. The author extracted data solely. Data was compared and synthesized among the research studies. Included study characteristics are found in Table 1.

RESULTS

Of the twelve studies included in this review, only one study was conducted solely in the United States.[10] A second study was a mixed site study of the United States and Europe.[11] However, the remaining ten were conducted across Germany, France and China (Table 1). All studies used a prospective cohort design of adult surgical patients. Samples ranged from 40 to 400 patients, with a mean of 124 patients. Overall, the mean age of the sample populations was greater than 60 years of age. Ten of the twelve studies focused only on cardiac surgery-associated AKI. All studies used Kidney Disease Improving Global Outcomes (KDIGO) guidelines[12] for diagnosing AKI by serum creatinine and urine output, as well as NephroCheck®, an FDA approved test to assess uTIMP-2*IGFBP7 levels.

AKI Development. All studies evaluated a primary end point of AKI development post-operatively. AKI development across studies reviewed is presented in Table 2. Zaouter et al.[13] show the highest incidence rate of 74% of any AKI development after elective cardiac surgery utilizing cardiopulmonary bypass. Cummings et al.[10] show the lowest incidence of 22.8% of any AKI development after cardiac surgery involving mixed procedures on and off pump.

Assessment of uTIMP-2*IGFBP7 Usefulness. Seventeen different time points or time ranges were assessed across these twelve studies. The most frequently assessed time points as seen in Figure 2, were preoperatively or upon induction of general anesthesia, admission to PACU or ICU after surgery, 4 hours post-operatively, 12 hours post-operatively and 24 hours post-

operatively. The studies varied regarding a primary end-point. Some studies only included advanced stage 2-3 AKI, while others included development of any stage AKI[12]. There was also variation among the cut-off values for the uTIMP-2*IGFBP7 testing.

Marginal Usefulness of uTIMP-2*IGFBP7. Five studies found uTIMP-2*IGFBP7 to have poor or fair usefulness for identifying AKI at individual time points on the day of surgery with AUROC values ranging from 0.646-0.78 (see Table 3).[10,13-16] On post-operative day one, Wetz et al.[17] found marginal usefulness with AUROC values of 0.706. This study showed the marker could not predict AKI or discriminate between mild and advanced stages of AKI.[17]

Good Usefulness of uTIMP-2*IGFBP7. As seen in Table 4, seven studies found the biomarker to have good usefulness within the first 24 hours after surgery with AUROC values ranging from 0.8-0.971.[10,11,14,18-21] Additionally, Oezkur et al.[22] reported odds ratio findings that demonstrated the biomarker having accurate predicting abilities for AKI following cardiac surgery at ICU admission. Dusse et al.[14] found post-operative day one marker usefulness to be the highest among all studies (AUROC 0.971) with 100% specificity to predict advanced stage AKI; compared to SCr (AUROC 0.629). Cummings et al.[10] demonstrated 100% sensitivity in marker performance among cardiac patients and 100% negative predictive value (NPV).

DISCUSSION

This review of studies assessing the usefulness of uTIMP-2*IGFBP7 in early identification of surgical-associated AKI shows an abundance of data in European adult surgical populations. Most of the studies reviewed showed good usefulness of uTIMP-2*IGFBP7 based on AUROC values ranging from 0.8-0.971 at various time points.[10,11,14,18-21] A main strength noted of uTIMP-2*IGFBP7 is the high NPV demonstrated across the studies. While validating the 0.3 $(ng/mL)^2/1000$ clinical threshold, Cummings et al.[10] reported a 100% sensitivity, meaning all AKI cases were identified by uTIMP-2*IGFBP7 and a 100% NPV using the max value of uTIMP-2*IGFBP7 post CPB. The NPV indicates the biomarker can also be used to accurately predict patients that will not experience AKI at this given threshold.[10] They further indicate that

uTIMP-2*IGFBP7 could detect AKI stage 2-3[12] disease at admission to ICU, while SCr could not.[10] Several studies also indicate that uTIMP-2*IGFBP7 may be useful in predicting AKI or identifying patients at high risk for AKI development. The biomarker was more useful than SCr and urine output at predicting moderate to severe AKI development within 12 hours of surgery[11] and within 72 hours of transapical or transaortic aortic valve implantation[14].

Most of the research has been conducted in cardiac surgical patients, some involving cardiopulmonary bypass, a known inflammatory process. During this review it was noted that there is limited data on adult patients from 20-50 years of age. Most of the studies reviewed were conducted in older adults, and the results may not be generalizable based on the probability of older patients having increased numbers of comorbidities.

This review revealed an incidence rate of 22.8% to 74% acquiring a surgical-associated AKI. Gocze et al.[18] showed an incidence of 42% among the sample of major non-cardiac surgical patients, including transplant, vascular, trauma and hepatobiliary surgeries. The incidence rates among major cardiac and non-cardiac surgery are similar among these studies. However, authors caution widespread projection of the findings due to small samples and single site studies. With ten of the included studies being conducted on cardiac patients; there is question as to whether the biomarker uTIMP-2*IFGBP7 remains as useful in other populations. Of the eight studies that show good usefulness of uTIMP-2*IGFP7, two were in non-cardiac surgical patients[18] and a mixed surgical population including some cardiothoracic surgeries[11]. Both studies had comparative results to the pure cardiac surgical studies with AUROC values >0.8. Therefore, we plan to use a non-cardiac surgical population for a future pilot study.

Overall, this review of studies found that uTIMP-2*IGFBP7 has good sensitivity to renal tissue and is timelier than the traditional method of using SCr in identifying AKI in surgical patients. Gaining valuable time in identifying AKI allows for a longer potential therapeutic window between the renal injury event and loss of function.[2] There is a wealth of research on renal protective strategies that include fluid volume and renal blood flow management,

avoidance of nephrotoxic drugs, tight blood glucose management between 80-110 mg/dL, and the use of statin therapy to stabilize endothelial membrane functions.[2] There is no consensus on the best cut-off values for testing or the ideal measurement time post-operatively. While the test timing has yet to be perfected, uTIMP-2*IGFBP7 shows much promise as a novel renal biomarker for AKI identification in the surgical patient.

Limitations and Future Directions. Small sample populations and single site studies were limitations of many of the studies. Future studies should include larger samples with various major surgical patients. Other major surgeries to investigate may include complex orthopedic procedures, spine procedures, and complex abdominal procedures lasting over four hours. Authors caution generalized use of cut-off values for uTIMP-2*IGFBP until further studies are conducted in larger samples of differing surgical types. Another limitation may be the use of induction of general anesthesia as a time point for baseline urine samples[10,15,19] as profound hypotension on induction could lead to ischemia, a known cause of cellular stress[6].

The integrated information from the literature will be applied in designing a quantitative study for the evaluation of using uTIMP-2*IGFBP7 in a rural Level I hospital for surgical patients in the southeastern United States. The ideal population would be surgical patients for Whipple procedure generally lasting greater than 4 hours. Baseline uTIMP-2*IGFBP7 and SCr will be collected, along with serial samples of both every 4 hours for 24 hours postoperatively.

CONCLUSION

The timeliness of identifying AKI is crucial. This review shows not only renal tissue specificity of the novel renal biomarker uTIMP-2*IGFBP7, but also that the biomarker has high sensitivity for identifying AKI like the gold standard SCr. This biomarker also indicates injury more quickly than SCr. The biomarker can be tested during and quickly after surgery, as opposed to waiting 24-48 hours for a spike in SCr. This real time injury marker extends the therapeutic window and provides an opportunity to employ renal protective measures to potentially mitigate the injury and decrease the devasting outcomes. Urine TIMP-2*IGFBP7 may

represent a new concept of evaluating renal function. Exploring ideal time points for the measurement of uTIMP-2*IGFBP7 to identify surgical-associated AKI is needed and additional studies are warranted.

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Table 1

Characteristics of Studies Included in this Integrative Review

Study	Country	Study Design	Purpose	Sample	Age of Participants	Surgical Setting	AKI Definition/ Tool	Time of Measurement	Primary Endpt/ Cut-off values
Cummings et al.[10]	USA	PC	To evaluate TIMP-2*IGFBP7 as a postop marker of renal stress and AKI	400 adult RCT cohort of previous study published (Nov 2009- Dec 2014)	67 (58-75)	Cardiac surgery (mixed on pump and off pump)	KDIGO/ NephroCheck	Urine collected after induction of anesthesia (baseline), 30 min following initiation of CPB or off-pump grafting, following end of CPB or OpCAB, upon ICU adm, 6 hr after adm, and at 9am POD 1, 2, and 3. (8 samples)	Stage 2-3 AKI within 48 hr; cut-off >0.3 for stage 2-3 AKI
Gunnerson et al.[11]	Europe and North America	PC	To assess whether uTIMP-2*IGFBP7 accurately identifies patients at risk for AKI that are having surgery	375 patients (COMBO of Sapphire and Topaz study)	Mod-Sev AKI 67 (SD 13), No AKI 64 (SD 14)	Any surgery admitted to ICU	KDIGO/ NephroCheck	Urine collected at ICU adm. Sapphire study test sampled once, Topaz study tested sample 3x and reported median value.	Moderate-severe AKI (2/3) within 12 hr; cut-off 0.3 and 2
Zaouter et al.[13]	France	PC	To assess the ability of TIMP-2 and IGFBP7 and doppler renal resistive index (RRI) in detecting CSA-AKI at an early stage	50 (Sept-Nov 2014)	72.5±8	Elective CPB	KDIGO/ NephroCheck	Before GA induction, 1 hr, 4 hr, 12 hr, and 24 hr postop.	Incidence of AKI until POD 7; cut-off 0.3
Dusse et al.[14]	Germany	PC	To evaluate the ability of TIMP-2*IGFBP7 to early predict AKI after TAVI	40 patients (Jan-Sept 2014)	81.2±5.6	TAVI (either transapical or transaortic)	KDIGO/ NephroCheck	Urine within 4 hr after surgery, then 2x daily until discharge from ICU and a max of 4 days (whichever occurs first). SCr prior and 4 hr after surgery, and at least 2x daily post-op.	New occurrence AKI stage 2-3 within 48hr after surgery; Cut-off POD 1 - 1.03. Max value in 24h cut-off 0.91.

Study	Country	Study Design	Purpose	Sample	Age of Participants	Surgical Setting	AKI Definition/ Tool	Time of Measurement	Primary Endpt/ Cut-off values
Finge et al.[15]	France	PC	To assess the ability of TIMP-2*IGFBP7 to predict postop AKI 3hr postoperatively in patients undergoing CPB during cardiac surgery	93 patients in final analysis (of 108 eligible) (Apr-Sept 2014)	62-81	CPB	KDIGO/ NephroCheck	Anesthesia induction and 3 hr postop.	Occurrence of AKI stage >0 within first 48 hr; assessing different cut off values - 0.3, 0.5, 2.
Zaouter et al.[16]	France	PC	To determine predictive value of biomarker in detecting AKI after a TAVI-procedure at an early phase.	62 (Sept 2016 - Feb 2017)	80 (SD 7)	TAVI	KDIGO/ NephroCheck	Preop, at first micturition post-procedure (or after catheterization for pts that did not empty bladder within 6 hr), and first micturition on morning POD1 (or 24 hr after admission for those with catheter)	Incidence of AKI
Wetz et al.[17]	Germany	PC	Aim to clarify the quantification of TIMP-2 and IGFBP7 as an adequate dx test to detect CSA-AKI by doing a thorough analysis of the diagnostic strength	42 (Aug 2013 - Feb 2014)	median 72	Elective and non-elective CABG with CPB	KDIGO/ NephroCheck	Pre-operative baseline, end of surgery, 4 hr after arrest of CPB, 8am POD1.	Development of AKI; assessed both cut-off 0.3 and 2
Gocze et al.[18]	Germany	PC	To evaluate use of TIMP-2*IGFBP7 to early predict AKI after major surgery	107 adult patients (May-Nov 2013)	mean 60.03 (SD 14.78)	Major non-cardiac surgery	KDIGO/ NephroCheck	Urine sample taken soon after transfer to ICU from OR.	Cut-off >0.3

Meersch et al.[19]	Germany	PC	To evaluate TIMP-2*IGFBP7 as an early marker of CSA-AKI and marker for renal recovery	50 adult patients (June-Sept 2013)	71±12	CPB	KDIGO/ NephroCheck	Urine pre-op (immediately post anesthesia induction) and 4 hr, 12 hr, and 24 hr after coming off CPB; serum Cr collected preop, 4 hr, 12 hr, 24 hr, 48 hr, 72 hr, and hospital discharge.	Any AKI after cardiac surgery; cut-off value 0.5

Study	**Country**	**Study Design**	**Purpose**	**Sample**	**Age of Participants**	**Surgical Setting**	**AKI Definition/ Tool**	**Time of Measurement**	**Primary Endpt/ Cut-off values**
Pilarczyk et al.[20]	Germany	PC	To evaluate uTIMP-2*IGFBP7 as an early predictor of AKI after CABG	60 adult patients (Jan-Oct 2014)	AKI 2/3 76.2±3.9; AKI 0/1 68.8±9.1	CPB	KDIGO/ NephroCheck	Urine collected 4 hr after surgery and then every 12 hr post-operatively until discharge; along with UOP and SCr.	Stage 2-3 AKI within 48hr; cut-off value 0.15 at 4hr, 0.89 POD 1
Wang et al.[21]	China	PC	To assess the ability of TIMP-2 and IGFBP7 to be an excellent predictor of AKI following cardiac surgery in Asian populations	57 adult patients (May 2016)	60 (49-65)	Cardiac surgery	KDIGO/ NephroCheck	Urine samples collected prior to surgery, in 2 hr intervals from 0 hr to 12 hr after ICU admission, and 24 hr after ICU admission.	Moderate-sev AKI (2/3) within 7 days following surgery.
Oezkur et al.[22]	Germany	PC	To investigate predictive value of uTIMP-2*IGFBP7 associated with CSA-AKI at various time points	150 patients (Apr-Dec 2014)	median 67	Cardiac surgery, including CPB	KDIGO/ NephroCheck	PreOp, ICU-adm, 24 hr, 48 hr.	AKI within first 48hr after surgery; cut-off 0.3 for categorical and as a continuous variable

Abbreviations: Endpt, endpoint; PC, Prospective cohort design; AKI, acute kidney injury; KDIGO, Kidney Disease Improving Global Outcomes guidelines; CPB, cardiopulmonary bypass; OpCAB, off-pump coronary artery bypass; POD, post-operative day; CSA-AKI, cardiac surgery-associated acute kidney injury; SCr, serum creatinine.

Table 2

AKI Development in Sample Populations from Articles Reviewed

Study	Sample n	Any AKI n	Stage 1 AKI[a] n	Stage 2-3 AKI[a] n
Cummings et al.[10]	400	91 (22.8%)	77 (19.3%)	14 (3.5%)
Gunnerson et al.[11]	375			35 (9%)
Zaouter et al.[13]	50	37 (74%)	21 (42%)	16 (32%)
Dusse et al.[14]	40	15 (37.5%)	7 (17.5%)	8 (20%)
Finge et al.[15]	93	34 (37%)		
Zaouter et al.[16]	62	22 (35.4%)	1 (1.6%)	21 (33.8%)
Wetz et al.[17]	42	16 (38%)	13 (31%)	3 (7%)
Gocze et al.[18]	107	45 (42%)	21 (20%)	24 (22%)
Meersch et al.[19]	50	26 (52%)	19 (38%)	7 (14%)
Pilarczyk et al.[20]	60	19 (31.6%)	13 (21.6%)	6 (10%)
Wang et al.[21]	57	20 (35%)	14 (24%)	6 (11%)
Oezkur et al.[22]	150	35 (23.5%)	27 (18%)	8 (5.5%)

Abbreviations: AKI, acute kidney injury.

[a]AKI stages based on KDIGO guidelines[12].

Table 3

Marginal Usefulness of uTIMP-2*IGFBP7 in Reviewed Articles

Study	Time Point	Performance (AUROC)	Assessing[a]
Cummings et al.[10]	Post CPB	0.71	AKI Stage 2-3
	ICU admission	0.68	AKI Stage 2-3
	6 hr post-operative	0.78	AKI Stage 2-3
	POD 1	0.75	AKI Stage 2-3
Zaouter et al.[13]	12 hr post-operative	0.69	All AKI
Dusse et al.[14]	4 hr post-operative	0.646	AKI Stage 2-3
Finge et al.[15]	3 hr post-operative	0.73	All AKI
Zaouter et al.[16]	Post-procedure	0.66	All AKI
	POD 1	0.71	All AKI
Wetz et al.[17]	POD 1	0.706	All AKI

Abbreviations: AUROC, area under the operator curve; CPB, cardiopulmonary bypass; AKI, acute kidney injury; POD, post-operative day.

[a]AKI stages based on KDIGO guidelines[12].

Table 4

Good Usefulness of uTIMP-2*IGFBP7 in Reviewed Articles

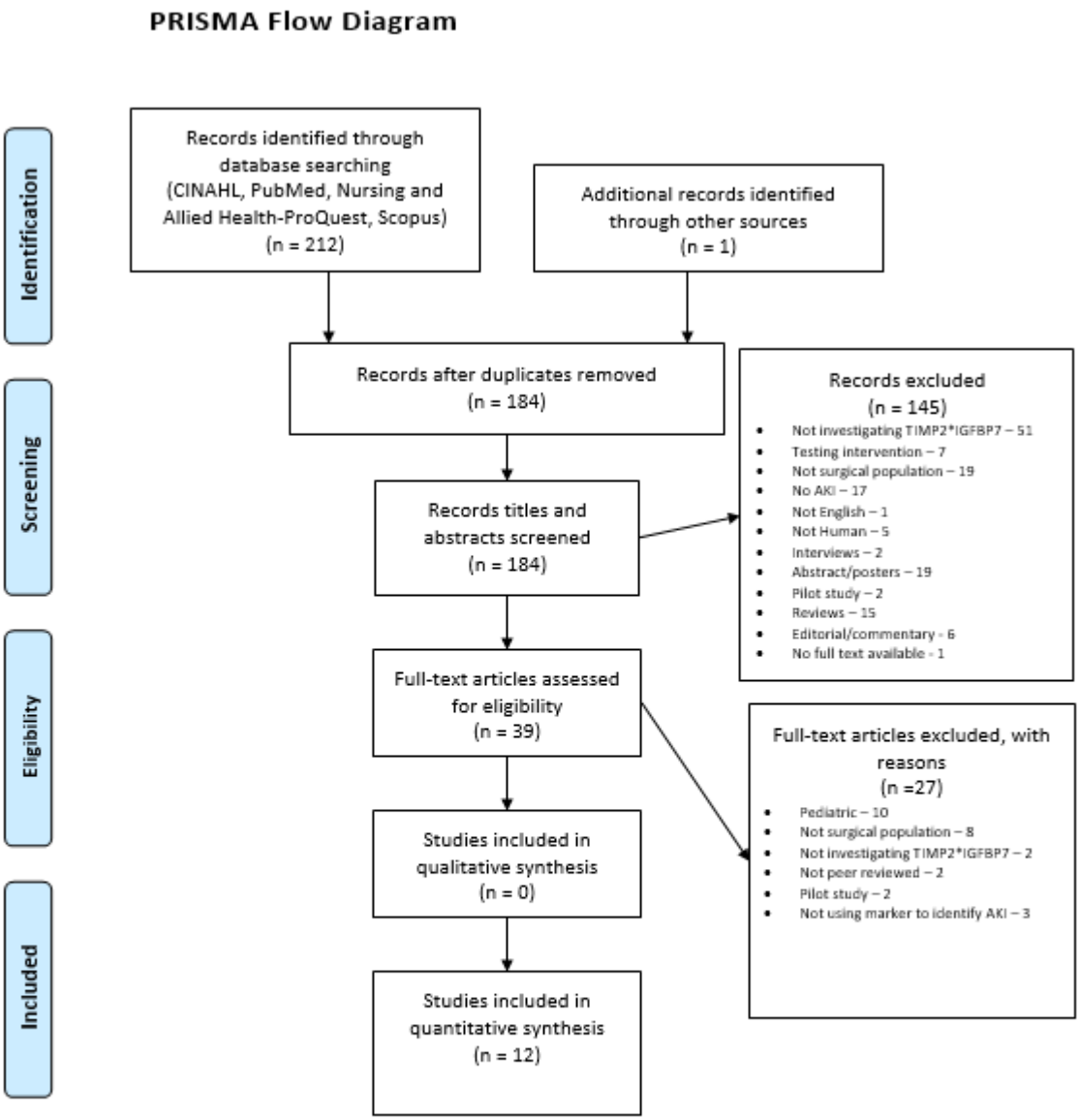
Study	Time Point	Performance (AUROC)	Assessing[a]
Cummings et al.[10]	Max value between intraoperative and 6 hr postOP	0.82	AKI Stage 2-3
Gunnerson et al.[11]	Within 12 hr postOP	0.84	AKI Stage 2-3
Dusse et al.[14]	Max value in 24 hr	0.869	AKI Stage 2-3
	POD 1	0.971	AKI Stage 2-3
Gocze et al.[18]	Admission to ICU	0.85	All AKI
Meersch et al.[19]	4 hr after CPB	0.81	All AKI
	Max value in 24 hr	0.9	All AKI
Pilarczyk et al.[20]	4 hr PostOP	0.861	AKI Stage 2-3
	POD 1	0.869	AKI Stage 2-3
Wang et al.[21]	4 hr PostOP	0.8	AKI Stage 2-3

Abbreviations: AUROC = area under the operator curve; hr, hour; postOP = postoperatively; POD = post-operative day; CPB = cardiopulmonary bypass.

[a]AKI stages based on KDIGO guidelines[12].

Figure 1

PRISMA Flow Diagram

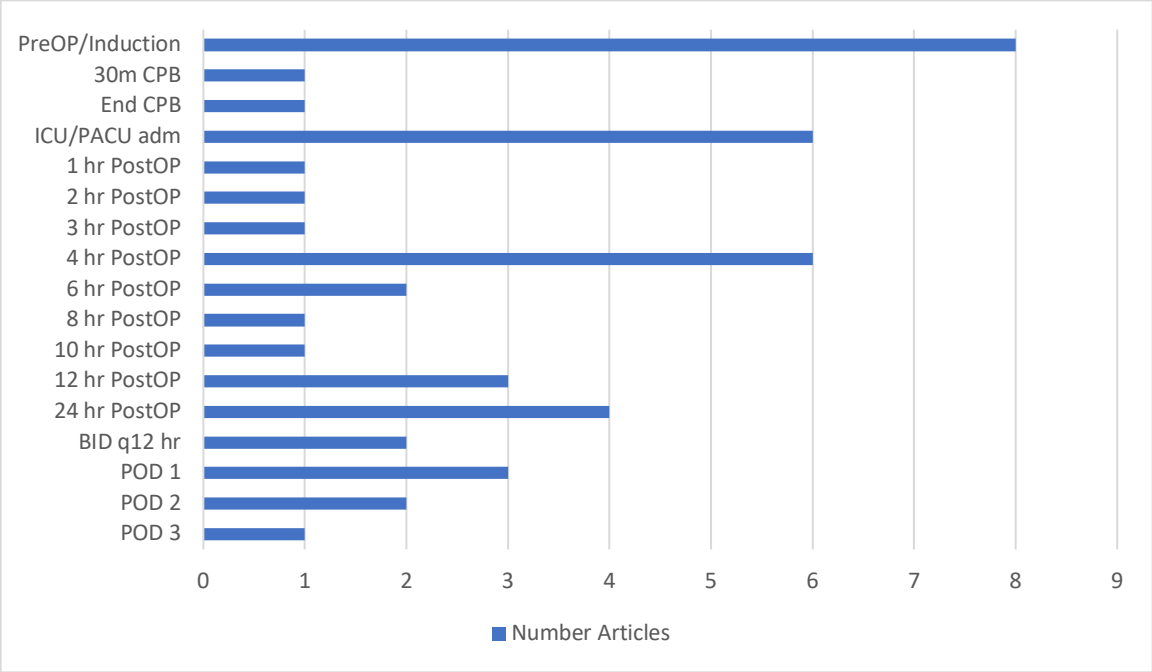


From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Abbreviations: CINAHL, Cumulative Index to Nursing & Allied Health Literature; TIMP-2*IGFBP7, tissue inhibitor of metalloproteinase-2* insulin-like growth factor binding protein 7; AKI, acute kidney injury.

Figure 2

uTIMP-2*IGFBP7 measurement time points across the studies



Abbreviations: uTIMP-2*IGFBP7, urinary tissue inhibitor of metalloproteinase-2* insulin-like growth factor binding protein 7, PreOP, preoperatively; CPB, cardiopulmonary bypass; PostOP, postoperatively; BID, twice daily; POD, post-operative day.

CHAPTER 5: PERIOPERATIVE PREDICTION OF SURGICAL-ASSOCIATED ACUTE KIDNEY INJURY UTILIZING URINARY [TIMP-2]*[IGFBP7] RENAL BIOMARKERS[3,4]

ABSTRACT

Objective: Acute kidney injury (AKI) is a postoperative complication following many types of major surgery. Urinary tissue inhibitor of metalloproteinase-2 and insulin-like growth factor binding protein 7 [TIMP-2]*[IGFBP7], two novel renal biomarkers of renal stress have shown promise in the early identification of AKI following cardiac surgery. This study was conducted to test the hypothesis that perioperative u[TIMP-2]*[IGFBP7] concentrations are associated with AKI development in non-cardiac intraabdominal surgery.

Methods: Urinary [TIMP-2]*[IGFBP7] was measured at three perioperative time points for 79 patients who presented for major intraabdominal surgery utilizing the NephroCheck® urine assay. Risk assessment scores were compared between participants who did and did not develop KDIGO Stage 2-3 AKI within 48 hours of surgery.

Results: Eight patients (10.1%) met the primary endpoint of Stage 2-3 AKI within 48 hours of surgery, and 24 patients (30.4%) developed a low-grade Stage 1 AKI. Using the cut-off predictive value of >0.3, baseline NephroCheck® risk scores exhibited an AUROC value of 0.85 and 100% sensitivity and negative predictive value (NPV). Postoperative day 1 samples also exhibited a high AUROC value at 0.84 with a 98% NPV. Larger, multi-site studies are warranted to further investigate the perioperative utility of these novel renal biomarkers.

Keywords: Acute kidney injury (AKI), surgical, urinary tissue inhibitor of metalloproteinase-2*insulin-like growth factor binding protein 7 (u[TIMP-2]*[IGFBP7])

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[3] The current chapter has been developed for submission to the American Association of Nurse Anesthesiology Journal.

[4] According to the author guidelines, this chapter is presented using the required AMA formatting.

INTRODUCTION

Acute kidney injury (AKI) claims the lives of 1.7 million patients per year globally.[1] Utilizing current standards for diagnosing AKI with serum creatinine (SCr), it is estimated that 31% of hospital-acquired AKI were avoidable and 43% of patients experience delays in treatment.[2] Better predictive models are needed to reduce the healthcare burden of AKI; use of novel renal biomarkers may have a role in improving care.

Within hours to days of an insult, AKI leads to an abrupt deterioration in renal function along with fluid and electrolyte disturbances that range from mild dysfunction to chronic kidney disease (CKD).[3] 30% to 40% of all hospital-acquired AKI cases develop during the perioperative period.[4] Development of perioperative AKI may contribute to sepsis, coagulopathy, increased hospitalization, prolonged mechanical ventilation,[4] and increase the risk of morbidity and mortality.[4,5] There is risk for requirement of renal replacement therapy (RRT), such as hemodialysis when a patient develops a severe AKI.[6] Kheterpal et al.[5] report an 8-fold increased risk of mortality with developing AKI perioperatively. McKinlay et al.[4] report a 12-fold increased risk of mortality associated with developing AKI after major abdominal surgery. Mortality following cardiac surgery, is estimated to range from 25%[7] to 60% of patients with severe renal injury requiring RRT.[8]

The risk-adjusted average cost increases by approximately $16,000 for a single episode of care for an AKI.[9] Due to the estimated annual expenditure in excess of $10 billion for hospital-acquired AKI[10], the Centers for Medicare and Medicaid Services (CMS) recently introduced AKI requiring in-patient hemodialysis as a 2020 cost measure for the Merit Based Incentive Payment System for providers. In exploring this topic regionally, there is a 15.9% death rate attributed to kidney disease in North Carolina[11], despite a task force set by the NC General Assembly to combat this health care concern in 2008.

AKI is considered a multivariate syndrome, due to the multifactorial inducers that lead to the complex disease state.[12] These poor outcomes may be mitigated or avoided with early

identification of AKI risk utilizing novel renal biomarkers and timely management of the injury. The traditional functional marker SCr may not spike until 24 hours to 7 days[13] post-injury when the window of reversibility may already be closed, indicating functional renal loss. Despite being the gold standard for diagnosing AKI, this pattern of not identifying the AKI in the early stages of inflammation led to SCr [4] being designated as a "functional marker" as opposed to a "damage biomarker"[14] and further the delayed rise in SCr does not correlate with the severity of the injury.[8]

Expression of the novel renal inflammatory protein biomarkers urinary tissue inhibitor of metalloproteinase-2 and insulin-like growth factor binding protein-7 (u[TIMP-2]*[IGFBP7]) indicates early tubule injury.[15] When stressed renal tubular epithelial cells exhibit a self-protective mechanism with a short period of arrest of their normal cell-cycle. These two renal inflammatory protein biomarkers flood out during stress periods to warn neighboring cells of the early injury.[15] These cells throughout the tubule may become stressed by known and unknown stresses including ischemia, inflammation, and toxicity.[13] Many of these stressors frequently occur during the perioperative period in addition to hypotension, use of renal toxic medications such as vasopressors and antibiotics, cardiopulmonary bypass, blood loss, and clamping of major vessels.[13] Measurement of this combination of cell-cycle arrest renal biomarkers is commercially available by the Astute Medical NephroCheck® meter,[16] quantifying u[TIMP-2]*[IGFBP7] into a risk assessment score predicting the development of moderate to severe AKI (Stage 2-3) in the next 12 hours, thus identifying AKI in the early phases of inflammation and injury instead of after functional renal loss.

The NephroCheck® is the only FDA-approved device to test for these renal biomarkers in the urine. Findings from a recent systematic review suggest these biomarkers were sensitive for indicating risk of developing a Stage 2 or 3 AKI 4 to 24 hours postoperatively.[17] The majority of studies were conducted in cardiovascular surgical patients, with two studies in other major surgical populations.[17] It is important to determine if these biomarkers remain sensitive for AKI

in other major surgical populations. The goal of this project was to investigate novel measures for identifying AKI in adults requiring major non-cardiac procedures compared to the standard clinical model of measuring later-rising SCr. Gocze et al.[18] reported a 22.4% incidence rate of Stage 2-3 AKI development following major non-cardiac surgery. This study was conducted to test the hypothesis that perioperative concentrations of u[TIMP-2]*[IGFBP7] are associated with postoperative AKI following major intraabdominal surgery and to elucidate the effectiveness of the NephroCheck® assay in early identification of risk for developing moderate to severe AKI. The first aim of this study was to explore the association between major non-cardiac intraabdominal surgery and the incidence of AKI. The second aim of this study was to evaluate the effectiveness of the NephroCheck® urine assay for u[TIMP-2]*[IGFBP7] in early identification of risk for developing moderate to severe AKI in major non-cardiac intraabdominal adult surgical patients.

METHODS

Study participants. A prospective cohort of participants requiring intraabdominal surgery were enrolled in the study between May and November 2022. This was a convenience sample based on the schedule and ability of a single primary investigator (PI) to collect all samples. After obtaining facility IRB approval, eighteen attending surgeons from a level I trauma center in the southeastern United States that routinely complete major non-cardiac intraabdominal surgeries were identified, informed about the study, and gave their signature of consent for their patients to be approached about the study. Patients were all scheduled for intraabdominal surgery in the following surgical services: colorectal, gynecological, urological, bariatric, nephrology, transplantation, general, and oncology.

Eligibility. Inclusion criteria were age greater than or equal to 21 years, based on FDA approval for intended use of the measure;[16] participants undergoing major non-cardiac intraabdominal surgery, English speaking, and cognitively intact and able to consent for participation. Exclusion criteria included trauma and emergency surgical patients, those with history of renal

transplantation, current COVID-19 positive patients, those undergoing current chemotherapy, and those with significant proteinuria (urinary albumin greater than 125mg/dL), hyperbilirubinuria (urinary bilirubin greater than 7.2 mg/dL), or elevated methylene blue concentrations (urine concentration greater than 0.49mg/L).

Procedures. The study was approved by the University and Medical Center institutional review board (UMCIRB) and all patients provided written informed consent to participate in the study. All patients received surgical, anesthetic, and postoperative care managemenet according to the standards of care of the medical center. Although not standardized, all participants received a general anesthetic with volatile anesthetics. Serum creatinine (SCr) lab values were drawn as part of the participants' routine surgical care. These values were reviewed as the gold standard for meeting criteria of AKI diagnosis,[19] along with postoperative urine output. Sterile 10 mL urine samples for NephroCheck® u[TIMP-2]*[IGFBP7] assays were collected at induction of general anesthesia once the urine foley catheter was placed, at 6 PM on the day of surgery, and between 6 AM and 7 AM postoperative day 1 (POD 1). The validity of the clinical performance of NephroCheck® was previously conducted and reported.[16]

The samples of urine collected by the PI were labeled and deidentified for transportation in a marked biohazard cooler with ice packs and tested for high levels of protein and bilirubin by chemistry dipstick. These two substances in high concentrations are known to interfere with the test results.[16] If high levels of either were detected, the urine sample was considered ineligible for the study and was excluded. Each sample was centrifuged to 1000xg at 4° C for 10 minutes per manufacturer requirements. Once completed, the supernatant was transferred to a clean specimen 1.7 mL microtube and allowed to reach room temperature for testing or immediately refrigerated or frozen. Prior to NephroCheck® testing, supernatant samples may be stored for 5 hours at room temperature or 20 hours in the refrigerator.[16]

A clinical lab scientist member of this research team oversaw meter installation and was integral to the planning of proper procedures. After thawing the samples, with the use of a

calibrated precision pipette, each sample was mixed and tested according to manufacturer procedures.[16] A risk-assessment score was produced by the NephroCheck® meter after quantification of u[TIMP-2]*[IGFBP7]. Adjudication by the board-certified Nephrologist member of this research team was performed for each participant. The Nephrologist was blinded to NephroCheck® results and provided with a clinical vignette of each patient's hospital course. The Nephrologist determined whether an AKI was sustained during this hospital admission and leveled the injury utilizing KDIGO guidelines.[19]

In the postoperative phase, a thorough review of the patient's electronic medical record (EMR) was completed by the PI for each participant. Each participant was followed for 30 days postoperatively. Using a standardized data collection tool, data was gathered to encompasses socio-demographics, preoperative assessment of vital signs, medication history, health history, surgical history, perioperative record to assess for known causes of AKI, post-operative record, and laboratory data. Nursing, physician, and anesthesia records were all reviewed. Arterial line blood pressures were documented with preference to non-invasive blood pressure measurements. Results were reviewed for lab data, electrocardiograms, and imaging such as MRIs and CT scans.

Outcomes. The primary endpoint was development of moderate to advanced Stage 2-3 AKI within 48 hours of surgery defined by a change in SCr or decrease of urine output according to the KDIGO Clinical Practice Guidelines.[19] Criteria for AKI diagnosis was defined by any of the following: 1) an increase in SCr by greater than or equal to 0.3 mg/dL within 48 hours; 2) an increase in SCr to greater than or equal to 1.5 times the baseline SCr, which is known or presumed to have been drawn within the prior week; or 3) urine volume less than 0.5 mL/kg/h for 6 hours.[19] Patients were categorized for perioperative insults and postoperative complications were recorded. Perioperative insults included periods of hypotension, hypovolemia, perioperative radio contrast dye use, antibiotics use, angiotensin converting enzyme inhibitor (AEC-I) use, kinked foley catheters or mechanical ureteral obstruction.

Hypotension was defined as a mean arterial blood pressure (MAP) less than 65 mmHg for more than 5 minutes. According to Sessler et al.,[20] MAPs less than 65 mmHg are associated with perioperative renal and myocardial injuries. Hypovolemia was defined as a pulse pressure variation (PPV) greater than 13%.[21] Postoperative complications included AKI diagnosis, sepsis, unplanned dialysis, urine output less than 0.5 mL/kg/hr, 28-day mortality, or unplanned readmission within 30 days of surgery.

Statistical Analysis. Data was analyzed with IBM SPSS (Version 27) predictive analytics software, in collaboration with the statistician of this research team. Descriptive statistics about patients' renal core structure including co-morbidities, patient demographics, surgery type, and any perioperative stressors were recorded. Frequencies revealing incidence rates of AKI related to different major intraabdominal surgeries were analyzed. Fisher's exact test was used to describe relationships between predictor variables and development of perioperative AKI. Descriptive statistics were analyzed comparing the traditional (SCr) and novel (NephroCheck®) methods of AKI identification by studying area under the operating curves (AUROC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) to assess the accuracy of traditional and novel methods of identifying AKI.

RESULTS

Eighty-one patients requiring intraabdominal surgery were included. Two participants were excluded from final analysis, as seen in Figure 1. Average age of the sample was 61 years and 59% were female. There was a statistical relationship between the body mass index (BMI) of those developing Stage 2-3 AKI being higher than the no AKI or Stage 1 AKI group ($p=.001$). Other demographic findings of the sample are displayed in Table 1. The most common preoperative medical condition was hypertension (HTN, 70%). HTN was the preoperative condition with the biggest difference between the AKI (n=8) at 100% and only 66% of the no AKI or Stage 1 AKI group (n=47). 39% of the sample had open intraabdominal procedures, compared to 61% that had robotic or laparoscopic intraabdominal procedures. Thirty-six

patients (45.6%) of the sample had surgery for oncologic diagnoses; six of the eight patients (75%) resulting with a Stage 2-3 AKI were in this group.

Eight participants (10.1%) met the primary endpoint of perioperative development of moderate to severe AKI (Stage 2-3). Additionally, 24 patients (30.4%) developed a low-grade AKI Stage 1 according to KDIGO staging criteria[19] by Nephrologist adjudication. Patients who developed stage 2-3 AKI displayed an average u[TIMP-2]*[IGFBP7] score of 1.40 at baseline, 0.93 at 6 PM day of surgery (DOS), and 2.26 on the morning of postoperative day 1 (POD 1). These mean perioperative urinary [TIMP-2]*[IGFBP7] scores may be viewed in Figure 2.

The AUROC (95% CI) values for prediction of Stage 2-3 AKI were 0.85 (0.76, 0.95), 0.77 (0.64, 0.91), and 0.84 (0.74, 0.94), respectively, for u[TIMP-2]*[IGFBP7] samples collected at baseline, 6 PM DOS, and the morning of POD 1 (see Figure 3). Baseline samples of u[TIMP-2]*[IGFBP7] yielded a 100% sensitivity for identifying true cases correctly and 58% specificity. The negative predictive value (NPV) was 100% at baseline. At 6 PM DOS, u[TIMP-2]*[IGFBP7] exhibited 57% sensitivity, 69% specificity, and 93% NPV. Samples on POD 1 yielded 86% sensitivity, 66% specificity, and 98% NPV (see Table 2).

Although not statistically significant, hypotension (HOTN) was documented in 29% of the sample and 13% of those who developed an AKI Stage 2-3. All patients experiencing HOTN averaged 27 minutes throughout the case; while the AKI Stage 2-3 patient experienced HOTN for 6 minutes throughout the case. The longest sustained hypotensive episode lasted for 45 minutes in a patient that did not experience AKI. 100% of the sample received intraoperative antibiotics. Cefazolin was the most commonly used perioperative antibiotic (64.5%; n= 51). Perioperative radiocontrast dye was not used in any case that developed a moderate to severe AKI. None of the thirteen patients who did receive perioperative contrast medium or Indocyanine green (ICG) fluorescent dye reached the primary endpoint. Seven of the eight patients that reached the primary endpoint of Stage 2-3 AKI experienced two perioperative insults and one

patient only experienced one perioperative insult, which did not exhibit a statistically significant relationship.

Thirty patients (38%) experienced the postoperative complication of unsatisfactory urine output; 1 patient had a postoperative AKI diagnosis from hospital care givers; the 28-day mortality rate was 2.5% of the sample (n=2); and 13.9% (n=11) had an unplanned readmission within 30 days of surgery. The length of stay for primary endpoint patients with Stage 2-3 AKI was significantly longer than AKI Stage I and no AKI groups (7.5 $\pm$ 4.6 days; *p=.001*).

DISCUSSION

The average age of this cohort was 61 years; comparable to the results of a recent systematic review of similar surgical study populations.[17] We attempted to address the gap in the science related to usefulness of perioperative renal biomarkers in patients aged 20 to 50 years by including younger patients for gynecologic and urologic procedures; however, our sample reached a similar average age as those previously conducted studies. Gocze et al.[18] reported a 22.4% incidence of Stage 2-3 AKI development following major non-cardiac surgery, in our sample only a 10.1% rate. This was perhaps due to inclusion of laparoscopic and robotic procedures in the cohort of intraabdominal surgeries. Hypertension (HTN) as a preexisting medical condition displayed largest difference between the no AKI-Stage I AKI group and the Stage 2-3 AKI group. All patients meeting the primary endpoint had HTN; but this is a well-documented relationship.[4,15]

While eight participants (10.1%) of this study met the primary endpoint, 24 (30.4%) developed a low-grade AKI Stage 1 based on KDIGO criteria.[19] Only one patient was formally diagnosed in their record with an AKI upon unplanned readmission. This alone is cause for concern. Each time a patient experiences an AKI, there is increased risk of prolonged hospitalization, CKD development, and morbidity and mortality.[4,5,7,8,19] AKI is a commonly unrecognized postoperative complication.[4] There may be usefulness in deploying the NephroCheck® to trigger postoperative intervention, especially with the push for ambulatory

surgery and decreased hospital stays along with the COVID-19 pandemic impact of over filled hospitals. With no formal follow-up on development of low-grade AKIs, there are no renal protective strategies employed and patients are at the mercy of spontaneous recovery. The mean u[TIMP-2]*[IGFBP7] risk scores were higher for the eight patients reaching the primary endpoint as seen in Figure 2, indicating renal tubule stress and subsequent development of AKI that can be quantified by measuring these biomarkers. Patients who did not develop the primary endpoint only exhibited small rises in biomarker levels throughout the perioperative period.

Urinary [TIMP-2]*[IGFBP7] performed best for prediction of Stage 2-3 AKI at baseline and POD 1 with the AUROC values of 0.85 and 0.84 respectively. Generally, poor to fair performance is defined as AUROC values of 0.5 to 0.79 and good to excellent performance is defined as AUROC values of 0.8 or greater.[22] Two studies found similar good use of these two biomarkers on POD 1. Pilaczyk et al.[23] studied a cohort of 60 coronary artery bypass grafting surgical patients utilizing cardiopulmonary bypass and reported AUROC 0.87 on POD 1. Waskowski et al.[24] studied a cohort of 93 patients for emergent or elective abdominal aortic surgery and reported AUROC 0.98 on POD 1. Further, both time points in this study showed excellent NPV, 100% and 98%, indicating the biomarkers can also be used to accurately predict patients that will not experience AKI at this given threshold. Additionally, day of surgery samples at 6 PM exhibited high NPV (93%), but only marginal performance to identify true cases of moderate to severe AKI (AUROC 0.77). Cummings and colleagues[25] reported a similar 100% NPV in their 400 adult cardiac surgical patient population, with good usefulness of the max value of biomarkers between intraoperative and 6 hours postoperative (AUROC 0.82). For the sample in this research, 6 PM DOS samples were not a static time postoperative. For those having surgery first thing in the morning compared to those that entered surgery late in the afternoon, there were vast ranges of recovery periods. Additionally, there was a range of surgery length in this sample. The average length of surgery was 4 hours, ranging from 1.5 to 8.5 hours. In all eight cases that experienced AKI Stage 2-3, the biomarkers outpaced the

criteria utilized for AKI diagnosis, whether a rise in SCr or a decrease in urine output. The baseline sample was positive for AKI (risk score > 0.3) in 100% of these eight cases indicating u[TIMP-2]*[IGFBP7] was faster than the gold standard SCr in identifying Stage 2-3 AKIs.

No significant relationships were observed in statistical analysis of the included perioperative insults: hypotension (HOTN), hypovolemia, use of renal toxic medications, or postrenal kinked catheter or mechanical obstruction. While only one of the patients experiencing AKI Stage 2-3 did experience HOTN intraoperatively, the cumulative time was low. A point of interest in this sample, was 90% of the patients experienced blood pressures lower than 20% below their baseline mean arterial pressure for an average of 69 minutes or on average 29.7% of the total procedure length time. One confounding variable may be identifying the patient true baseline blood pressure. Often “white coat syndrome” is experienced the day of surgery related to stress and anxiety about the impending procedure. Due to an extremely inconsistent charting of pulse pressure variation, it was too difficult to determine true hypovolemia in the cohort. This measure was not analyzed.

The mean length of stay (LOS) for those with Stage 2-3 AKI was significantly longer than the mean LOS for those with no AKI and for those with Stage 1 AKI (*p=.003*). Of the two patients that expired within 28 days only one had experienced a moderate to severe AKI. Four of the eleven patients that experienced an unplanned readmission within 30 days postoperatively were categorized as meeting the primary endpoint. There are a host of confounding factors during surgery that can lead to these poor outcomes.[4]

Limitations and Future Directions. We acknowledge several limitations to this research which include single-center, small pilot sample size, and reliance on facility charting for data. In considering sample size, it was cost prohibitive to recruit a properly powered sample for this study. We elected to conduct a pilot study with a sample larger than the majority of primary studies cited in the literature; however, we acknowledge that these results might not be generalizable. During the chart review, there were multiple lacking data points for perioperative

fluid input and output totals. Postoperative urine output was an especially important piece of data as this was used to stage AKI incidence according to KDIGO guidelines.[19] Due to lack of complete charting for postoperative urine output, there is a potential some AKI cases were not identified by the gold standard method. The rate of Stage 2-3 AKI was low, compared to a similar study of non-cardiac surgical patients.[18] Due to these limitations, the results of this pilot study may not be generalizable.

CONCLUSION

In conclusion, perioperative elevations of u[TIMP-2]*[IGFBP7] at baseline and postoperative day 1 had good usefulness in predicting moderate to severe AKI development and strong negative predictive values at each timepoint. At baseline, u[TIMP-2]*[IGFBP7] elevations were more expeditious in identifying AKI than the gold standard model of late-rising SCr and decreased urine output. Larger studies are warranted to further investigate the use of these novel renal biomarkers in major intraabdominal surgeries for the early indication of moderate to severe AKI.

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Table 1

Baseline and perioperative patient characteristics for all patients and separated by acute kidney injury (AKI) status within 48 hours of intraabdominal surgery.

Characteristic	All	Stage 0/1 AKI	Stage 2-3 AKI
Gender			
Female	47 (59%)	40 (56%)	7 (88%)
Male	32 (41%)	31 (44%)	1 (13%)
Age years mean (sd)	61 (27-88)	60.5±12.6	69.3±6.6*
Body mass index kg/m2 mean (sd)		30.6±5.8	39.1±12.1**
Race			
American Indian	2 (3%)	2 (3%)	0
Black or African American	22 (28%)	20 (28%)	2 (25%)
White	55 (70%)	49 (69%)	6 (75%)
Ethnicity			
Hispanic or Latino	3 (4%)	3 (4%)	0
Not Hispanic or Latino	75 (95%)	67 (94%)	8 (100%)
Unknown/Not Reported	1 (1%)	1 (1%)	0
Medical History			
Diabetes (Type II)	19 (24%)	16 (23%)	3 (38%)
Hypertension	55 (70%)	47 (66%)	8 (100%)
Autoimmune disease	10 (13%)	9 (13%)	1 (13%)
Pre-eclampsia with pregnancy	2 (3%)	2 (3%)	0
Crush injuries	3 (4%)	2 (3%)	1 (13%)
Congestive heart failure	1 (1%)	0	1 (13%)
Renal insufficiency	7 (9%)	6 (8%)	1 (13%)
Blood transfusion within 3 months	1 (1%)	1 (1%)	0
Sepsis	3 (4%)	2 (3%)	1 (13%)
None	17 (22%)	17 (24%)	0
ASA Status			
ASA 2	32 (41%)	30 (42%)	2 (25%)
ASA 3	41 (52%)	36 (51%)	5 (63%)
ASA 4	6 (8%)	5 (7%)	1 (13%)
Surgery			
Open	31 (39%)	23 (32%)	8 (100%)
Laparoscopic/Robotic	48 (61%)	48 (68%)	0

Surgery Specialty			
Bariatric	1 (1%)	0	1 (13%)
Colorectal	12 (15%)	10 (14%)	2 (25%)
General	19 (24%)	15 (21%)	4 (50%)
Gynecology	10 (13%)	9 (13%)	1 (13%)
Nephrology	10 (13%)	10 (14%)	0
Transplantation	1 (1%)	1 (1%)	0
Urology	26 (33%)	26 (37%)	0
Postoperative Complications			
AKI Diagnosis	1 (1%)	0	1 (13%)
28-day mortality	2 (3%)	1 (1%)	1 (13%)
Unplanned readmission within 30 days	11 (14%)	7 (10%)	4 (50%)
Unsatisfactory urine output	30 (38%)	22 (31%)	8 (100%)
Length of Hospitalization days mean (±sd)		2.6±3.5	7.5±4.6**

Note: All N=79, stage 0/1 AKI N=71, stage 2/3 AKI N=8.

*p<.05. **p<.01.

Table 2

AUROCs, sensitivity, specificity, and predictive values for development of Stage 2-3 AKI at different perioperative measurements of u[TIMP-2]*[IGFBP7].

Timepoint	AUROC	Sensitivity	Specificity	PPV	NPV
Baseline	0.85	100%	58%	22%	100%
DOS 6 PM	0.77	57%	69%	17%	93%
POD 1	0.84	86%	66%	21%	98%

Abbreviations: PPV, positive predictive value; *NPV*, negative predictive value.

Figure 1

Consort diagram. Acute kidney injury (AKI) is the Kidney Disease Improving Global Outcomes (KDIGO)[19] stage reached within 48 hours of surgery.

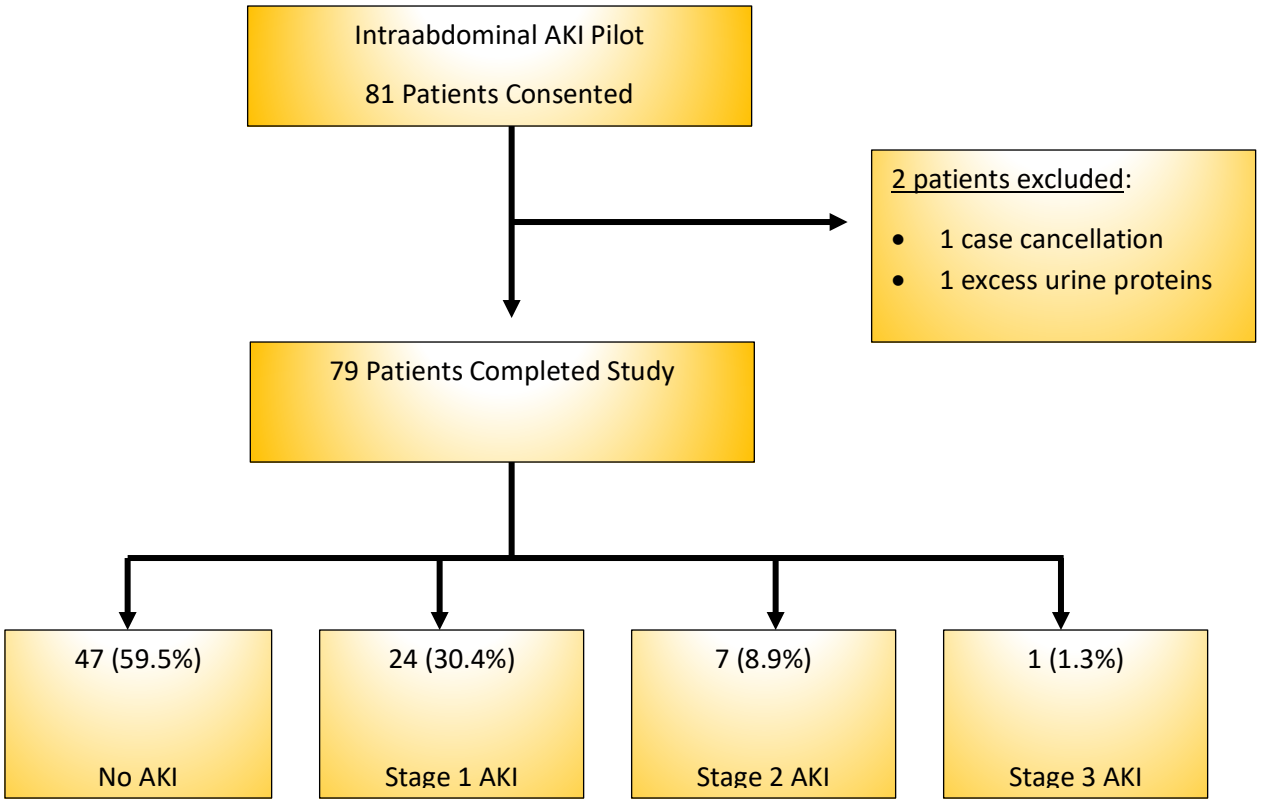


Figure 2

Mean perioperative urinary [TIMP-2]*[IGFBP7] concentrations in patients with no acute kidney injury (blue), stage 1 AKI (orange), and stage 2 or 3 AKI (gray). *AKI,* acute kidney injury; *DOS,* day of surgery; *POD,* postoperative day.

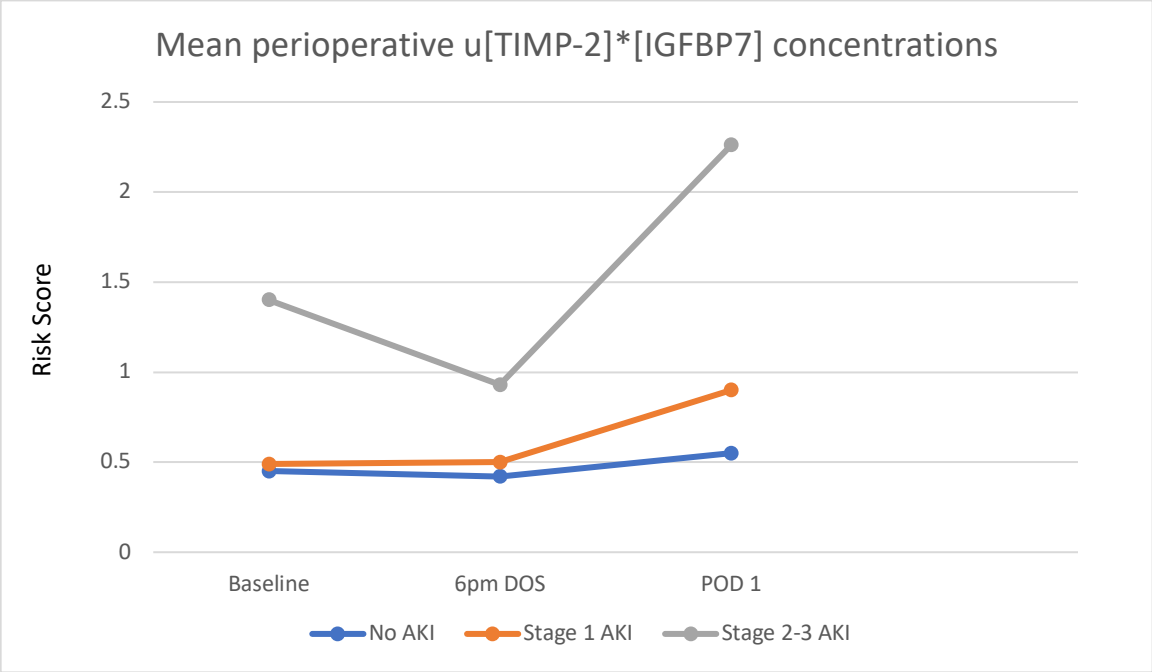
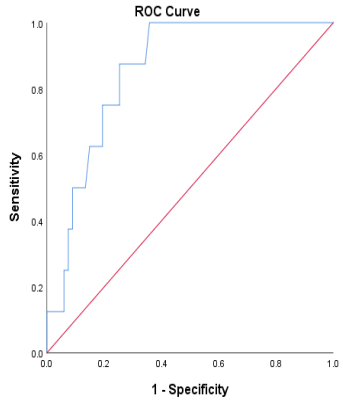


Figure 3

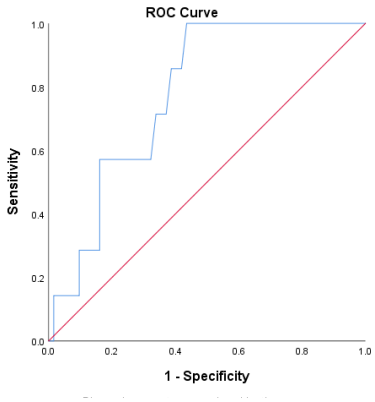
ROC Curves and Analyses for NephroCheck®



Baseline

AUROC 0.85

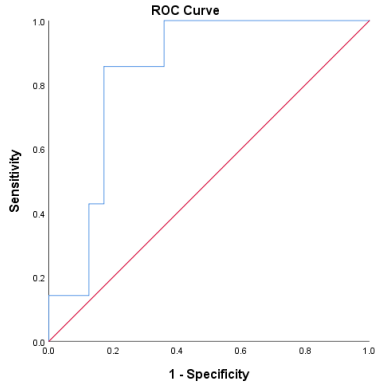
(95%CI, 0.76, 0.95)



DOS 6 PM

AUROC 0.77

(95%CI, 0.64, 0.91)



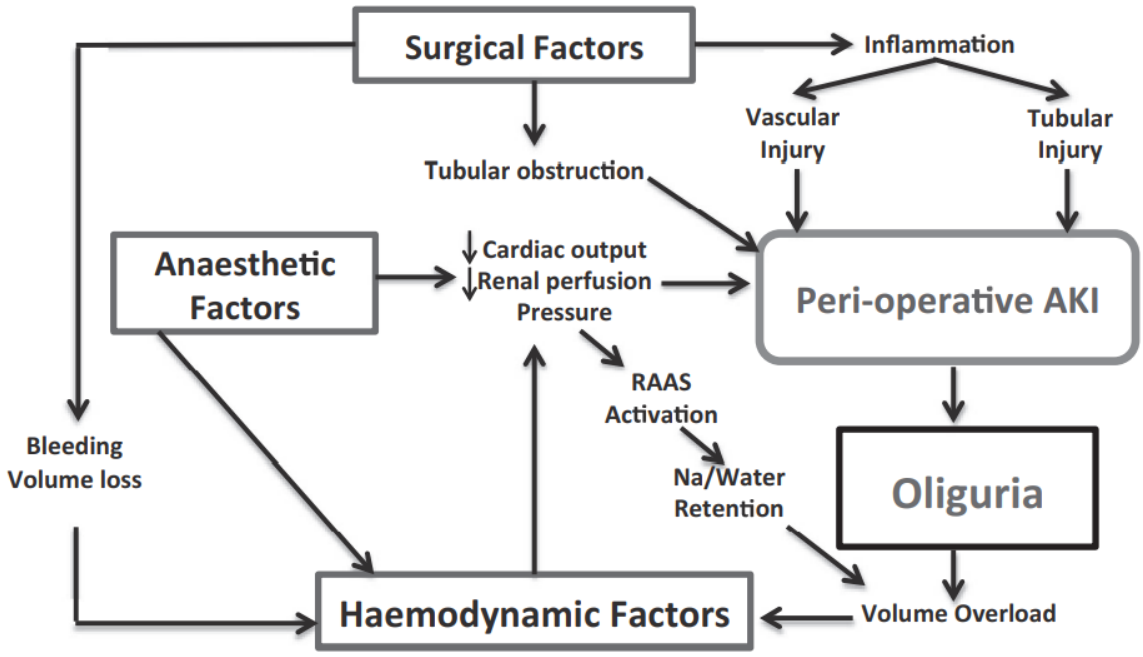
POD 1

AUROC 0.84

(95%CI, 0.74, 0.94)

Appendix A

Potential Pathophysiology of Perioperative AKI



Note: From McKinlay et al., 2018, p. 88.

Appendix B

KDIGO Clinical Practice Guidelines for Defining and Staging AKI (2012)

AKI is defined as any of the following (not graded):

- Increase in SCr by ≥ 0.3 mg/dL (≥ 26.5 μmol/L) within 48 hours; or
- Increase in SCr to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or
- Urine volume < 0.5 mL/kg/hr for 6 hours

Staging of AKI:

Stage	Serum creatinine (SCr)	Urine output
1	1.5-1.9 times baseline OR ≥ 0.3 mg/dL (≥26.5 μmol/L) increase	< 0.5 mL/kg/h for 6-12 hours
2	2.0-2.9 times baseline	< 0.5 mL/kg/h for ≥ 12 hours
3	3.0 times baseline OR Increase in SCr to ≥ 4.0 mg/dL (≥353.6 μmol/L) OR Initiation of renal replacement therapy	< 0.3 mL/kg/h ≥ 24 hours OR Anuria for ≥ 12 hours

Appendix C

Data Collection Tool

HISTORY AND PHYSICAL			
Participant #:	Gender:	DOB:	Ht/Wt:
Race: Ethnicity:	Baseline Vitals: BP _____ HR_____ RR_____ SaO2_____ EKG _____	Previous abnormal labs: (defined as) GFR <60 Cr > 1.1 mg/dL women/ 1.3 mg/dL men BUN >20 Urine albumin > 30	GFR _____ Cr/BUN _____ U/A _____ Urine albumin_____ Ur bilirubin _____ H/H _____
Response patterns to stressors (Previous AKI after surgery):	□ Yes Date: _____ □ No	Surgical History r/t stressing the kidneys:	□ Procedures utilizing contrast dye □ any great vessel clamping □ Trauma
Medical History:	□ Diabetes I or II □ Hypertension □ Autoimmune disorders □ History of pre-eclampsia □ Crush injuries □ CHF □ renal insufficiency □ Blood transfusion – in last 3 months □ Sepsis	Medications History[1]:	□ long term antibiotic use □ long term steroid therapy □ Contrast dyes □ antiretrovirals □ long term NSAID use □ Cimetidine □ Insulin/Metformin □ Heroin/methamphetamine □ ACE inhibitors □ARBs □ Diuretics

Note. Rules for data collection:

- Response patterns to stressors include previous documented AKI after surgery and treatment
- Medical and Surgical Hx to be extracted from primary physician, specialty physician and anesthesia H&P
- ASA classification and anesthetic data to be extracted from anesthesia preop evaluation and anesthesia record
- Surgery type and known causes of AKI to be extracted from electronic surgical anesthesia record
- Baseline SCr lab values and repeated measures to be extracted from results review in EMR.
- NephroCheck® specimen preparation and lab values will be run in research lab and results documented.
- Antibiotics involved in injury: aminoglycosides, cephalosporins, amphotericin B, bacitracin, and vancomycin[1]. Angiotensin converting enzymes = ACE inhibitors; angiotensin receptor blockers = ARBs. [1] (Thompson et al., 2020)
- Post-operative phase data to be extracted from notes, diagnoses, discharge data, and nursing notes in the EMR.

DAY OF SURGERY			
ASA Class:	Surg Start/End:	Scheduled Procedure:	
Known causes of AKI evidenced in surgical record: (preop → PACU D/C)	Prerenal: □ Hypotension – MAP < 65 mmHg □ Hypovolemia – PPV > 13%	Intrarenal: □ Contrast dye □ antibiotic use - _____ □ ACEI - _____	Postrenal: □ kinked catheter □ ureteral obstruction
Anesthesia:	□ GETA/volatile _____ _____ Duration _____ FGF rate □ TIVA □ Regional POPM	Perioperative Intake/Output per hr: 1: _____ 6: _____ 2: _____ 7: _____ 3: _____ 8: _____ 4: _____ 9: _____ 5: _____ 10: _____	Totals: □ Crystalloid: _____ LR or NS □ Colloid: _____ □ Blood: _____ □ EBL: _____ □ UOP: _____
Meds:	PreOP Meds: □ Ketorolac □ Caldolor □ Statin	Intraop Meds: □ Ketamine □ NMB: _____ □ Diuretic: _____ □ Phenylephrine: _____ mcg	**PACU VS:** Temp:_____ HR: _____ RR: _____ BP: _____ Sats: _____
UR SPECIMEN:			
Collection time:	*Centrifuge time:*	*Refrigerated Y/N:*	*NephroCheck® time:*
Baseline -	Baseline -	Baseline -	Baseline -
DOS -	DOS -	DOS -	DOS -
POD 1 -	POD 1 -	POD 1 -	POD 1-
UR SPECIMEN PREPARATION:	*uProtein:*	*uBilirubin:*	
Baseline:			
DOS:			
POD 1:			
LAB PROTOCOL RESULTS:	NephroCheck®		Serum Creatinine:
Baseline:		Baseline:	
DOS:		POD 1:	
POD 1:		POD 2:	

POST-OPERATIVE PHASE			
Complications:	□ AKI □ Sepsis □ Unplanned dialysis □ UOP <30ml/hr postop □ 28 day mortality	Discharge Date: LOS:	Readmission Y or N
Post-operative I/Os:			
6hr	12hr	18hr	24hr
Crystalloid _____	Crystalloid _____	Crystalloid _____	Crystalloid _____
Colloid _____	Colloid _____	Colloid _____	Colloid _____
UOP _____	UOP _____	UOP _____	UOP _____
PRE-RENAL AKI ADDENDUM			
*if Hypotension checked above: defined as MAP < 65 mmHg, document the number of minutes spent in hypotension during the case (for A-line gather data per minute; for NIBP gather data each 3 minutes)			
*if Hypovolemia checked above: defined as PPV > 13%, document the pulse pressure variation during periods of hypotension to determine the likelihood of hypovolemia and fluid responsiveness. If PPV not recorded in EMR; utilize BP data over one breath cycle to calculate with the equation PPV = $((PP_{max} - PP_{min}) / ((PP_{max} + PP_{min})/2)) \times 100$ (Hussein et al., 2018).			
SERUM CREATININE ADDENDUM			
*if patient hospitalized longer than 2 days Post-op; collect SCr level each morning until discharge. SCr levels may not spike for 24 hours to 7 days after the renal injury that leads to an AKI (van Duijl et al., 2019)			

Appendix D

Characteristics of Studies Included in Final Literature Review

Study	Country	Study Design	Purpose	Sample	Age of Participants	Surgical Setting	AKI Definition/ Tool	Time of Measurement	Primary Endpt/ Cut-off values
Cummings et al., 2019	USA	PC	To evaluate TIMP-2*IGFBP7 as a postop marker of renal stress and AKI	400 adult RCT cohort of previous study published (Nov 2009- Dec 2014)	67 (58-75)	Cardiac surgery (mixed on pump and off pump)	KDIGO/ NephroCheck	Urine collected after induction of anesthesia (baseline), 30 min following initiation of CPB or off-pump grafting, following end of CPB or OpCAB, upon ICU adm, 6 hr after adm, and at 9am POD 1, 2, and 3. (8 samples)	Stage 2-3 AKI within 48 hr; cut-off >0.3 for stage 2-3 AKI
Gunnerson et al., 2016	Europe and North America	PC	To assess whether uTIMP-2*IGFBP7 accurately identifies patients at risk for AKI that are having surgery	375 patients (COMBO of Sapphire and Topaz study)	Mod-Sev AKI 67 (SD 13), No AKI 64 (SD 14)	Any surgery admitted to ICU	KDIGO/ NephroCheck	Urine collected at enrollment. Sapphire study test sampled once, Topaz study tested sample 3x and reported median value.	Moderate-severe AKI (2/3) within 12 hr; cut-off 0.3 and 2
Zaouter, Potvin et al., 2018	France	PC	To assess the ability of TIMP-2 and IGFBP7 and doppler renal resistive index (RRI) in detecting CSA-AKI at an early stage	50 (Sept-Nov 2014)	72.5±8	Elective CPB	KDIGO/ NephroCheck	Before GA induction, 1 hr, 4 hr, 12 hr, and 24 hr postop.	Incidence of AKI until POD 7; cut-off 0.3
Dusse et al., 2016	Germany	PC	To evaluate the ability of TIMP-2*IGFBP7 to early predict AKI after TAVI	40 patients (Jan-Sept 2014)	81.2±5.6	TAVI (either transapical or transaortic)	KDIGO/ NephroCheck	Urine within 4 hr after surgery, then 2x daily until discharge from ICU and a max of 4 days (whichever occurs first). SCr prior and 4 hr after surgery, and at least 2x daily post-op.	New occurrence AKI stage 2-3 within 48hr after surgery; Cut-off POD 1 - 1.03. Max value in 24h cut-off 0.91.

Study	Country	Study Design	Purpose	Sample	Age of Participants	Surgical Setting	AKI Definition/ Tool	Time of Measurement	Primary Endpt/ Cut-off values
Finge et al., 2017	France	PC	To assess the ability of TIMP-2*IGFBP7 to predict postop AKI 3hr postop in patients undergoing CPB during cardiac surgery	93 patients in final analysis (of 108 eligible) (Apr-Sept 2014)	62-81	CPB	KDIGO/ NephroCheck	Anesthesia induction and 3 hr postop.	Occurrence of AKI stage >0 within first 48 hr; assessing different cut off values - 0.3, 0.5, 2.
Zaouter, Priem et al., 2018	France	PC	To determine predictive value of biomarker in detecting AKI after a TAVI-procedure at an early phase.	62 (Sept 2016 - Feb 2017)	80 (SD 7)	TAVI	KDIGO/ NephroCheck	Preop, at first micturition post-procedure (or after catheterization for pts that did not empty bladder within 6 hr), and first micturition on morning POD1 (or 24 hr after adm for those with catheter)	Incidence of AKI
Wetz et al., 2015	Germany	PC	Aim to clarify the quantification of TIMP-2 and IGFBP7 as an adequate dx test to detect CSA-AKI by doing a thorough analysis of the diagnostic strength	42 (Aug 2013 - Feb 2014)	median 72	Elective and non-elective CABG with CPB	KDIGO/ NephroCheck	Pre-operative baseline, end of surgery, 4 hr after arrest of CPB, 8am POD1.	Development of AKI; assessed both cut-off 0.3 and 2
Gocze et al., 2015	Germany	PC	To evaluate use of TIMP-2*IGFBP7 to early predict AKI after major surgery	107 adult patients (May-Nov 2013)	mean 60.03 (SD 14.78)	Major non-cardiac surgery	KDIGO/ NephroCheck	Urine sample taken soon after transfer to ICU from OR.	Cut-off >0.3
Meersch et al., 2014	Germany	PC	To evaluate TIMP-2*IGFBP7 as an early marker of CSA-AKI and marker for renal recovery	50 adult patients (June-Sept 2013)	71±12	CPB	KDIGO/ NephroCheck	Urine pre-op (immediately post induction) and 4 hr, 12 hr, and 24 hr after coming off CPB; serum Cr collected preop, 4 hr, 12 hr, 24 hr, 48 hr, 72 hr, and hospital discharge.	Any AKI after cardiac surgery; cut-off value 0.5

Study	Country	Study Design	Purpose	Sample	Age of Participants	Surgical Setting	AKI Definition/ Tool	Time of Measurement	Primary Endpt/ Cut-off values
Pilarczyk et al., 2015	Germany	PC	To evaluate uTIMP-2*IGFBP7 as an early predictor of AKI after CABG	60 adult patients (Jan-Oct 2014)	AKI 2/3 76.2±3.9; AKI 0/1 68.8±9.1	CPB	KDIGO/ NephroCheck	Urine collected 4 hr after surgery and then every 12 hr post-operatively until discharge; along with UOP and SCr.	Stage 2-3 AKI within 48hr; cut-off value 0.15 at 4hr, 0.89 POD 1
Wang et al., 2017	China	PC	To assess the ability of TIMP-2 and IGFBP7 to be an excellent predictor of AKI following cardiac surgery in Asian populations	57 adult patients (May 2016)	60 (49-65)	Cardiac surgery	KDIGO/ NephroCheck	Urine samples collected prior to surgery, in 2 hr intervals from 0 hr to 12 hr after ICU admission, and 24 hr after ICU admission.	Moderate-sev AKI (2/3) within 7 days following surgery.
Oezkur et al., 2017	Germany	PC	To investigate predictive value of uTIMP-2*IGFBP7 associated with CSA-AKI at various time points	150 patients (Apr-Dec 2014)	median 67	Cardiac surgery, including CPB	KDIGO/ NephroCheck	PreOp, ICU-adm, 24 hr, 48 hr.	AKI within first 48hr after surgery; cut-off 0.3 for categorical and as a continuous variable

Waskowski et al., 2021	Switzerland	PC	To investigate uTIMP-2*IGFBP7 as early biomarker for AKI in aortic surgery (TIGER) study	93 patients (Jun 2018 to Sept 2019)	69.4± 9.9	Emergency or elective abdominal aortic surgery (open repair w/ infra- or suprarenal clamping, or EVAR)	KDIGO/ NephroCheck	After induction (baseline), after end of anesthesia (before ICU adm), morning POD-1.	Stat sig in total TIMP-2*IGFBP7 levels at POD1 in pt w/ or w/o any postop AKI in first 7 days; cut-off 0.3 and 2.0
Pilarczyk et al., 2022	Germany	PC	To analyze predictive accuracy of Cyc-C and uTIMP-2*IGFBP7 in thoracic aortic surgery	101 patients (Dec 2016 to Mar 2018)	68.51±11.46 no AKI/AKI I 72.72±6.19 AKI II/III	Thoracic aortic surgery with moderate hypothermic circ arrest	KDIGO/ NephroCheck	Baseline within 1 hr surgery, 2 hr PO, 4 hr PO, 8 AM POD1.	AKI II-III within 48 hours/varying cut-offs.
Kanchi et al., 2023	India	PC	To test a single value of postop NC at 4 hrs PO to predict AKI in off-pump CABG	90 patients (Dec 2017 to Nov 2018)	53.49±9.05	Off-pump CABG	KDIGO/ NephroCheck	Baseline and 4 hr postop.	Any AKI/cut-off 0.3

Abbreviations: Endpt, endpoint; PC, Prospective cohort design; AKI, acute kidney injury; KDIGO, Kidney Disease Improving Global Outcomes guidelines; CPB, cardiopulmonary bypass; OpCAB, off-pump coronary artery bypass; POD, post-operative day; CSA-AKI, cardiac surgery-associated acute kidney injury; SCr, serum creatinine.

Appendix E

IRB Approval

IRB: Study Correspondence Letter

umcirb@ecu.edu <umcirb@ecu.edu>
Tue 02/15/2022 09:10 AM
To: Ciuca, Angela Marie <ciucaa19@students.ecu.edu>

EAST CAROLINA UNIVERSITY
University & Medical Center Institutional Review Board
4N-64 Brody Medical Sciences Building· Mail Stop 682
600 Moye Boulevard · Greenville, NC 27834
Office **252-744-2914** · Fax **252-744-2284** ·
rede.ecu.edu/umcirb/

Notification of Initial Approval: Expedited

From: Biomedical IRB
To: Angela Ciuca
CC: Linda Bolin
Date: 2/15/2022
Re: UMCIRB 21-000826
uTIMP-2*IGFBP7 and AKI non-cardiac surgery

I am pleased to inform you that your Expedited Application was approved. Approval of the study and any consent form(s) occurred on 2/14/2022. The research study is eligible for review under expedited category # 1,3,5. The Chairperson (or designee) deemed this study no more than minimal risk.

As the Principal Investigator you are explicitly responsible for the conduct of all aspects of this study and must adhere to all reporting requirements for the study. Your responsibilities include but are not limited to:

1. Ensuring changes to the approved research (including the UMCIRB approved consent document) are initiated only after UMCIRB review and approval except when necessary to eliminate an apparent immediate hazard to the participant. All changes (e.g. a change in procedure, number of participants, personnel, study locations, new recruitment materials, study instruments, etc.) must be prospectively reviewed and approved by the UMCIRB before they are implemented;

2. Where informed consent has not been waived by the UMCIRB, ensuring that only valid versions of the UMCIRB approved, date-stamped informed consent document(s) are used for obtaining informed consent (consent documents with the IRB approval date stamp are found under the Documents tab in the ePIRATE study workspace);

3. Promptly reporting to the UMCIRB all unanticipated problems involving risks to participants and others;

4. Submission of a final report application to the UMICRB prior to the expected end date provided in the IRB application in order to document human research activity has ended and to provide a timepoint in which to base document retention; and

5. Submission of an amendment to extend the expected end date if the study is not expected to be completed by that date. The amendment should be submitted 30 days prior to the UMCIRB approved expected end date or as soon as the Investigator is aware that the study will not be completed by that date.

The approval includes the following items:

Name	Description
AKI Study Data Collection Tool	Data Collection Sheet
AKI Study Informational Flyer	Recruitment Documents/Scripts
AKI Study Merged Informed Consent and HIPAA Authorization	Consent Forms
AKI Study Protocol for Recruitment and Script to Potential Participants	Recruitment Documents/Scripts
AKI Study Waiver for Contact Information	HIPAA Documentation
CIUCA AKI Proposal	Study Protocol or Grant Application
PI Interview for eligibility and health history	Surveys and Questionnaires

For research studies where a waiver or alteration of HIPAA Authorization has been approved, the IRB states that each of the waiver criteria in 45 CFR 164.512(i)(1)(i)(A) and (2)(i) through (v) have been met. Additionally, the elements of PHI to be collected as described in items 1 and 2 of the Application for Waiver of Authorization have been determined to be the minimal necessary for the specified research.

The Chairperson (or designee) does not have a potential for conflict of interest on this study.

Appendix F

ECU COVID-19 Human Subject Research Risk Assessment Form

Updated 7.01.2020

ECU COVID-19 Human Subject Research Risk Assessment Form

College ECU College of Nursing

Department Nursing Sciences

Faculty Name Dr. Linda Bolin, Dissertation Chair/ Angela Ciuca, PhD(c) student

Study Title and IRB Number

Early Identification of Perioperative Acute Kidney Injury Utilizing Novel Renal Biomarkers

(uTIMP-2*IGFBP7 and AKI non-cardiac surgery - UMCIRB 21-000826)

OSHA has developed COVID-19 planning guidance to reduce the impact of the COVID-19 outbreak conditions on businesses, workers, customers, and the public. OSHA has divided job tasks into four risk exposure levels: very high, high, medium, and lower risk. In order to assess the ability to safely re-start human subject research, we need to determine the most appropriate OSHA risk level for your research protocol. This will help facilitate the safe involvement of study participants, research staff, and students in your research.

Lower Exposure Risk: Research protocols that do not require contact with people known to be, or suspected of being, infected with SARS-CoV-2 nor frequent close contact with (i.e., within 6 feet of) the general public.

- Minimal contact with the study participants.

Medium Exposure Risk: Research protocols that require frequent and/or close contact with (i.e., within 6 feet of) people who may be infected with SARS-CoV-2, but who are not known or suspected COVID-19 patients.

- Research participants in this risk group may have frequent contact with lab personnel where maintaining 6 feet distance is not possible.
- Research protocols that require direct contact with study participants, such as placement of wearable devices.

High Exposure Risk: Research protocols with high potential for exposure to known or suspected sources of COVID-19 and/or potential high risk for transmission with people who may be infected with SARS-CoV-2, but who are not known or suspected COVID-19 patients. Examples for this category include:

- Research protocols that involve lab personnel exposed to known or suspected COVID-19 patients.
- Research personnel collecting or handling specimens from people who are not known or suspected COVID-19 patients.

Very High Exposure Risk: Research protocols with high potential for exposure to known or suspected sources of COVID-19 during specific laboratory procedures. Examples in this category include:

- Research personnel performing aerosol-generating procedures (e.g., intubation, cough induction procedures, bronchoscopies, some dental procedures and exams, or invasive specimen collection) on known or suspected COVID-19 patients.
- Research personnel collecting or handling specimens from known or suspected COVID-19 patients (e.g., manipulating cultures from known or suspected COVID-19 patients).

Updated 7.01.2020

Research Protocol Review

Assigned Risk Level: LOW [ ] MEDIUM [x] HIGH [ ] VERY HIGH [ ]

Rationale for Risk Level Assignment:

In your rationale, provide a brief summary of your research protocol, detail frequency and type of contact required with study participants in accordance with your research protocol, and indicate who your study population is. Also, refer to the **CDC guidelines** for determining if your study population is considered higher risk for severe illness :

COVID+ patients are excluded from this study. During urine specimen collection, the PI will obtain urine samples from the participant's existing foley catheter that was inserted prior surgery. Urine specimens will be collected at three time points during the first 24 hours of admission. All participants in this study were screened for COVID prior to surgery.

Angela Ciuca, PhDc Student	DocuSigned by: Angela Ciuca CE0A5241EB684FC...	1/18/22
Lab PI Name	Signature	Date
Pam Reis, PhD, Program Director	DocuSigned by: Pamela Reis 1FA749F0FCB24CC...	1/18/2022 | 2:51 PM EST
Department Chair Name	Signature	Date
Heather Wright, PhD	DocuSigned by: Heather Harris Wright 2255352184BC402...	1/20/2022 | 9:23 AM EST
Associate Dean for Research Name	Signature	Date
Linda Bolin, PhD, Faculty Chair	DocuSigned by: Linda P. Bolin PhD 6F5DA0C46B2244F...	1/18/2022 | 2:46 PM EST
Facility Study Site Director Name	Signature	Date

Appendix G

Attending Physician Signature Forms

ATTENDING PHYSICIAN SIGNATURE FORM

Protocol Title: **Early Identification of Perioperative Acute Kidney Injury Utilizing Novel Renal Biomarkers**

Principal Investigator Name: Angela Ciuca, DNAP, CRNA, PhD student

The following physicians acknowledge their willingness to participate in the above named research study, have read the protocol describing the study, and agree to allow their patients to participate.

Signature	Print	Date
	Armando Perez-Guzman	11/15/21
	Rebecca Smith	11/15/21
	Rebecca Bl	11/15/21
	ZERVOS	11/15/21
	PAGE	11/16/21

ECU

ATTENDING PHYSICIAN SIGNATURE FORM

Protocol Title: **Early Identification of Perioperative Acute Kidney Injury Utilizing Novel Renal Biomarkers**

Principal Investigator Name: Angela Ciuca, DNAP, CRNA, PhD student

The following physicians acknowledge their willingness to participate in the above named research study, have read the protocol describing the study, and agree to allow their patients to participate.

Signature	Print	Date
	DeMARK	5/26/22
	AK Crockett	5/27/22
	M Romine	6/8/22
	Paige Fisher	6/8/2022
William E Brown MD	W.E. Brown MD	6/8/2022

UMCIRB version 3/11/11

ECU

CAPTURE YOUR MOTIVATION

ATTENDING PHYSICIAN SIGNATURE FORM

Protocol Title: **Early Identification of Perioperative Acute Kidney Injury Utilizing Novel Renal Biomarkers**

Principal Investigator Name: Angela Ciuca, DNAP, CRNA, PhD student

The following physicians acknowledge their willingness to participate in the above named research study, have read the protocol describing the study, and agree to allow their patients to participate.

Signature	Print	Date
	WAQAR AKRAM	06/08/22
	Jonathan H. Taylor	6-8-22
	[illegible]	6/9/22
	Matt Collins	6/5/22
	Matthew Pamin	6/10/2022

ECU

ATTENDING PHYSICIAN SIGNATURE FORM

Protocol Title: **Early Identification of Perioperative Acute Kidney Injury Utilizing Novel Renal Biomarkers**

Principal Investigator Name: Angela Ciuca, DNAP, CRNA, PhD student

The following physicians acknowledge their willingness to participate in the above named research study, have read the protocol describing the study, and agree to allow their patients to participate.

Signature	Print	Date
Jill Sutton	Jill Sutton	6·10·2022
	Honaker	6-10-22
	Dave Semer	6-14-22

Attending Physicians:

1. Armando E Perez Ginnari, MD

   ECU Physicians – General and Specialty Surgery

2. Rebecca A. Snyder, MD, MPH, FACS, FSSO

   ECU Physicians – Surgical Oncology

3. Patrick Brillant, MD

   Physicians East – Colon and Rectal Surgery

4. Emmanuel E. Zervos, MD

   ECU Physicians – Surgical Oncology

5. Alexander A Parikh, MD, MPH, FACS, FSSO

   ECU Physicians – Surgical Oncology

6. Eric J. Demaria, MD

   ECU Physicians – General and Specialty Surgery; Bariatric Surgery

7. Kerianne Crockett, MD

   ECU – Obstetrics & Gynecology

8. Margaret Romine, MD

   ECU Physicians – Surgical Immunology and Transplantation

9. Paige Fisher, MD

   Physician's East – Obstetrics & Gynecology

10. William Brown, MD

    Physician's East – Obstetrics & Gynecology

11. Warqaa M. Akram, MD

    ECU Physicians – Surgical Oncology, Colorectal Surgery

12. Jonathan Taylor, MD

    Physician's East – Urology

13. Hale Stephenson, MD

    Physician's East – Obstetrics & Gynecology

14. Matthew Collins, MD

    ECU Health - Urology

15. Matthew Romine, MD

    ECU Health – General Surgery

16. Jill Sutton, MD

    ECU Health – Obstetrics & Gynecology

17. Michael D. Honaker, MD

    ECU Health – Surgical Oncology

18. Diane Semer, MD

    Physician's East – Oncology

Appendix H

Surgical Team Provider (STP) Protocol for Recruitment

Early Identification of Perioperative Acute Kidney Injury Utilizing Novel Renal Biomarkers

Protocol for Recruitment

STUDY INFORMATION: A research study is being conducted by a PhD of Nursing Science student at East Carolina University. This study is being done to learn more about identifying acute kidney injuries (AKI) more quickly after major non-cardiac surgery. Between 30-40% of hospital-acquired acute kidney injuries occur during the perioperative period with the stress of surgery and anesthesia. This injury pattern has a continuum from mild dysfunction to chronic kidney disease. Currently, our gold standard to monitor for AKI is the serum creatinine test that is a lagging indicator (24-48 hours after injury) and only peaks when there is damage and loss of50% of renal function. Novel renal inflammatory biomarkers are expressed by renal tubular cellsduring periods of stress. This novel test is highly specific for a risk assessment for development of a high stage AKI within the next 12 hours. With earlier identification, the risk of long-term outcomes can be decreased.

Protocol for Approaching Eligible Patients:

- During pre-surgical workup identify eligible participants.
- **Eligible** patients include:
  - ≥ 21 years of age
  - Scheduled for major non-cardiac intraabdominal surgery
    - Surgeries that will likely last > 3 hours where the patient will have a foley catheter
    - Surgeries scheduled for Tuesday, Thursday, or Friday
  - English speaking
  - Cognitively intact (Investigator will obtain informed consent for the study)
- **Ineligible** patients include:
  - Trauma and emergency surgical patients
  - History of renal transplant
  - COVID positive patients
  - Current chemotherapy regimens
  - Proteinuria (urine albumin > 125 mg/dL)
  - Severe hyperbilirubinuria (urine bilirubin > 7.2 mg/dL)
  - Methylene blue concentrations above 0.49 mg/L
- Read the **script to eligible participants**.
- Share the **Study Flyer** with interested participants.
- For those amenable complete Participant Communication Log (PCL).
- At the end of each day, please keep the PCL in a secured locked location. The PI will contact you and collect these.

Thank you for your assistance with this study,

Angela Ciuca, DNAP, CRNA, PhD student at ECU College of Nursing, Principal Investigator
Linda P. Bolin, PhD, RN, ANP, FAHA; Chair of Dissertation Committee
For any further questions please contact: 864-650-4377 or ciucaa19@students.ecu.edu

Appendix I

Script to Eligible Participants

"You have been identified as a potential participant for a research study. The purpose of this study is to identify acute kidney injuries (AKI) more quickly after major surgery. Results of the study may help decrease the risk of long-term complications and improve future patient outcomes. If you consent to this study, there will be a brief interview (10-15 minutes) about your health history before surgery. For this study, the investigator will obtain urine samples from your foley catheter during your admission for surgery at Vidant Medical Center. Three urine samples will be collected from your foley catheter at the beginning of surgery, in the evening of your surgical day, and in the morning of the day after surgery. There is no cost to participate.

Participation is voluntary. Your care will not be altered by your decision. If you consent, you may withdraw from the study at any time and you will continue to receive the same care.

Participants that are eligible for this study include adults older than 21 years of age, scheduled for major non-cardiac intraabdominal surgery, English speaking and cognitively intact. The contact person for this study is Angela Ciuca, a PhD nursing candidate at ECU. She can be reached at 864-650-4377 and her contact information is at the bottom of the study informational flyer for your convenience should you have questions about the study."

Appendix J

Informational Study Flyer

Early Identification of Perioperative Acute Kidney Injury Utilizing Novel Renal Biomarkers

Thank you for your willingness to learn about this study.

What is the purpose? To identify acute kidney injuries (AKI) more quickly after major surgery. Results of the study may help decrease the risk of long-term complications and improve future patient outcomes.

Who can participate?

- ≥ 21 years of age
- Scheduled for major non-cardiac intraabdominal surgery
- English speaking
- Cognitively intact and able to consent to the study

What you need to do? If you consent to this study, there will be a brief interview about your health history before surgery. During the study, the investigator will obtain three urine samples from your foley catheter at the beginning of surgery, in the evening after surgery, and in the morning the day after surgery.

Where will it take place? In the surgical area and recovery areas that you will be admitted to in the hospital.

How long will it take? 10-15 minutes to obtain your health history. Urine will be collected during your surgical procedure and during your recovery phase until discharge. This time will vary from participant to participant.

- Your care during your surgical stay **will not be altered** by these labs or this study.
- Participation in this study is **voluntary**.
- You may choose not to participate; this decision will have no effect on your care.
- If you participate, you may leave the study at any time, and you care will not be affected.
- There is **no cost** to participate in the study.

Contact Information: If you have additional questions or concerns prior to your surgery date, please contact Angela Ciuca, DNAP, CRNA, PhD Candidate at 864-650-4377 or ciucaa19@students.ecu.edu.

Appendix K

Participant Communication Log

Participant Communication Log (PCL)

SURGEON: _____
RN/Staff: _____

AMENABLE PATIENT NAME:	PLANNED SURGERY/ DATE OF SURGERY:	CONTACT INFO: (PHONE/EMAIL)

Appendix L

Eligibility Questionnaire

Participant #: _____

Eligibility and Interview for Potential Participants of AKI Study:

Eligibility:

Are you at least 21 years of age? YES NO

DOB: _____

Are you scheduled for major non-cardiac intraabdominal surgery? YES NO

What procedure? _____

Surgery date: _____

Are you English speaking? YES NO

Have you had a kidney transplant? YES NO

Are you currently COVID positive? YES NO

Positive date: _____ Surgery date: _____

Are you currently taking chemotherapeutic agents? YES NO

Agent: _____ End date for chemotherapy: _____

After establishing eligibility – an intake interview about health history:

What is your race? _____ Ethnicity? _____

What is your gender? _____

Have you had an AKI before? YES NO UNKOWN

If Yes, do you know what it was related to? _____

If Yes, do you know the date: _____

Have you had surgery before? YES NO What surgeries? _____

Did you have procedures utilizing contrast dye? YES NO

Did you have any great vessel clamping? _____

Did you ever have a trauma that stressed your kidneys? _____

Medical History? Circle if yes

Diabetes I or II	Hypertension	Autoimmune disorders
History of Pre-eclampsia	Crush injury	CHF
Renal insufficiency	Sepsis	Blood transfusion within last 3 months

Participant #: _____

Medication History? Circle if yes

Long-term Antibiotic use	Long-term steroid use	Contrast dyes
Antiretrovirals	Long-term NSAID use	Cimetidine
Insulin/Metformin	Heroin/Methamphetamine	ACE inhibitors
ARBs	Diuretics	

Appendix M

PI Potential Participant Communication Log

Early Identification of Perioperative Acute Kidney Injury Utilizing Novel Renal Biomarkers

DATE AND TIME	ELIGIBLE PATIENT	PLANNED SURGERY/SURGEON/ DATE OF SURGERY:	TYPE CONTACT	CONTACT INFO: (PHONE/EMAIL ADDRESS)

Appendix N

Informed Consent to Participate in Research

Informed Consent to Participate in Research

Information to consider before taking part in research that has no more than minimal risk.

Title of Research Study: **Early Identification of Perioperative Acute Kidney Injury Utilizing Novel Renal Biomarkers**

Sponsor/Funding Source: Sigma Theta Tau - Beta Nu Chapter Research Grant; American Association of Nurse Anesthetists Foundation Research Grant
Sponsor Protocol #: 22-0072

Principal Investigator: Angela Ciuca, DNAP, CRNA, PhD Student
Institution, Department or Division: ECU College of Nursing
Address: 3116 Health Sciences Building, Mail Stop 162, Greenville, NC 27858
Telephone #: 864-650-4377
Study Coordinator: Linda Bolin, PhD, RN, ANP, FAHA
Telephone #: 252-744-6357

Participant Full Name: _____ Date of Birth: _____
Please PRINT clearly

(If you are a patient at ECU or Vidant, a copy of this form will be placed in your medical records.)

Researchers at East Carolina University (ECU) study issues related to society, health problems, environmental problems, behavior problems and the human condition. To do this, we need the help of volunteers who are willing to take part in research.

Why am I being invited to take part in this research?

The purpose of this research is to learn about identifying acute kidney injuries (AKI) more quickly after major surgery. You are being invited to take part in this research because you are scheduled for a major non-cardiac surgical procedure. The decision to take part in this research is yours to make. By doing this research, we hope to learn if novel renal biomarkers used to assess risk of developing surgical-associated AKIs identify patients more quickly than standard diagnostic tests do. If you volunteer to take part in this research, you will be one of about 160 people to do so.

Are there reasons I should not take part in this research?

I understand I should not participate in this research if I am less than 21 years old, am taking current chemotherapy agents, have had a kidney transplant, am COVID positive, have excessive amounts of protein in my urine, or have excessive amounts of bilirubin in my urine.

What other choices do I have if I do not take part in this research?

You can choose not to participate, and it will not alter your care you expect to receive at this facility.

Where is the research going to take place and how long will it last?

The initial phone interview should take 10-15 minutes after you have indicated you would like more information about the study to your Surgeon's staff. The urine samples will be collected at Vidant Medical Center during your surgical stay at three time points – at the beginning of surgery, on the evening of your surgery day, and in the morning of your

Date: _____

first post-operative day. The total amount of time you will be asked to volunteer for this study is approximately 30 minutes.

What will I be asked to do?
You will be asked to do the following:

- Complete a preoperative question and answer session based on your medical history with the study PI
- After induction of anesthesia for your surgery, a foley catheter will be placed as part of your normal care to drain your bladder. A sterile sample of urine will be collected from the foley catheter.
- At 6pm on your surgery day, another sterile sample of urine will be collected from the foley catheter.
- On the morning of post-operative day 1, a third sample of sterile urine will be collected from the foley catheter.

What might I experience if I take part in the research?
We don't know of any risks (the chance of harm) associated with this research. Any risks that may occur with this research are no more than what you would experience in everyday life. We don't know if you will benefit from taking part in this study. There may not be any personal benefit to you, but the information gained by doing this research may help others in the future.

Will I be paid for taking part in this research?
We will not be able to pay you for the time you volunteer while being in this study

Will it cost me to take part in this research?
It will ***not cost you*** any money to be part of the research. The sponsor of this research will pay the costs of all urine biomarker testing. It is estimated each of the three urine tests will cost $100.

Who will know that I took part in this research and learn personal information about me?
ECU and the people and organizations listed below may know that you took part in this research and may see information about you that is normally kept private. With your permission, these people may use your private information to do this research:

- The sponsors of this study.
- Any agency of the federal, state, or local government that regulates human research. This includes the Department of Health and Human Services (DHHS), the North Carolina Department of Health, and the Office for Human Research Protections.
- The University & Medical Center Institutional Review Board (UMCIRB) and its staff have responsibility for overseeing your welfare during this research and may need to see research records that identify you.
- People designated by Vidant Health.

How will you keep the information you collect about me secure? How long will you keep it?
The information collected about you will be kept on a password protected drive. Only the PI and members of the research team will have access to identified data. Data will be entered into a secure data base and any personal identifiers of yours will be removed. The resulting deidentified data for this research will be shared with your surgeon, the sponsoring agency of this research, and will be used in presentations to educate health care providers. Data will be kept for a minimum of 6 years after study closure.

What if I decide I don't want to continue in this research?
You can stop at any time after it has already started. There will be no consequences if you stop and you will not be criticized. You will not lose any benefits that you normally receive.

Date: _____ 2

Who should I contact if I have questions?
The people conducting this study will be able to answer any questions concerning this research, now or in the future. You may contact the Principal Investigator at 864-650-4377 (days, between 8am and 6pm).

If you have questions about your rights as someone taking part in research, you may call the University & Medical Center Institutional Review Board (UMCIRB) at phone number 252-744-2914 (days, 8:00 am-5:00 pm). If you would like to report a complaint or concern about this research study, you may call the Director for Human Research Protections, at 252-744-2914 and the Vidant Health Risk Management Office at 252-413-4473 or Vidant Health's Center for Research and Grants at 252-847-1177. You may also contact Vidant Health's Privacy Office at 252-847-6545 or VH_Privacy@vidanthealth.com.

Is there anything else I should know?
Identifiers might be removed from the identifiable private information or identifiable biospecimens and, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you or your Legally Authorized Representative (LAR). However, there still may be a chance that someone could figure out the information is about you.

Will I receive anything for the use of my private identifiable information or identifiable biospecimens?
If the research conducted on your private identifiable information or identifiable biospecimens leads to a commercially valuable product, you will not be eligible for any of the profits either because it will be impossible to identify the information or biospecimen that led to the product or because you are transferring ownership of that sample.

Will my identifiable biospecimen be used for whole genome sequencing?
Whole genome sequencing is the process of determining the complete DNA sequence of an individual at a single time. However, further analysis must usually be performed to provide any biological or medical meaning of this sequence. For this research, whole genome sequencing will not occur.

UMCIRB HIPAA Privacy Authorization

East Carolina University (ECU)/Vidant Health (VH): Research Participant Authorization to Use and Disclose Protected Health Information for Research

For use only with the research consent form for UMCIRB#: 21-000826
Principal Investigator: Angela Ciuca
Title: Early Identification of Perioperative Acute Kidney Injury Utilizing Novel Renal Biomarkers

Location where research will be conducted
The members of the research team will conduct the research study at:
☐ East Carolina University (ECU) ☐ VH ☒ ECU & VH ☐ Other

When taking part in research, protected health information (PHI) is collected, used, and shared with others who are involved in the research. Federal laws require that researchers and health care providers protect your PHI. Also, federal laws require that we get your permission to use collected PHI for the research. This permission is called authorization.

Date: _____ 3

In order to complete the research project in which you have decided to take part, the research team needs to collect and use some of your PHI as described below.

What types of protected health information (PHI) about me will be used or disclosed?
(Select all that apply.)

ECU Health Care Component:
[☒] ECU Physicians
[☐] School of Dental Medicine
[☐] **Speech, Language, and Hearing Clinic**
[☐] **Physical Therapy**
[☐] **Student Health**
[☐] Other ECU Health Entity
(please list):

Vidant Health Entity:
[☒] Entire Vidant Health system
[☐] Vidant Medical Center
[☐] **Other Vidant Health Entity**
(Please list):

Type of ECU Records:
[☒] Medical/clinic records
[☐] Billing records
[☒] Lab, Pathology and/or Radiology results
[☐] **Mental Health records**
[☒] PHI previously collected for research
[☒] Records generated during this study
[☐] Other:

Type of Vidant Records:
[☒] Medical/clinic records
[☐] Billing records
[☒] Lab, Pathology and/or Radiology results
[☐] **Mental Health records**
[☒] PHI previously collected for research
[☒] Records generated during this study
[☐] Other:

Who will use or disclose my PHI?
[☒]Principal Investigator
[☒]Other members of the research team
[☒]Other providers involved in your care during research procedures, outpatient/inpatient stays during which research is being performed, or physician office visits during which research is being performed.

Who will receive my PHI?
[☐] Sponsor or other funding source to provide oversight for entire research project
[☒] Research investigators to conduct and oversee the research project
[☒] Principle Investigator and research team members to participate in the various research activities
[☐] FDA or other regulatory agencies to provide regulatory oversight
[☒] UMCIRB to provide continuing review of the research project
[☒] Institutional officials in connection with duties for monitoring research activity
[☐] Other providers involved in your care during research procedures, outpatient/inpatient stays during which research is being performed, or physician office visits during which research is being performed.
[☐] Researchers at other sites—List sites:
[☒] Data and Safety Monitoring Board and its staff
[☐] Contract Research Organization and its staff
[☐] Other

We will share only the PHI listed above with the individuals/agencies listed above. If we need to share other PHI or if we need to send PHI to other individuals/agencies not listed above, we will ask for your permission in writing again

Date: _____ 4

How my PHI may be released to others:
ECU and VH are required under law to protect your PHI. However, those individuals or agencies who receive your PHI may not be required by the Federal privacy laws to protect it and may share your PHI with others without your permission, if permitted by the laws governing them.

What if I do not sign this form?
You will not be eligible to participate in this study if you do not sign this Authorization form.

How may I revoke (take back) my authorization?
You have the right to stop sharing your PHI. To revoke (or take back) your authorization, you must give the Principal Investigator your request to revoke (or take back) your authorization in writing. If you request that we stop collecting your PHI for the study, you may be removed from the study. If you are removed from the study, it will not affect your ability to receive standard medical care or affect payment, health plan enrollment or benefit eligibility. PHI collected for the research study prior to revoking (or taking back) your Authorization will continue to be used for the purposes of the research study. Also, the FDA (if involved with your study) can look at your PHI related to the study even if you withdraw this authorization.

Restrictions on access to my PHI:
You will not be able to see your PHI in your medical record related to this study until the study is complete. If it is necessary for your care, your PHI will be provided to you or your physician.

How long may the PHI about me be used or disclosed for this study?
Research information continues to be looked at after the study is finished so it is difficult to say when use of your PHI will stop. There is not an expiration date for this authorization to use and disclose your PHI for this study.

If you have questions about the sharing of PHI related to this research study, call the principal investigator Angela Ciuca at phone number 864-650-4377. Also, you may telephone the University and Medical Center Institutional Review Board at 252-744-2914. In addition, if you have concerns about confidentiality and privacy rights, you may phone the Vidant Health Privacy Officer at 252-847-6545 or VH_Privacy@vidanthealth.com or the Privacy Officer at East Carolina University at 252-744-5200.

Authorization

To authorize the use and disclosure of your PHI for this study in the way that has been described in this form, please sign below and date when you signed this form. A signed copy of this Authorization will be given to you for your records.

Date: _____ 5

I have decided I want to take part in this research. What should I do now?

The person obtaining informed consent will ask you to read the following and if you agree, you should sign this form:

- I have read (or had read to me) all of the above information.
- I have had an opportunity to ask questions about things in this research I did not understand and have received satisfactory answers.
- I know that I can stop taking part in this study at any time.
- By signing this informed consent form, I am not giving up any of my rights.
- I have been given a copy of this consent document, and it is mine to keep.

Participant's Name (PRINT)	**Signature**	**Date**

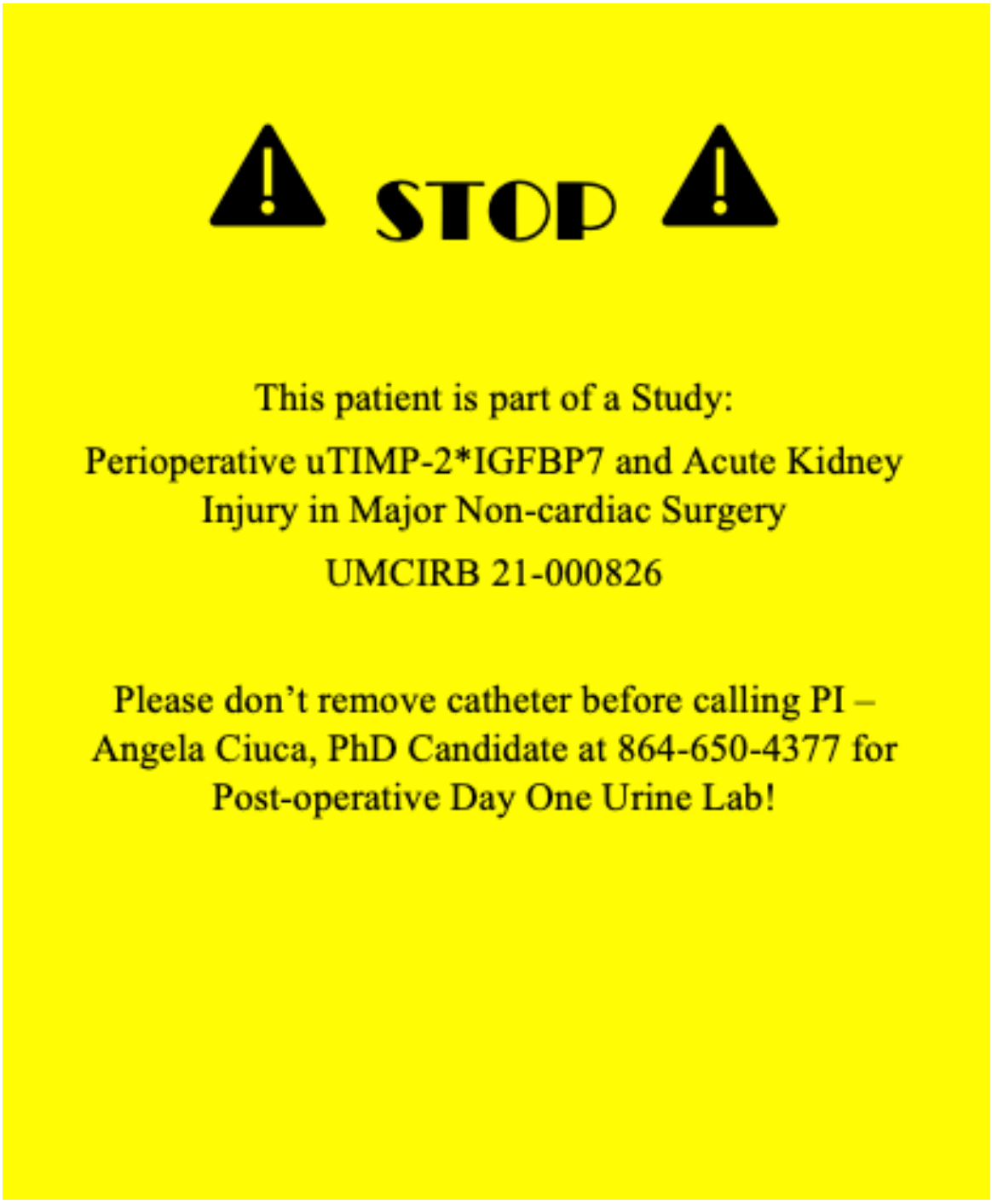
Person Obtaining Informed Consent: I have conducted the initial informed consent process. I have orally reviewed the contents of the consent document with the person who has signed above and answered all of the person's questions about the research.

Person Obtaining Consent (PRINT)	**Signature**	**Date**

Principal Investigator (PRINT)	***Signature***	***Date***

Appendix O

Study Alert Sign for Chart



Appendix P

Lab Specimen Training

College of Allied Health Sciences
Department of Clinical Laboratory Science
East Carolina University
Health Sciences Building • Greenville, NC 27858
252-744-6063

January 28, 2022

Dr. Linda Bolin, Dissertation Chair and Angela Ciuca, PhD Nursing Candidate attended a 1 hour hands-on clinical lab science training to include the following skills in preparation for Angela's dissertation research:

- Reviewed and practiced basic specimen handling
- Practiced specimen transfer between collection containers and centrifuge tubes
- Reviewed and practiced centrifuging procedures
- Reviewed specimen collection and preparation process for the NephroCheck® urine assay
- Reviewed how to transfer the supernatant to a storage container
- Proper handling for dip stick testing a sample
- Practiced reading dip stick results at the proper time
- Reviewed and practiced using a 100 µL pipette to mix conjugate liquid and sample fluids
- Reviewed basic safety procedures and using personal protective equipment
- Reviewed proper techniques for labeling specimen containers

This training was provided by Dr. Guyla Evans, PhD, MLS(ASCP)^{CM}, SC^{CM}, Interim Department Chair and Dissertation Committee Member.

Signature: _____ Date: 1/28/2022

Appendix Q

NephroCheck® Meter Calibration and Verification

NephroCheck Method Comparison
25-Jul-22

ECU College of Nursing
2150 West 5th Street
Greenville, NC 27858
(864) 650-4377

	541095	WILSON			
SP #	AKI	AKI	MEAN	STD DEV	% CV
1	0.17	0.19	0.18	0.01	7.86%
2	0.71	0.6	0.66	0.08	11.88%
3	0.04	0.04	0.04	0.00	0.00%
4	3.8	2.75	3.28	0.74	22.67%
5	1.13	1.21	1.17	0.06	4.83%
6	0.33	0.27	0.30	0.04	14.14%
7	0.13	0.12	0.13	0.01	5.66%
8	1.02	0.98	1.00	0.03	2.83%
9	0.08	0.09	0.09	0.01	8.32%
10	0.7	0.82	0.76	0.08	11.16%

NephroCheck Test Kit Lot #/Expiration: 22NPK0019A 5-Jan-2023

Analyst Who Performed Testing: Angela Cuica
Data Prepared By: Michael Kastner

NEPHROCHECK METHOD VALIDATION WORKSHEET

Customer /Account #:	ECU College of Nursing			
Contact Name:	Angela Ciuca			
Contact Email Address:	ciucaa19@students.ecu.edu			
Contact Phone Number:	(864) 650-4377			
Instrument Functional Location(s):	Inst. #1	541095	Inst. #2	N/A
Date of Testing:	25-Jul-2022			
Name of Person Performing Testing:	Angela Ciuca			
Assay Name:	NephroCheck			
NephroCheck Test Kit Lot Number/Expiration:	22NPK0019A		5-Jan-2023	

NEPHROCHECK CAL/VER KIT TESTING

	541095	N/A	TARGET	1 SD	2 SD
LEVEL 1	0.08		0.079	0.018	0.036
LEVEL 2	0.25		0.236	0.05	0.11
LEVEL 3	0.96		1.079	0.25	0.49
LEVEL 4	2.01		2.795	0.64	1.28
LEVEL 5	6.74		7.319	1.67	3.35

NEPHROCHECK CAL/VER INFORMATION	
Lot Number:	22LCK0016C
Expiration:	12-Sep-2022

CONTROL PRECISION - Using NephroCheck LQC Kits

Functional Location:			541095		
Low Control			High Control		
AKI	IGFBP-7	TIMP-2	AKI	IGFBP-7	TIMP-2
0.25155	64.5	3.9	2.9218	208.7	14
0.17714	52.1	3.4	2.64358	201.8	13.1
0.23751	60.9	3.9	2.4635	189.5	13
0.17408	51.2	3.4	2.8755	202.5	14.2
0.23976	66.6	3.6	2.538	188	13.5
0			0		
0			0		
0			0		
0			0		
0			0		

NEPHROCHECK LQC INFORMATION		
LC Lot Number:	22LCK0016C	
Expiration:	12-Sep-2022	
Analyte	Mean	2 SD
IGFBP-7	68.3	24.5
TIMP-2	3.6	1.3
HC Lot Number:	22LCH0015C	
Expiration:	12-Sep-2022	
Analyte	Mean	2 SD
IGFBP-7	220.9	79.3
TIMP-2	13.4	4.7

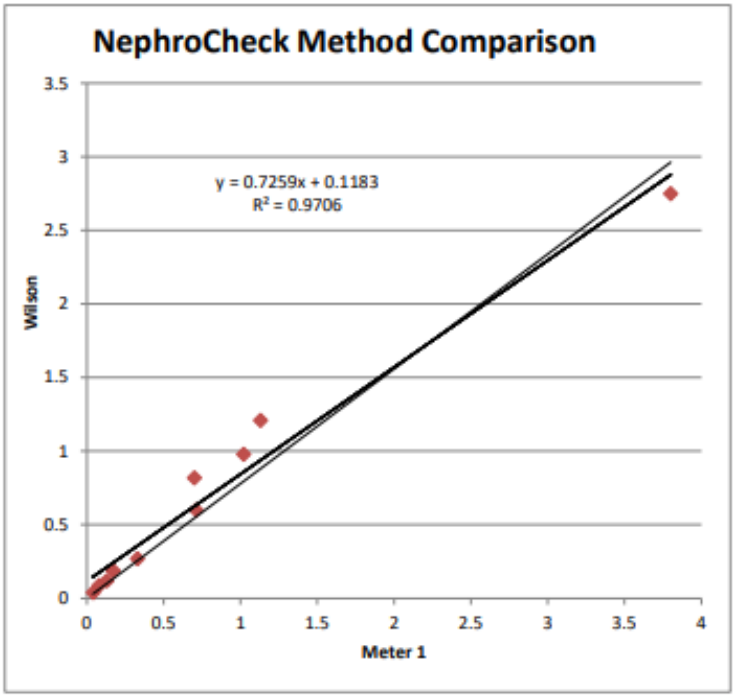
NephroCheck Meter to Meter Data

	541095	N/A	WILSON	N/A
SP #	AKI	AKI	AKI	AKI
0.19	0.17		0.19	
0.6	0.71		0.6	
0.04	0.04		0.04	
2.75	3.8		2.75	
1.21	1.13		1.21	
0.27	0.33		0.27	
0.12	0.13		0.12	
0.98	1.02		0.98	
0.09	0.08		0.09	
0.82	0.7		0.82	

NephroCheck Precision
25-Jul-22

ECU College of Nursing
2150 West 5th Street
Greenville, NC 27858
(864) 650-4377

Sample ID	Meter 1	WILSON
1	0.17	0.19
2	0.71	0.6
3	0.04	0.04
4	3.8	2.75
5	1.13	1.21
6	0.33	0.27
7	0.13	0.12
8	1.02	0.98
9	0.08	0.09
10	0.7	0.82

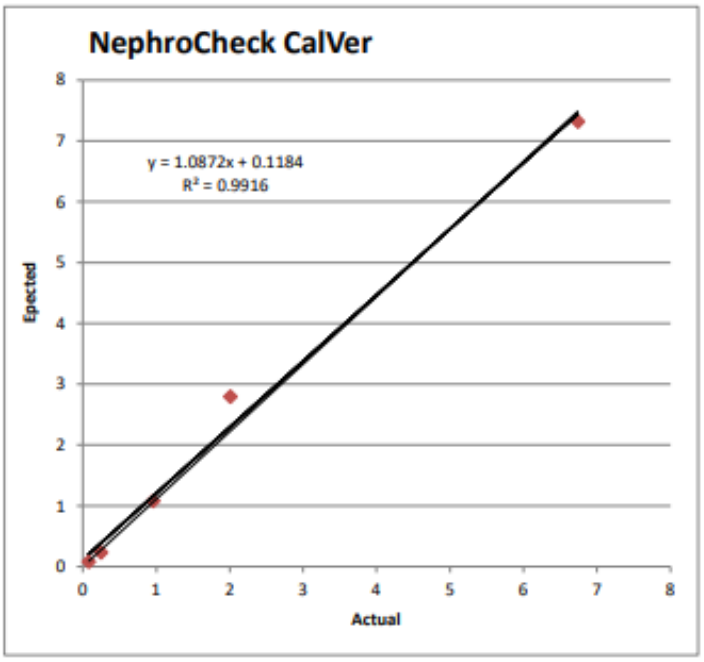


NephroCheck Test Kit Lot #/Expiration: 22NPK0019A 5-Jan-2023

NephroCheck Calibration Verification
25-Jul-22

ECU College of Nursing
2150 West 5th Street
Greenville, NC 27858
(864) 650-4377

Sample ID	Actual	Expected
1	0.08	0.079
2	0.25	0.236
3	0.96	1.079
4	2.01	2.795
5	6.74	7.319



NephroCheck Test Kit Lot #/Expiration: 22NPK0019A 5-Jan-2023

Analyst Who Performed Testing: Angela Cuica
Data Prepared By: Michael Kastner

NephroCheck Precision
25-Jul-22

ECU College of Nursing
2150 West 5th Street
Greenville, NC 27858
(864) 650-4377

	Low Control				High Control		
	AKI	**IGFBP-7**	**TIMP-2**		**AKI**	**IGFBP-7**	**TIMP-2**
	0.25155	64.5	3.9		2.9218	208.7	14
	0.17714	52.1	3.4		2.64358	201.8	13.1
	0.23751	60.9	3.9		2.4635	189.5	13
	0.17408	51.2	3.4		2.8755	202.5	14.2
	0.23976	66.6	3.6		2.538	188	13.5
MEAN	0.22	59.06	3.64	**MEAN**	2.69	198.10	13.56
STD DEV	0.04	7.07	0.25	**STD DEV**	0.20	8.96	0.53
% CV	17.26%	11.97%	6.90%	**% CV**	7.55%	4.52%	3.92%

NephroCheck Test Kit Lot #/Expiration:	22NPK0019A	5-Jan-2023
NephroCheck LQC LC Kit Lot #/Expiration:	22LCK0016C	12-Sep-2022
NephroCheck LQC HC Kit Lot #/Expiration:	22LCH0015C	12-Sep-2022
Instrument Functional Location:	541095	
Analyst Who Performed Testing:	Angela Cuica	
Data Prepared By:	Michael Kastner	

Appendix R

NephroCheck® Specimen Collection and Preparation Instructions

Specimen Collection and Preparation

The NEPHROCHECK® Test is intended for use with adult human urine specimens only. Other specimen types have not been characterized.

Non-Frozen / Non-Refrigerated Samples

1. Collect a fresh urine sample of approximately 10 mL in a clean specimen collection cup without additives. For patients with indwelling bladder catheters, the collection bag should first be emptied and then a fresh sample of urine should be collected. Alternatively, the sample may be collected from an urometer, if present. Transport the urine sample to the laboratory that will run the NEPHROCHECK® Test.

   NOTE: Samples should be transferred to the laboratory and centrifuged within one hour of sample collection.

2. Thoroughly mix the urine in the specimen collection cup by inverting the container 8–10 times. Transfer the urine sample from the specimen collection cup to a clean centrifuge tube. Centrifuge the urine sample for approximately 10 minutes in refrigerated centrifuge set to an rcf of 1000 x g and temperature of 4°C (39.2°F). After centrifuging the sample, transfer the supernatant to a clean receptacle. Allow supernatant to reach room temperature and test the supernatant within 5 hours of sample collection. If testing cannot be completed within 5 hours of sample collection, supernatants may be refrigerated immediately after centrifugation and tested within 20 hours of sample collection.

Frozen / Refrigerated Samples

1. To test frozen or refrigerated samples, thaw or warm urine supernatants in a room temperature (18–25°C; 64.4–77°F) water bath until thawed and warmed to room temperature but no longer than 20 minutes.
2. Once the supernatant is thawed and/or warmed to room temperature, gently invert the sample tube 1–2 times to mix sample. Ensure supernatant is well-mixed before testing. Test the supernatant immediately after mixing.

   NOTE: Precipitates may be present in supernatant tube. Always invert the sample tube 1–2 times to ensure sample is well mixed before testing to ensure accurate measurement results.

3. Supernatants must be loaded into a NEPHROCHECK® Test cartridge within one hour of placing the supernatant into the water bath.
4. Avoid repeated freezing and thawing of the supernatant.

(Astute Medical, 2017, p. 4)

Appendix S

NephroCheck® Test Procedure

NEPHROCHECK® Test Procedure

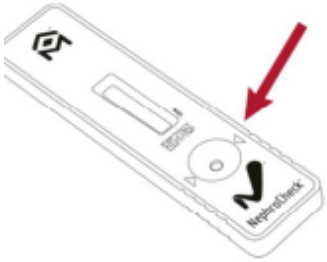
- The Test procedure requires the use of a calibrated precision pipette for the following:
  - Addition of NEPHROCHECK® Test Buffer Solution and urine sample into the NEPHROCHECK® Test Conjugate Vial
  - Introduction of sample into the NEPHROCHECK® Test cartridge

To perform the NEPHROCHECK® Test, follow these steps:

1. Preparation:
   a. Highlight and select Run Patient on the Astute140® Meter Main Menu.
   b. Manually enter the Patient ID or scan the Patient ID into the ASTUTE140® Meter using a barcode scanner (if connected). After confirming that the correct Patient ID and/or Sample ID have been entered, select **Run Patient**. The ASTUTE140® Meter drawer will automatically open. (NOTE: Patient identification schemes (i.e. IDs) that contain the following special characters "+", "&" or "@" should be entered into the ASTUTE140® Meter only with a barcode scanner—these characters should not be entered into the ASTUTE140® Meter using an external keyboard.)
   c. Remove the NEPHROCHECK® Test Kit components from 2-8°C storage and allow the Test cartridge to reach the operating temperature of 18–25°C (64–77°F).
   d. Remove the new NEPHROCHECK® Test cartridge from the foil pouch and place on a flat surface.
   e. Remove the NEPHROCHECK® Test Conjugate Vial from the pouch.
   f. Each NEPHROCHECK® Test Conjugate Vial contains a single conjugate bead. Remove the cap from the NEPHROCHECK® Test Conjugate Vial. Visually inspect the cap and vial to ensure that the conjugate bead has not adhered to the cap and is present in the vial. If the bead has adhered to the cap, place the cap on the vial and tap three times. Repeat if necessary until the bead drops into the vial. Do not touch the bead or attempt to remove the bead from the cap by any other means.
   g. Pipette 100 µL of the NEPHROCHECK® Test Buffer Solution into the NEPHROCHECK® Test Conjugate Vial containing the conjugate bead. This will result in reconstitution of the conjugate bead into solution. Discard the pipette tip in accordance with local regulations.

      NOTE: The conjugate liquid in the vial is to be used as soon as it is reconstituted.

      NOTE: Each bottle of NEPHROCHECK® Test Buffer Solution contains enough buffer solution to run all of the tests supplied in the NEPHROCHECK® Test Kit. Do not discard the buffer solution until all tests supplied in the NEPHROCHECK® Test Kit have been used. Store the unused portion of the buffer at 2–8°C (35.6–46.4°F).
   h. Using a new pipette tip, add 100 µL of centrifuged urine supernatant or liquid control sample to the NEPHROCHECK® Test Conjugate Vial that now contains the reconstituted conjugate bead solution. Mix thoroughly (mix at least three times using the pipette tip).
   i. Pipette 100 µL of mixed sample/conjugate solution onto the sample port on the NEPHROCHECK® Test cartridge. Avoid introducing bubbles into the sample port when adding the sample / conjugate solution into the NEPHROCHECK® Test cartridge. Wait approximately one minute for the sample to be absorbed into the round well.



2. Run the NEPHROCHECK® Test:

   a. Holding the NEPHROCHECK® Test cartridge by the grips on the sides of the cartridge, place the cartridge in the ASTUTE140® Meter drawer with the Astute Medical logo towards the inside of the meter drawer. Keep the NEPHROCHECK® Test cartridge horizontal and avoid tipping the test cartridge during placement into the ASTUTE140® Meter drawer.

   b. Close the ASTUTE140® Meter drawer. In approximately 20 minutes, a single numerical test result will be displayed.

   c. Eject the ASTUTE140® Meter drawer. Remove the NEPHROCHECK® Test cartridge and discard it and the conjugate vial in accordance with local regulations.

3. Review the NEPHROCHECK® Test Results:

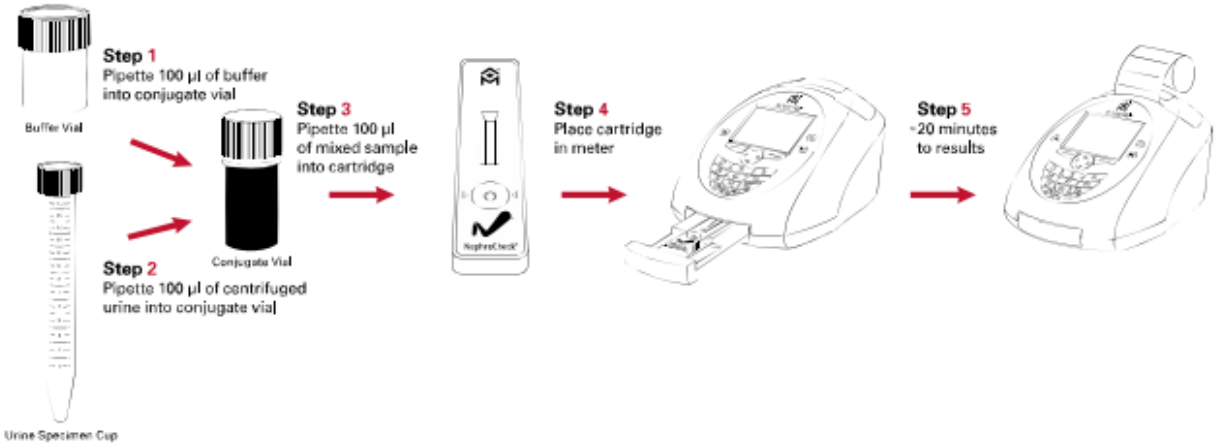
   Upon completion of running the test, follow instructions in the ASTUTE140® Meter User Manual to print results (if desired) or upload results to the Laboratory Information System (LIS).

   If the NEPHROCHECK® Test should fail, a Meter error message will indicate that the result is invalid and that a new cartridge should be run. If the procedure fails a second time, contact Astute Technical Support (See "Ordering and Contact Information").

   The ASTUTE140® Meter converts the fluorescent signal from each of the two immunoassays (TIMP-2 and IGFBP-7) contained within the NEPHROCHECK® Test cartridge into a single numerical result. The NEPHROCHECK® Test result (AKIRISK® Score) is calculated by the ASTUTE140® Meter as the product of the measured concentrations of the two biomarkers, TIMP-2 and IGFBP-7 (measured as ng/mL), divided by 1000:

$$\text{NEPHROCHECK® Test Result (AKIRISK® Score)} = \frac{([\text{TIMP-2}]*[\text{IGFBP-7}])}{1000} \quad (\text{units} = (\text{ng/ml})^2/1000)$$

NEPHROCHECK® Test Preparation Process



(Astute Medical, 2017, p. 4-6)

Appendix T

PACU AKI Study Tip Sheet

AKI STUDY TIP SHEET

Purpose: NephroCheck urine assay assesses for urine TIMP-2 and IGFBP7, two urine protein biomarkers. These biomarkers serve as an early indicator for risk of developing a high-stage acute kidney injury (AK). Participants in this study will have three urine specimens taken from foley catheters at induction, at 6pm on day of surgery, and at 6am post-op day 1.

Participating Surgeons:

Akram	Brillant	Brown	Collins
Crockett	Demaria	Fisher	Honaker
Parikh	Perez-Ginnari	Romine, Matt	Romine, Margaret
Semer	Snyder	Stephens	Sutton
Taylor	Zervos		

Typical Intraabdominal Procedures for Participants:

Total abd hysterectomy	Robotic or Open Colorectal
PCNL	Nephrectomy/Partial nephrectomy
Robotic prostatectomy	Open abdominal procedures
Whipple	Panniculectomy

TIPS:

- Pt will have a bright yellow card taped to chart if participating
- Eligible patients will be 23 hr observation or admissions
- If no order to continue foley is available, but you see a patient with study card, please contact the surgeon/resident
- Maintain foley and please pass in report to floor RN that patient will keep foley through 7 am POD1

PI Contact:

- Angela Ciuca, DNAP, CRNA, PhD Candidate; ECU CON
- 864-650-4377 ciucaa19@students.ecu.edu